# Snapshots of a life in science: letters, essays, biographical notes, and other writings (1990-2016)

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# Preface

**What follows is a collection of letters, e-mails, essays, lecture introductions, eulogies, notes, and other assorted writings produced over a period of roughly twenty-five years. While many of the entries here reflect the life of an academic scientist and teacher, there are also letters about a wide variety of other topics. Taken together, they paint a portrait of one person's experiences, interests, and opinions.**

**This collection is incomplete in various ways. It omits letters and e-mails related to matters that are proprietary, confidential, or that are otherwise too sensitive for free dissemination. In some instances, names have been removed. Several individuals agreed to have their letters or e-mails included in this collection. I am grateful to each of them. In alphabetical order, they are: Sylvia Arber, Ben Barres, Dean Bok, Leon Kass, Richard Nakamura, Chris Potter, Vanitha Ramakrishnan, King-wai Yau, and Semir Zeki.**

**I hope that you, the reader, will find this collection interesting. Please feel free to download, reproduce, and share it. I ask only that you indicate the source of the material if you use it.**

**Jeremy Nathans**
**March, 2017**

# Introductions for Lectures or Prizes

**Lubert Stryer, on the occasion of a symposium in his honor – October 2003**

**Lubert Stryer is a Professor of Neurobiology at Stanford Medical School.**

I first met Lubert in the late 1970's. David Julius and I visited him here at Stanford. At that time, David and I were undergraduates at M.I.T. and were both working in Alex Rich's lab. Alex had given us a sample of tRNA to deliver to Lubert for some spectroscopic experiments. Why this mission wasn't entrusted to Federal Express now eludes me. When we arrived, two undergraduates still green behind the ears, Lubert was his usual high energy self. He treated us royally - including a tour of SLAC where we saw his x-ray post at the synchrotron. Needless to say, this left quite an impression.

When I arrived at Stanford a couple of years later as a student in the M.D./PhD program, I had no idea how big an effect Lubert would have on my scientific trajectory. I joined Dave Hogness's lab for my thesis work, but one year into it I heard a spectacular pair of talks on vision that changed my research direction. One talk was given by Denis Baylor, and in it he described the beautiful work that he and his postdocs King Yau and Trevor Lamb were doing on photoreceptor physiology using the suction electrode technique. The second was given by Lubert, and in it he described his discovery, with his postdocs Bernard Fung and Jim Hurley, of the transducin-cGMP phosphodiesterase cascade that mediates phototransduction. These two lectures stimulated me to think and read about vision, and as a result I decided to switch my thesis, and in particular, to apply molecular genetic approaches to figuring out the structure of rod and cone pigments and the basis of inherited variation in human color vision. I should add that Dave was fully supportive of this somewhat unorthodox thesis project, and both he and Lubert were especially supportive during the rather dry first two years of the work.

At regular intervals during my time at Stanford, Lubert would call me in the lab with an invitation to come over and talk. Those were wonderful discussions and they remain as some of my fondest memories of that time. The discussions always involved thinking creatively, critically, and usually mathematically about something. I remember for example, Lubert describing work that he and Greg Yamanaka had done to dissect the free energy of the GDP-GTP cycle in transducin. Another conversation involved his analysis of outer segment cGMP-gated channels with respect to their abundance, the fraction that are open, and cGMP binding and release kinetics.

In each case, Lubert was digging deep below the surface. The questions were: what is the biological problem that the system has been selected (in the Darwinian sense) to solve? For example, is it signal-to-noise ratio, or kinetic performance, or a need to drive a reaction closer to irreversibility?

Here is an analogy from astronomy. Most experimentalists collect data and - if they are smart, hardworking, and lucky - they may realize that there are patterns in the data. For example, Kepler formulated his second law of planetary motion because, in looking at his data, he realized that for each planet equal areas are swept out in equal times. But this "law", like Kepler's other two, is essentially just curve fitting the data. It required Newton's insight to realize that equal areas swept out in equal times represented the conservation of angular momentum, and, with the other two, can be explained by the law of l/r squared attraction. Lubert has brought a Newtonian eye to biology and I think it is this drive for a deep understanding that is at the core of his scientific style.

Let me return to the theme that I started with: Lubert's influence on others. Lubert has had an enormous positive influence on those around him through his generosity, enthusiasm, wisdom, and collegiality. It is an honor to be a part of his scientific family.

**Seymour Benzer, 2001 Passano Awardee – April 2001**

It is a great pleasure to welcome Dr. Seymour Benzer, Professor of Neurobiology at the California Institute of Technology, to Johns Hopkins. In considering whether to refer to our guest as Dr. Benzer - which seems too formal - or Seymour - which seems perhaps too informal - I have opted for the later because, if nothing else, it seems a better fit for a man whose lab traditions include cutting the hair of his postdoctoral fellows. Seymour is the recipient of this year's Passano Award, an award that was started 60 years ago by the Passano family to honor outstanding biomedical researchers.

If one were to pick a single person whose insights and interests have defined the development of molecular biology during the past half century, Seymour would be a good choice. Like many of molecular biology's early converts he came from physics. As a graduate student at Purdue University during the Second World War, Seymour worked on semiconductor physics as part of the larger military interest in radar development. This work culminated with the invention of the transistor at Bell Labs in 1948. Seymour's reaction to the spectacular scientific success and imminent commercial impact of semiconductor physics was characteristic - instead of riding the wave, he decided that it was time to look for a new challenge far from the crowd.

In 1948, Seymour took Max Delbruck's famous Phage Course at the Cold Spring Harbor Laboratory. He was instantly converted. Five years later, he began a remarkable series of experiments with two genes in a bacterial virus called T4 that would reveal for the first time both the inner structure of the gene and the full power of genetic analysis. Among other things, these experiments showed that mutations were nonrandom (i.e there were mutational hotspots), that each mutagen gives rise to a distinctive spectrum of mutations, that mutational alterations can be very small and most likely alter only a single base pair, that units of genetic function could be defined by the cis-trans test (defining "the cistron"), and that protein substructure could be studied by genetic methods. This work established the idea of doing genetic screens to saturation and it revealed a hitherto unsuspected richness within the internal structure of the gene. Prior to this work, genes were studied as the fundamental units of mutation, recombination, and inheritance - but with no clear way to further dissect these attributes. This work also led to a series of elegant experiments that revealed the basic properties of the genetic code and the specificity of transfer RNA in protein synthesis.

Thus, by the early 1960s Seymour again found himself at the center of an incredibly exciting field, and again his reaction was telling. I will quote from an autobiographical essay that Seymour wrote in 1966: "This all got more and more exciting, until it dawned on me how many people were doing the same things. ... Delbruck saved me when he wrote to my wife to tell me to stop writing so many papers."

What happened next will be the subject of this lecture. Seymour switched again - this time into behavioral genetics using the fruit fly, Drosophila melanogaster. At that time, behavioral biology was considered a hopeless mechanistic quagmire, but Seymour brought a boldness and a clarity of thinking that had been honed to a fine edge in his previous work on gene structure and function. Over the next several decades he and his students, at first working virtually alone, greatly enriched and in several cases laid the foundations for what are now a series of vibrant research areas each with a major impact in human biology and medicine. An incomplete list would include: potassium channel molecular biology, biological clocks, learning and memory, eye development, neurodegenerative disorders, and aging. I think it is no exaggeration to say that Seymour's Drosophila work has ushered in the golden age of genetic neurobiology.

Throughout his long and illustrious career, several attributes stand out in Seymour's work: his originality, his incisive choice of experimental system, and his ability to see far ahead of the present. Seymour also has a playfulness that strikes me as an integral part - maybe the core - of his scientific style. About thirty-five years ago, Arthur Koestler wrote a book about scientific and artistic creativity entitled "The Act of Creation". In it, Koestler notes that good scientific ideas are like good jokes: they have a spark to them that catches you by surprise and makes you either see something entirely new or makes you see a familiar thing in a new way.

Seymour, we congratulate you on your Passano Award and we thank you for so many wonderful sparks.

**Alexander Rich, 2002 Passano Awardee – April 2002**

It is a pleasure to introduce Alexander Rich, the recipient of the 2002 Passano Award. I should add that introducing Alex is a special pleasure for me because I spent two wonderful years working in his laboratory as an undergraduate 25 years ago, and it was that experience that convinced me to go into biomedical research.

This award was started 60 years ago by the Passano family to honor outstanding biomedical researchers. It also honors Williams and Wilkins, the publishing company that the Passano family ran for many years. Williams and Wilkins has played a prominent role in biomedical publishing for close to a century.

Today's award has a nice historical connection with two earlier Passano Awards. As an undergraduate, Alex got his first taste of research by working with two great protein biochemists, Edwin Cohn and John Edsall. Cohn received the first Passano Award, in 1945, for his work on serum proteins and their clinical application during the Second World War, and Edsall received the Passano Award in 1966 for his work on the physical chemistry of proteins.

Now, I'd like to tell you a little bit about Alex. Alex was both an undergraduate and a medical student at Harvard, receiving his M.D. degree in 1949. Then he did something unusual. Instead of seeking further medical training, as I presume most of his classmates did, Alex applied to work as a postdoctoral fellow with Linus Pauling, arguably the greatest chemist of the 20th century. The application was successful and Alex spent the next five years with Pauling at Caltech. I think one of the things that rubbed off from Pauling was the approach of asking biological questions in terms of chemical principles and three dimensional structure, and, reciprocally, to extract biological insight from chemistry and from structure.

At a deeper level, one also sees in both Pauling's and Alex's scientific personalities a similar set of mutually reinforcing traits. In my view, these are: a wide ranging scientific curiosity; an extensive fund of chemical and biological knowledge; an ability to see familiar things in a fresh light; and a deep concern for the societal implications of science. After Caltech, Alex spent three years at N.I.H. and one year at the Cavendish Laboratory in Cambridge. He then moved to M.I.T. in 1958 where he is now the Sedgwick Professor of Biophysics. Over the years, Alex has received many awards, among them the National Medal of Science in 1995.

Alex has been chosen for the Passano Award in recognition of his contributions to structural biology and, in particular, the structural biology of nucleic acids. This work spans over 50 years, and encompasses an extraordinary breadth of fundamental contributions. Let me list a few. First, in work in the early 1950s unrelated to nucleic acids, Alex and Francis Crick used fiber diffraction to determine that collagen forms a triple stranded coiled-coil of alpha helices. This was the first time that higher order packing was determined for any protein. We now know that coiled coils are a ubiquitous and extraordinarily versatile motif, controlling processes such as transcription factor dimerization and the entry of viruses - including influenza and HIV - into cells. Later in the 1950s, Alex showed for the first time that separated nucleic acids could spontaneously anneal to form double helical base-paired polymers - the experimental

principle that is at the heart of all nucleic acid hybridization technologies. In 1960 he reported that RNA and DNA could anneal to form a hybrid double helix and presciently predicted from this purely chemical observation that "transfer of information between nucleic acids" was a plausible process - i.e. that RNA molecules might carry the information encoded within the DNA.

It was at this time that Alex became increasingly interested in protein synthesis. In the early 1960s he observed and correctly interpreted the function of polyribosomes, or polysomes for short. These are large complexes consisting of an mRNA with multiple translating ribosomes bound to it. I understand that Alex initially considered calling them a "multisomes", but John Kendrew reminded him that this would be mixing Latin with Greek - "multi" being Latin for "many" and "soma" being Greek for body. So for linguistic consistency, "poly", which is Greek for "many", was chosen instead of "multi", hence "polysomes". At about this time, Alex also made the profound evolutionary discovery that intracellular organelles, in this case chloroplasts, contained DNA. This observation is, of course, at the root of the theory of a bacterial origin of chloroplasts and mitochondria and it underlies the vast field of organellar genetics that has followed.

In the mid-1960s, Alex set out on an ambitious project to crystallize a tRNA and solve its structure by X-ray diffraction of single crystals. No RNA structure had ever been solved before, and the largest protein structure solved at that time, hemoglobin, had required decades of work. But within 5 years, Alex and a postdoctoral fellow, Sung-Hou Kim, had succeeded in getting a high resolution structure of yeast phenylalanine tRNA. This structure revealed for the first time the protein-like complexity of tertiary interactions within folded RNA. When I was a student in Alex's lab there was a big metal model of this tRNA. It was about four feet long and had all of the atoms. This, of course, was in the days before computer graphics, so to analyze and refine a crystal structure you had to build a model of it by hand. I think anyone who had spent some time in the 1970s looking at that beautiful structure was not at all surprised by the subsequent discoveries of the catalytic and recognition activities that we now routinely ascribe to RNA.

In the late 1970s, Alex's lab made another important discovery related to nucleic acid structure. Andrew Wang, a research associate, and Alex found, quite by accident, that certain DNA sequences could adopt a left-handed zig-zag helical configuration rather than the familiar right-handed and uniform helix associated with A or B DNA. They christened this new structure Z-DNA, but I won't say anything more about it since it will be the topic of today's lecture.

Alex has also had other, more eclectic, scientific interests. For example, he has always been interested in the origin of life, and from 1969 to 1980 he was a member of the Biology team associated with the Viking Mission to Mars, and in that capacity he helped design the equipment that looked for evidence of respiration in Martian soil samples.

Aside from his numerous and seminal scientific contributions, Alex has had an enormous influence on the scientific community and on individual scientists. To take just two examples from the first category, Alex worked for many years with the State Department, the Pugwash Commision, and the National Academy of Sciences to promote peaceful scientific exchanges with the Soviet Union and with China, and he also worked for many years with the New York Academy of Sciences judging science books for children.

With regard to his influence on individual scientists, Alex is first and foremost a warm colleague and friend, and also a valuable source of good advice. Alex's influence has also involved the special charm of his personal style, which I hope I can at least partially illustrate with a few brief vignettes. Here's one: when I was working in his lab I noticed that Alex drove a rather old and not particularly spiffy car, in fact it was what one might refer to as a clunker. One day Alex enlightened me about his philosophy regarding cars. The idea was to buy a used car with at least 100,000 miles on it, the logic being that if it had lasted that long it was reasonably likely to go another 100,000 miles.

Here's another vignette: I had the opportunity to participate with Alex in writing up for publication a little crystal structure that I had solved in his lab under the tutelage of Andy Wang. The process consisted of Andy and me getting all of the data together and Alex getting comfortably horizontal on the sofa in his office. Then after about a minute of throat-clearing and blowing of the nose, probably important for optimal cerebral functioning, Alex dictated the paper into a tape recorder in what was very nearly its final form.

Finally, here's a story that illustrates Alex's legendary good humor. One evening when Alex was heading home (this would be around midnight since Alex generally worked the early afternoon to midnight shift) he stopped at the office of Ned Seeman, a very bright crystallography postdoc who had the personal characteristic of saying exactly what was on his mind pretty much anytime and anywhere. Alex said to Ned, "I understand there is a bug in one of the computer programs. I guess we'll have to fix it tomorrow." To which Ned responded, "Alex what do you mean by 'we' will have to fix it?" Actually the original response included some more colorful language that I have omitted in the interests of good taste. Not skipping a beat, Alex just smiled and replied "Ned, I should think that by now you know what I mean by 'we'."

Alex, congratulations. It's great to have you here today.

**Mario Capecchi, 2004 Daniel Nathans Lecturer – May 2004**

Welcome to the fourth Annual Daniel Nathans Lecture in Molecular Genetics. We are honored to have Dr. Mario Capecchi as our lecturer this year.

Dr. Capecchi is a professor at the University of Utah and an investigator of the Howard Hughes Medical Institute. He is best known for his pioneering studies of gene transfer in mammalian cells, and, in particular, for his discovery that cells in culture can catalyze homologous recombination and that this recombination event can be used to direct genetic alterations to any predetermined region of the genome. In the late 1980s, Dr. Capecchi and his students showed that these approaches could be made to work in mouse embryonic stem cells. They then showed that the genetically altered ES cells could be used to produce a line of mice carrying the predetermined alteration. Over the past 15 years, Dr. Capecchi and his students have used this approach to carry out a series of beautiful studies on the role of a variety of genes, most especially the HOX genes, in patterning the mammalian embryo.

It would be no exaggeration to say that this group of conceptual and methodologic advances stands as one of the great milestones in biomedical science. Among its many applications is the modeling of human genetic diseases in mice. Some fields, like cellular immunology, have been completely transformed by it. As one measure of the impact of this technology, it is nearly impossible to flip through a current biomedical research journal without seeing one or more papers focused on the analysis of a mouse carrying a targeted mutation. For this work, Dr. Capecchi has received many awards, including the Lasker Award, the National Medal of Science, and the Kyoto Prize.

Like all great scientific advances, Dr. Capecchi's required a combination of original thinking, scientific skill, hard work, and luck. But this work also required more than the usual dose of tenacity. Dr. Capecchi has related the response he received from an NIH study section when he proposed looking for homologous recombination in mammalian cells: he was told that the experiment was so unlikely to succeed that it wasn't even worth trying. This story has a happy second half. A few years later when he had shown that the experiment had, in fact, succeeded, the comment on his resubmitted grant was "we are glad you didn't follow our advice". I've had several similar experiences, except mine haven't gotten beyond the first half of the story.

Other aspects of Dr. Capecchi's experience also deserve reflection. In the 1970s, Dr. Capecchi left a junior faculty position at Harvard Medical School for the University of Utah, a location that was considered, at least at that time, to be somewhat off the beaten track. At Utah, he worked with a small research team, he set his sights on an extremely ambitious goal, and he remained focused on that goal for many years. Perhaps being a bit removed from the crowd had something to do with his ultimate success.

But the most remarkable part of this story is Dr. Capecchi's personal journey. Let me mention this briefly. Dr. Capecchi was born in Italy in 1937, and raised by a mother who was openly anti-fascist. Shortly before his fourth birthday, his mother was arrested and sent to a concentration camp. Mario was sent to live with a peasant family, but before age six he found himself living on the streets in wartime Italy. Between the ages of six and nine he lived on the streets under near-starvation conditions. Mario's mother miraculously survived the war and finally found him in late 1946, in an orphanage, severely malnourished.

At this point, mother and son had a stroke of extraordinary good fortune – they were able to come to the U.S. and live with Mario's uncle (his mother's brother). As is so often the case with young people, Mario blossomed - like a seed that just needed the right soil and some sunlight. He excelled in athletics and academics, and within 15 years of leaving the orphanage and Italy he was a graduate student in Jim Watson's lab working on the biochemistry of protein synthesis.

Dr. Capecchi's professional journey is a testament to scientific imagination and tenacity, and his personal journey is a testament to the triumph of the human spirit. Dr. Capecchi, we are honored by your visit and we look forward to your lecture.

**Rich Roberts, 2006 Daniel Nathans Lecturer – January 2006**

It is a special pleasure to introduce Rich Roberts, who will deliver the 2006 Daniel Nathans lecture. To a greater extent than has been the case for most of the previous lecturers, Rich is a direct beneficiary of Dan's influence. From early on in Rich's career, he and Dan were linked by a strong bond of mutual respect and affection; and, of course, also by a mutual interest in restriction enzymes and their application to problems in molecular genetics.

Rich was born in Derby, England, but spent most of his early years in Bath. I understand that this makes him a Bathonian rather than a Ba'athist. As a child, Rich developed an affinity for all sorts of puzzles and mathematical games. He also became interested in chemistry, and set up a substantial home chemistry lab. Apparently his home survived these activities, although one wonders about the added cost in home insurance payments. Set on becoming a chemist, Rich attended the University of Sheffield. By his own reckoning, Rich's high school and college careers were a checkered mixture of boredom and excitement. From an autobiographical essay he writes the following about biochemistry: "I loathed it". But he hit his stride in organic chemistry and decided to stay at Sheffield for a Ph.D. in natural products chemistry with David Ollis.

As a doctoral student – in 1967 and 1968 – Rich re-encountered Biochemistry in a much more interesting guise: molecular biology. Thus, after obtaining his doctorate, he decided to join Jack Strominger at Harvard as a postdoctoral fellow, and he plunged into molecular biology by sequencing a tRNA involved in bacterial cell wall synthesis. This project included a one-month stint in Fred Sanger's lab at the MRC to learn the latest in RNA sequencing from the master himself, an experience that must have been the scientific equivalent of a pilgrimage to Mecca.

In 1972, shortly before moving to the Cold Spring Harbor Laboratory to set up his own independent research program, Rich heard a seminar that profoundly affected his thinking. I will quote here from Rich's autobiographical essay: "Earlier in 1972, I attended a seminar at Harvard Medical School given by

Dan Nathans. He described an enzyme, Endonuclease R, that could cleave DNA into specific pieces (this is the one that Kent Wilcox, Tom Kelly, and Ham Smith had discovered). This was to shape much of my subsequent research career. Sanger had developed RNA sequencing because there were plenty of small RNA molecules to practice on, but no suitable DNA molecules. I realized that Nathans' restriction enzyme gave an immediate way to isolate small DNA molecules. Surely there must be more restriction enzymes with different specificities."

With this idea in mind, Rich began his research program at Cold Spring Harbor by grinding up all sorts of bacteria and using the then-new technique of agarose gel electrophoresis to look for restriction enzymes with different cleavage specificities. His lab soon became the place to be – or at least the place to know - for restriction mapping of DNA. In the mid-1970s this resource got a big boost when Donald Comb, the founder of New England Biolabs, teamed up with Rich to produce and market restriction enzymes to the research community. In the thirty years since that time, NEB has grown from three people working in Don Combs' basement into two large and highly successful companies with several hundred employees – NEB and Cell Signaling Technologies. The latter sells antibodies and signal transduction products. As you may have seen in the NEB catalogue, in addition to selling more and better enzymes at lower prices, the company has been a strong supporter of preserving biodiversity and minimizing the human impact on the environment. The company also conducts research on parasitic and other infectious diseases that afflict the poorer citizens of the planet.

At Cold Spring Harbor, Rich focused on using the new molecular genetic tool kit to dissect the structure and function of Adenovirus 2, one of the centerpieces of the viral oncogenesis theme at Cold Spring Harbor in those days. In 1977, Rich and his colleagues Richard Gelinas, Louise Chow, and Tom Broker discovered that Adenovirus 2 late mRNAs were assembled from RNA segments derived from noncontiguous segments of the viral genome. The implication was that mRNAs were first synthesized as long precursors that were then processed by the removal of introns to generate the mature mRNA. This work was reported in a paper with the unusual title "An amazing sequence arrangement at the 5' ends of adenovirus 2 messenger RNA". Just for fun, I recently did a PubMed search to see how many papers have been published with the word "amazing" in the title. There are about a hundred over the past 30 years, but none of the other papers have as legitimate a claim to that adjective as this one. In 1993, Rich and Phil Sharp shared the Nobel Prize in Physiology or Medicine for the discovery of split genes.

Rich's main scientific interests since the late 1970s have been DNA sequencing and the analysis of DNA sequences, the structure and function of restriction enzymes and their companion enzymes, the modification methylases, and microbial evolution. I won't say any more about these areas as they will be the topics of today's lecture. After serving for 18 years as the Chairman of the Scientific Advisory Board at New England Biolabs, Rich moved to NEB in 1992, serving as Research Director from 1992 to 2005, and since 2005 as Chief Scientific Officer. Over the past twenty years he has also held numerous advisory and editorial positions.

Before I turn over the podium, let me make a few personal comments. I had the good fortune to work in Rich's lab in the summer of 1978 as part of the undergraduate research program at Cold Spring Harbor. The three first letters of the program's name - U, R, P – make the acronym URP and in consequence the students in the program were referred to as "URPs", which to me always sounded as if one or more consonants were missing from the front – perhaps a "T" and a "W". Rich's lab was unbelievably crowded. There were five desks with two people per desk in a single office room, and about 6 feet of bench space per person in the single lab room. But it was great fun, and everyone had the sense that incredible things were happening and that we were lucky to be present at a special time and place. I have strong memories of Rich's enthusiasm, smarts, and self-confidence; these were quite inspiring. I also thoroughly enjoyed Rich's dry and often irreverent sense of humor. Rich would occasionally hold up one of my less-than-perfect autoradiograms, squint at it for a few seconds, and then with a hint of a smile pronounce that it looked like an "URP gel". Translation: maybe we better run that one again. I might add that lab safety was not Rich's strong suit, as he could occasionally be seen pouring an acrylamide gel with

his coffee cup on the lab bench a few feet away and a cigarette between his fingers. But Rich was careful to keep the ashes out of the acrylamide, and in the end his gels looked better than anyone else's.

Rich it is pleasure and an honor to welcome you to Johns Hopkins. We look forward to your lecture.

**Napoleone Ferrara, 2006 Passano Awardee – April 2006**

It is a pleasure to welcome Dr. Napoleone Ferrara to Johns Hopkins and to introduce him on this occasion of the 2006 Passano Award Lecture. Dr. Ferrara is being honored for his pioneering work in vascular biology, and in particular for his discovery of vascular endothelial growth factor (VEGF, for short) and for his leadership in developing anti-VEGF therapies for human disease. Dr. Ferrara's work was carried out at Genentech, a biotechnology company in South San Francisco, where he currently holds the position of Genentech Fellow in the Department of Molecular Oncology.

I would also like to say a few words about the Passano Award itself. This award was started 65 years ago by the Passano family to recognize outstanding biomedical researchers. The motivation for the award grew out of the Passano family's close ties to the Williams and Wilkins Publishing Company, a prominent publisher of medical and biomedical textbooks and journals. In addition to this award, the Passano family also very generously supports the careers of a number of young clinician-scientists at Johns Hopkins and at the University of Maryland Medical Center.

Dr. Ferrara was born and raised in Catania in Sicily, the only child of a judge and a schoolteacher. An uncle who was a pathologist was an early source of inspiration for a medical career. As a student at the University of Catania Medical School, Dr. Ferrara had his first taste of laboratory research while working with Professor Umberto Scapagnini in the Department of Pharmacology. This work focused on reproductive endocrinology and resulted in several publications. After receiving his M.D. in 1981, Dr. Ferrara trained in Obstetrics and Gynecology, and, at that point, could have gone on to a career as a practicing clinician.

Instead, Dr. Ferrara made a career-altering decision. He left Italy and came to the United States to be a postdoctoral fellow in Reproductive Endocrinology with Dr. Richard Weiner in the Department of Obstetrics, Gynecology, and Reproductive Sciences at the University of California in San Francisco. In Weiner's lab, Dr. Ferrara worked on pituitary follicular cells; several years later, these cells would play a critical role in his purification and identification of VEGF. After two years in the laboratory, a clinical year in Portland, Oregon convinced Dr. Ferrara that he loved the laboratory more than the clinic. When he started a second postdoctoral fellowship at UCSF, it was in the laboratory of Denis Gospodarowicz at the Cancer Research Institute. This was the heyday of the fibroblast growth factors (or FGFs) and Gospodarowicz was one of the leaders in this field. Dr. Ferrara worked in the Gospodarowicz laboratory for two years and focused on basic FGF and its role in angiogenesis.

When, in the late 1980s, the time came to find a job – as inevitably it does for postdoctoral fellows – Dr. Ferrara joined Genentech, one of the first and most successful biotechnology companies. As a card-carrying obstetrician/gynecologist with research experience in reproductive endocrinology, Dr. Ferrara was a natural choice for an ongoing project at Genentech that aimed to develop the polypeptide hormone Relaxin as a treatment to promote cervical relaxation during labor. Unfortunately for this idea, it eventually became apparent that Relaxin's potency is far greater in rodents than in primates, and this application of Relaxin ultimately failed in clinical trials.

But Genentech gave Dr. Ferrara the freedom to also pursue his own ideas. Thus, while the Relaxin project was struggling, Dr. Ferrara returned to the pituitary follicular cells that he had worked with as a postdoctoral fellow and pursued the observation that these cells secrete a pro-angiogenic activity. Since this will be the subject of today's lecture, I will say only a little bit more about what happened next. In

less than a year, and working essentially on his own, Dr. Ferrara used an endothelial cell proliferation assay to purify the angiogenic activity to apparent homogeneity. Then, he and his colleague Bill Henzel determined by amino acid sequencing that the factor corresponded to a previously unknown polypeptide.

The paper that describes this work – with Ferrara and Henzel as the only authors – was published in 1989. I cannot resist noting that this paper was not published in Nature or Science or Cell or the New England Journal of Medicine or the Journal of Clinical Investigation, or any of a host of other prestigious journals. It was published in Biochemical and Biophysical Research Communications (BBRC). The title is "Pituitary follicular cells secrete a novel heparin-binding growth factor specific for vascular endothelial cells."

The abstract reads as follows: "A growth factor for vascular endothelial cells was identified in the media conditioned by bovine pituitary follicular cells and purified to homogeneity by a combination of ammonium sulfate precipitation, heparin-sepharose affinity chromatography and two reversed phase HPLC steps. The growth factor was a cationic, heat stable and relatively acid stable protein and had a molecular weight, as assessed by silver-stained SDS-PAGE gel, of approximately 45,000 under non reducing conditions and approximately 23,000 under reducing conditions. The purified growth factor had a maximal mitogenic effect on adrenal cortex-derived capillary endothelial cells at the concentration of 1-1.2 ng/ml (22-26 pM). Further characterization of the bioactivity of the growth factor reveals that it exerts mitogenic effects also on vascular endothelial cells isolated from several districts but not on adrenal cortex cells, lens epithelial cells, corneal endothelial cells, keratinocytes or BHK-21 fibroblasts, indicating that its target cell specificity is unlike that of any previously characterized growth factor. Microsequencing reveals a unique N-terminal amino acid sequence. On the basis of its apparent target cell selectivity, we propose to name this factor vascular endothelial growth factor (VEGF)."

Sixteen years after this initial 1989 paper, PubMed lists over 15,000 papers on VEGF. Not bad for a side project.

Dr. Ferrara, we welcome you and we look forward to your lecture.

**Tom Sudhof, 2008 Passano Awardee – April 2008**

It is a pleasure to introduce Tom Sudhof, the recipient of the 2008 Passano Award. This award was started 65 years ago by the Passano family to honor outstanding biomedical researchers. The award was a natural outgrowth of the Passano family's role in running the Williams and Wilkins Publishing company, a company that has played a prominent role in publishing medical and biomedical textbooks and journals for over a century. Because both the Passano family and the Williams and Wilkins Company are in Baltimore, the Passano Awards are conferred here, and as part of that event each awardee gives a lecture.

Tom Sudhof, the 2008 awardee, is chairman of the Department of Neuroscience at the University of Texas Southwestern Medical School and an Investigator of the Howard Hughes Medical Institute. He is being recognized today for his groundbreaking discoveries related to the structure, function, and development of synapses. In particular, Tom and his colleagues have systematically defined the protein components of synaptic vesicles and the manner in which intracellular calcium triggers vesicle fusion with the plasma membrane to produce neurotransmitter release. This work caps a half-century quest that began with Bernard Katz's discovery that neurotransmitters are released in discrete packets.

Tom's interest in synapses began 30 years ago when he was a medical student at the University of Gottingen. He worked at that time and for two years after his medical internship in the laboratory of V.P. Whittaker, who had been purifying and characterizing components of synapses, including synaptic vesicles, since the early 1960s. Tom appreciated that the new molecular genetic approaches made possible by recombinant DNA technology would be essential for tackling the question of synaptic

function. Therefore, in 1983, Tom began a postdoctoral fellowship in the laboratory of Michael Brown and Joe Goldstein at UT Southwestern. In the Brown and Goldstein lab, Tom worked on the structure and regulation of the LDL receptor gene. I note that Brown and Goldstein were honored in 1978 with a Passano Award, and in 1985 with the Nobel Prize in Medicine for their work on cholesterol homeostasis.

When he started his own lab at UT Southwestern in 1986, Tom focused on using molecular genetic methods to define the protein constituents of synaptic vesicles. In a relatively short period, he and his colleagues, together with several other research groups, had produced a nearly complete picture of the molecular players in this system. I don't want to give away any punch lines that Tom has for us in the upcoming lecture, so I won't go into further details, except to say that Tom has pursued this work in a most creative manner. He has used biophysical, structural, electrophysiological, and genetic approaches, and over the past decade has widened his study of synapses beyond the mechanics of neurotransmitter release to include the cell-cell recognition events that determine when and where synapses form.

Tom, congratulations on your Passano Award. We are honored to have you here today and we look forward to an exciting lecture.

**Irv Weissman, 2009 Passano Awardee – April 2009**

It is a pleasure to introduce Irv Weissman, the recipient of the 2009 Passano Award. Edward Passano established this award 65 years ago to honor outstanding biomedical researchers. The award was a natural outgrowth of the Passano family's central role in the Williams and Wilkins Publishing Company, a company that has played a prominent role in publishing medical and biomedical textbooks and journals for over a century. Because both the Passano family and the Williams and Wilkins Company are in Baltimore, the Passano Awards are conferred here, and as part of that event each recipient gives a lecture.

Irv Weissman is the Ludwig Professor of Clinical Investigation in Cancer Research in the Departments of Pathology and Developmental Biology at the Stanford Medical School, and the Director of the Stanford Institute for Stem Cell Biology and Regenerative Medicine. He is being recognized today for the identification and characterization of hematopoietic stem cells, the stem cells that give rise to all of the cell types within the blood.

Irv grew up in Montana and received his undergraduate education at Montana State University. He then attended medical school at Stanford, and he has remained there ever since. After a postdoctoral fellowship with Henry Kaplan, a radiation oncologist who pioneered the treatment of Hodgkin's lymphoma, Irv joined the Stanford faculty in the Department of Pathology.

For his entire career, Irv's scientific interests have been focused on the intersection of the immune system, cell recognition, and cancer. Beginning in high school and continuing as an undergraduate, he worked in a tissue transplantation laboratory at the Montana Deaconess Hospital in Great Falls, Montana. As a faculty member, he pursued his interest in mammalian immunology in his lab at Stanford while also directing a second research lab at the Hopkins Marine Station in nearby Monterey to look at self-recognition phenomena among primitive marine organisms - essentially the ancestral counterpart of vertebrate self-recognition in the context of tissue transplantation. At Stanford, Irv's lab pioneered a number of areas. Irv and his colleagues discovered how immune cells home to specific organs, both in the context of normal immune function and leukemia; and they relentlessly pursued the identification and isolation of stem cells for all of the cell types within the blood – red cells, macrophages, granulocytes, and platelets - and then mapped out the step-wise commitment of the progeny of these cells among the various hematopoietic lineages.

Irv's personal and scientific styles have a number of distinguishing features. First, he is constitutively cheerful and optimistic. I can't imagine Irv without a grin on his face. This is an important attribute

when one is going after tough problems.  Second, Irv has an unusual creativity and an openness to new ideas.  And third, he has a phenomenal energy level.  In addition to his labs at Stanford and the Marine Station, he founded several highly successful biotechnology companies and served for as the Director of Stanford's Cancer Center while retaining his position as Director of the Center for Stem Cell Biology and Regenerative Medicine.

Irv has also been involved in a number of causes in the public arena, relating both to wilderness conservation and stem cell biology.  In looking over his CV, I noticed that he has been the external director for two Montana organizations involved in land use and trout conservation.  I suspect that involvement in trout conservation is tied to Irv's passion for fishing, which to the non-fisherman appears as an inexplicable desire to stand immobile for hours in freezing water.  Among, Irv's many honors is the 1994 Montana Conservationist of the Year Award.

Irv, congratulations on your Passano Award.  We are honored to have you here today and we look forward to your lecture.

**Comments at the McGovern Institute (MIT) regarding Ed Scolnick and Merck - April 2009**

Let me start by thanking my hosts from the McGovern Institute for a wonderful day.  I heard a lot of great science from McGovern Institute faculty, and I had a chance to renew old friendships and begin some new ones.  As you know, I was an undergraduate at MIT 30 years ago, and I have many fond memories of my time here.  I am particularly grateful to the faculty, staff, postdocs, and graduate students who were here at that time and did a superb job of teaching and mentoring undergraduates.

The Scolnick Award was created six years ago by the pharmaceutical company Merck, in association with the McGovern Institute.  It honors Ed Scolnick, who served as president of Merck Research Laboratories for 17 years and brought to fruition an extraordinary number and range of vaccines and medicines to meet major unmet medical needs.  For me, it is a special honor to be associated with Merck and with Ed in the context of today's events.  I first met Ed almost 15 years ago when he invited me to serve on the Scientific Advisory Board of the Merck Research Laboratories.  In that capacity, I saw Ed's sound judgment, his remarkable breadth and depth of knowledge, and his extraordinary leadership.

The list of Merck's accomplishments in research and development during Ed's time there is truly remarkable.  I will mention just a few.  Merck developed the first statins, Mevacor and Zocor, and demonstrated their clinical efficacy in preventing heart disease.  Merck developed one of the first HIV protease inhibitors, Crixivan, and pioneered its use in combination with other anti-retroviral drugs.  Merck developed Fosomax, a new class of anti-osteoporosis drugs that has helped millions of elderly women lead longer and healthier lives.  And Merck developed Gardasil, the first vaccine against the human papilloma viruses responsible for cervical cancer.  This vaccine has the potential to virtually eliminate this common and deadly cancer from our species.

Importantly, Merck has not only served the larger community as a source of medicines and vaccines, but throughout its existence it has exemplified the highest standards of corporate responsibility and ethical behavior.  Let me give you two examples.  In the late 1940s, when research sponsored by Merck led to the discovery of streptomycin, the first effective antibiotic to treat tuberculosis, Merck allowed other pharmaceutical companies to independently produce and market this drug so that it might more effectively reach the millions of tuberculosis patients world-wide who were in desperate need of effective treatment.  More recently, Merck's discovery that Ivermectin kills a wide variety of invertebrate parasites has led the company to make freely available many millions of doses of Ivermectin to treat River Blindness, a parasitic infection that is endemic in some of the poorest parts of Central Africa and Latin America.

Finally, let me add that I have had the pleasure over the past two years of renewing my relationship as an advisor to Merck Research Laboratories, now under the leadership of Ed's successor, Peter Kim. As before, it is an honor to be associated – even in a small way - with the remarkable scientists and clinicians at Merck.

**David Julius, 2010 Passano Awardee – April 2010**

It is a great pleasure to introduce David Julius, the recipient of the 2010 Passano Award. Edward Passano established this award 66 years ago to honor outstanding biomedical researchers. The award was a natural outgrowth of the Passano family's central role in the Williams and Wilkins Publishing Company, a company that has held a prominent place in the world of medical and biomedical publishing for over a century. Because both the Passano family and the Williams and Wilkins Company are in Baltimore, the Passano Awards are conferred here; and, as part of that event, each recipient gives a lecture.

Dave is Chairman of the Department of Physiology at the University of California at San Francisco, where he has worked for more than 20 years. He is being recognized today for the identification and characterization of the ion channels that mediate thermosensation – that is, the sensing of increments and decrements in temperature - and for insights into the integration of the thermosensation and pain pathways.

For more than a century, one of the central goals of neuroscience research has been the molecular identification of sensory receptors. Beginning with the isolation of rhodopsin from frog retinas in the 1870s, numerous lines of research have led to sensory receptors that activate G-proteins. We now know that these include the receptors for vision, olfaction, and taste. A second class of receptors has emerged from the study of the mechanical senses, including osmo-regulation in bacteria and hearing and balance in vertebrates. These receptors are ion channels, although at present the molecular identities of the channels in the vertebrate inner ear remain to be determined.

As for thermosensation, over 50 years ago, there was clear electrophysiologic evidence for discrete classes of thermosensory neurons, but until Dave's work the molecular nature of the receptors was completely mysterious. Since that is the story that Dave is going to tell us today, I am not going to say anything more about it, except to note that it is a tour-de-force of clear thinking and incisive experimentation.

Dave's personal scientific journey led, in an interesting way, to thermosensation. He grew up in Brooklyn and was educated in the New York City public schools. He then attended MIT as an undergraduate, majoring in Life Sciences. I was also an undergraduate at MIT, and I first met Dave there in 1977 when we were both working in Alex Rich's lab. As an undergraduate, Dave was already an accomplished biochemist. He was investigating the specificity of aminoacylation reactions - that is, the condensation of the acyladenylate of an amino acid with the 3' hydroxyl of the terminal nucleotide on tRNA. To do this, he was constructing tRNAs in which the terminal sugar was chemically modified and examining the specificity of the reaction with respect to the 2' vs 3' hydroxyl on the tRNA. Dave published his first two papers based on this undergraduate research. Dave then earned his PhD from the University of California at Berkeley, working jointly in the laboratories of Jeremy Thorner and Randy Schekman. As a graduate student Dave, defined the pathway of biosynthesis and processing of the yeast mating pheromone, alpha factor. In the course of this work, Dave identified the first pro-hormone convertase, the dipeptidyl peptidase KEX2.

Dave's first direct step on the road to the thermosensory receptors began when, as a postdoctoral fellow with Richard Axel, he developed a general method for identifying receptors or ion channels by functional expression in Xenopus oocytes. One strength of this method is that it makes few assumptions about the molecular nature of the receptor or channel. Dave initially applied this approach to identify the first of

many G-protein coupled serotonin receptors, and, then, as an independent investigator, he used it to identify and characterize ionotropic serotonin and ATP receptors. As we will hear, this approach has come to full fruition with its application to thermosensation.

In addition to doing terrific science, Dave has been an exemplary mentor, leader, and source of wisdom - both at UCSF and beyond. He is on the board of directors of the McKnight Foundation, and is a member of the scientific advisory boards of the Pew Scholars program, the Damon Runyan Cancer Research Foundation, and the Machiah Foundation. He has also advised a number of biotech and pharmaceutical companies. Among Dave's many endearing qualities, is his somewhat off-beat sense of humor. I recall as an undergraduate hearing Dave singing in the lab. It was a beautiful song from West Side Story - "I just met a girl named Maria" - except Dave had substituted "urea" for "Maria". A biochemist to the core.

Dave, congratulations on your Passano Award. We are honored to have you here today and we look forward to your lecture.

**Introduction to the 2013 Lasker Clinical Prize Winners – September 2013**

In the New Testament, we read in the Gospel of Mark that Jesus performed the miracle of restoring hearing to a deaf man. Two thousand years later, modern medical science has developed a device that can deliver the same miraculous result, although, I should note, not with the same rapidity as the procedure described in the Gospel. That device is the cochlear implant, a surgically implanted system that functions as an electronic ear, converting sounds, such as speech, into tiny electrical impulses that activate the auditory nerve.

Today we honor three pioneers – Graeme Clark, Ingeborg Hochmair, and Blake Wilson - who have devoted their professional lives to making the cochlear implant a reality. Their work, together with that of many hundreds of engineers, audiologists, and surgeons, has brought the gift of hearing to several hundred thousand profoundly hearing-impaired individuals, a number that is climbing rapidly.

In industrialized countries, approximately one in every 1,000 people is born with severe congenital hearing loss, mostly from genetic causes; in developing countries, the incidence is even higher because of intrauterine infections. Severe hearing loss can also be caused by events after birth, with the result that by early adulthood one in several hundred people has a significant hearing impairment. In later life, many individuals experience a progressive decline in hearing, especially those who have been chronically exposed to loud sounds.

The psychological effects of hearing loss can be profound. Many people have noted that, compared to vision loss, hearing loss is more often accompanied by social isolation. As Helen Keller perceptively observed, "vision connects us to things, but hearing connects us to people". For the very young, hearing impairment brings a special challenge: language acquisition begins in infancy, and for children with normal hearing this occurs via exposure to spoken language. If alternate routes are not effectively developed, a deaf child's acquisition of language will be severely impaired.

What exactly is a cochlear implant and how does it bypass damage in the middle or inner ear to restore hearing? First, we need a brief description of how the ear works. Sound consists of pressure waves propagated in the air. Complex sounds such as speech or music are made up of waves of different frequencies. The challenge for the ear is to analyze the sound intensity at each frequency. This analysis is done in a small structure called the cochlea, a spiral-shaped object that looks like a snail shell embedded in the temporal bone. Along the length of the spiral are a series of nerve cells that function as sensors of the vibratory stimulus. Now here's a critical part of Nature's design: different frequencies are sensed by nerve cells at different locations within the cochlea and those locations are laid out in order of frequency along the length of the cochlea. At one end of the cochlea the nerve cells sense low-pitched

sounds: for example, the roar of a lion. At the other end the nerve cells sense high-pitched sounds: for example, the squeak of a mouse. At locations between these two extremes are all of the in-between frequencies, in order from lowest to highest. Importantly, the second order nerve cells that convey sound information from the cochlea to the brain - and that generally escape damage in the hearing impaired ear - are similarly arrayed in order of frequency within the cochlea.

The cochlear implant consists of two parts. One part is worn next to the ear: it includes a microphone, a light-weight battery, a power transmitter, a signal processor, and a radio transmitter. The second part is implanted inside the skull in a delicate microsurgical procedure: it includes a power receiver, a radio frequency receiver, and a series of stimulating electrodes with each electrode located at a different position along the length of the cochlea. The signal processor on the outside separates the incoming sound into its individual frequency components and communicates that information to the implanted receiver, which then stimulates the appropriate electrodes. Because, as noted earlier, the cochlea is organized by frequency, each electrode stimulates a cluster of nerve cells that are tuned to a similar and limited set of frequencies. In practice, the recipient of a cochlear implant generally needs many weeks or months of practice until the brain learns to make sense of the new and relatively crude patterns of electrode activity.

The development of cochlear implants involved solving numerous bioengineering challenges, and improvements are still ongoing. Drs. Clarke, Hochmair, and Wilson have contributed at multiple points and in diverse ways to the development of this technology.

Dr. Clarke is a surgeon and an auditory physiologist. Beginning in the 1960s, he built a multidisciplinary team to develop the cochlear implant. Dr. Clarke's team implanted its first multi-channel prototype in the late 1970s and received FDA approval for the procedure in 1985. I will mention a charming story that illustrates the creative mind at work. While at the beach one day, Dr. Clarke was playing with turban shells – the spiral shells that look like a cochlea – and he realized that if one wants to thread a fine twig as far as possible into the shell's interior, then the twig needs to be of gradually varying stiffness, with the part of the twig that is being threaded into the tightest spiral being the most flexible. He then applied this insight to design a wire bundle of varying stiffness for the cochlear implant so that when the surgeon threaded it into the cochlea, it did minimal damage to the surrounding tissues.

Dr. Hochmair is an electrical engineer. In collaboration with her husband Dr. Erwin Hochmair, she began working on cochlear implant technology in the 1970s. The Hochmairs developed a multi-channel prototype in the late 1970s and later founded the MED-EL Corporation to further develop and commercialize the cochlear implant. Dr. Ingeborg Hochmair has served as CEO and chief technology officer of MED-EL since its founding, and under Dr. Hochmair's leadership, MED-EL has solved many of the bioengineering challenges in cochlear implant design and manufacturing.

Dr. Wilson is also an electrical engineer. Beginning in the 1980s and working at the Research Triangle Institute in North Carolina, he developed signal processing algorithms - most famously the method of continuous interleaved sampling – which has greatly improved the performance of cochlear implants, especially in the context of speech recognition. I note that Dr. Wilson's work was funded by the NIH with the idea that his algorithms would be made freely available – thus allowing the cochlear implant manufacturers to incorporate his algorithms into their devices with no delays or constraints.

Drs. Clark, Hochmair, and Wilson, on behalf of the Lasker Foundation and the many millions of hearing impaired individuals world-wide, we salute you for your seminal contributions to the development of the cochlear implant.

**Helen Hobbs and Jonathan Cohen, 2016 Passano Awardees – April 2016**

It is a great pleasure to introduce Drs. Jonathan Cohen and Helen Hobbs, the recipients of the 2016 Passano Award. Edward Passano established this award more than 70 years ago to honor outstanding biomedical researchers. The award was a natural outgrowth of the Passano family's central role in the Williams and Wilkins Publishing Company, a company that has held a prominent place in the world of medical and biomedical publishing for over a century. Because both the Passano family and the Williams and Wilkins Company are in Baltimore, the Passano Awards are conferred here; and, as part of that event, the recipients give a lecture.

Drs. Cohen and Hobbs are professors at the University of Texas Southwestern Medical School in Dallas. They have worked together for more than 20 years and they now co-direct a research team in the Departments of Internal Medicine and Molecular Genetics and in the Eugene McDermott Center for Human Growth and Development. They are being recognized today for their pioneering application of human genetics to disorders of lipid metabolism.

Dr. Hobbs received her bachelor's degree in Human Biology from Stanford and her MD from Case-Western Reserve Medical School. She was a resident and chief resident in internal medicine at UT Southwestern, and then continued her training at UT Southwestern as a postdoctoral fellow with Mike Brown and Joe Goldstein. She joined the faculty at UT Southwestern in 1987, and in 2002 was appointed an Investigator of the Howard Hughes Medical Institute. Dr. Hobbs is currently a Professor in the Departments of Internal Medicine and Molecular Genetics where she holds the Montgomery and McDermott Professorships, and directs the McDermott Center for Human Growth and Development.

Dr. Cohen received his bachelor's degree and his Ph.D. in Physiology from the University of Cape Town in South Africa, and then came to UT Southwestern for postdoctoral training, first with Scott Grundy and then with Dr. Hobbs. He has been on the faculty at UT Southwestern since 1992 and is currently a Professor in the Department of Internal Medicine where he holds the Prothro Professorship.

For more than a century, one of the central goals of cardiovascular medicine has been to identify and treat atherosclerosis, one of the major risk factors for heart disease and stroke. The amount of atherosclerotic plaque varies widely among people. For most of us, it increases with age, and with it comes all the sequelae of increasingly clogged arteries. As Sir William Osler memorably remarked: "You are only as old as your plumbing".

The connection between genetics and atherosclerosis goes back at least 80 years, and it took center stage 40 years ago when Mike Brown and Joe Goldstein – working together at UT Southwestern – showed that mutations in the gene coding for the low density lipoprotein receptor are responsible for familial hypercholesterolemia. Today, we are going to hear the latest chapter in the story of human lipid metabolism and the way in which genetics can be used to peel back the layers of this endlessly fascinating onion. I can't resist noting that there is something familiar about a pair of scientists from UT Southwestern working together on lipids, atherosclerosis, and human genetics, and coming to Baltimore to receive the Passano Award. Drs. Brown and Goldstein received their Passano Award in 1978.

Helen and Jonathan, my congratulations to both of you. We are honored to have you here today and we look forward to your lecture.

# About Other Scientists

**David Hogness, scientist and mentor – October 2007**

**David Hogness is a founding member of the Department of Biochemistry at Stanford Medical School and one of the creators of the recombinant DNA technology.**

In September 1979, I arrived at Stanford as an M.D.-Ph.D. student intent on studying genes with the then-new recombinant DNA technology. At the time that I joined David Hogness' laboratory in January 1980, Dave was the most accomplished Drosophila molecular biologist in the world. His laboratory had already (l) identified the molecular structures of Drosophila transposable elements and rRNA genes, (2) isolated and sequenced the Drosophila histone genes (among the first eukaryotic protein coding genes to be sequenced), (3) developed colony hybridization and differential hybridization with cDNA and then used these techniques to identify and isolate genes controlled by the steroid hormone ecdysone, and (4) developed chromosomal walking and jumping and then applied these techniques to isolate the Bithorax complex.

In recalling my years in Dave's lab, I especially remember Dave's light touch as a lab director. Dave created a remarkable environment for creative science, in large part by attracting the right sort of students and postdocs and then giving them only a limited amount of explicit guidance. In the early 1980s, Dave had his sights set on the big biological questions, in particular the question of how genes control development. Yet he also maintained an excellent command of the day-to-day details of experimental methodology, with the result that his critiques of experimental design and interpretation were highly rigorous.

Dave loved to discuss scientific ideas and experiments, and his influence on his students was mostly through these discussions, which could happen anytime and anywhere. A discussion with Dave usually started spontaneously in the hallway with one or two students, and could last from a few minutes to over an hour. Dave's thinking, as revealed in these discussions, as well as in his writing, was a remarkable combination of precision and creativity.

Among my fondest memories are the many non-scientific conversations with Dave, either at the lab, at Dave's and Judy's house, where we were frequently invited for dinners or evening gatherings, or while driving somewhere together. Dave’s curiosity stretched in all directions: it included politics, history, society, and other people. Since I was also a medical student, Dave gave me detailed descriptions of the ups and downs of his diverticulitis, a common condition in which small out-pouchings in the intestine lead to repeated bouts of inflammation. Dave's view of his own medical condition was characteristic: it was simply one additional aspect of the world that attracted his curiosity, and his description of it was that of a completely unself-conscious observer.

Finally, Dave set a strong example in the uniform and honorable manner in which he interacted with other people, regardless of their station in life. It was a great privilege to learn from Dave's example and to enjoying his company for six wonderful years.

**John Mollon – November 1997**

**John Mollon is a visual psychophysicist with a special interest in human color vision. He is a Professor in the Department of Psychology at Cambridge University.**

Dr. D. A. Livesey
University of Cambridge
Cambridge CB2 1TT
United Kingdom

Dear Dr. Livesey,

This letter is in response to yours of October 15 regarding the consideration of Dr. John Mollon for a Professorship. I have followed Dr. Mollon's research closely for the past 15 years, as my interests in the molecular biology of visual pigments are close to his. I can therefore give you an accurate assessment of his work and where it stands within the field of vision research.

I think it is fair to say that Mollon is among the five top visual psychologists in the world today. This rating reflects both the originality and breadth of his contributions, which range from animal physiology/retinal anatomy to evolutionary biology to human cortical psychophysics to combining historical and molecular genetic detective work. What sets Mollon apart from all others - especially with respect to color vision - is his encyclopedic knowledge of the field and its historical roots, his ability to perform incisive experiments that build on those roots, and the beauty and clarity of his writing. Moreover, as far as I am aware, all of Mollon's experimental work has stood the test of time - a testament to his meticulous approach and his critical judgment. This cannot be said of everyone in this area. Take any of Mollon's papers - from last year or from 20 years ago - and it can be profitably read today; indeed, it is likely to reveal to the reader some fresh insight that was missed on earlier readings.

Mollon is in many ways the intellectual heir to both William Rushton and Mathew Alpern, the dominant British and American color vision psychophysicists of the previous generation, respectively. By temperament Mollon more closely resembles Alpern. Mollon is modest, as was Alpern, whereas Rushton was flamboyant – a curious reversal of the usual British and American temperaments. Over the past ten years, I have had three or four scientific discussions with Mollon, and, with the possible exception of Alpern, I cannot think of anyone else whose insights into color vision physiology and psychology are deeper or more carefully considered.

In summary Mollon is the sort of scholar who comes along but once in a long while. The University of Cambridge is very lucky to have him. Please feel free to contact me if I can be of further assistance.

Yours sincerely,

Jeremy Nathans

**Lubert Stryer - October 2006**

October 18, 2006

Ms. Cindy Yablonski
The Protein Society

Dear selection committee members,

It is a pleasure and an honor to write on behalf of Dr. Lubert Stryer who is being nominated for the first Carl Brändén Award. I have known Lubert since 1979, when I arrived at Stanford University to begin graduate and medical school. Lubert's energy, insight, and enthusiasm had an enormous influence on my career and research interests, and 25 years later they remain as some of the dominant and happiest memories of my time at Stanford.

Lubert has made several seminal and enduring scientific contributions. In the 1960s, together with his first graduate student, Richard Haugland, Lubert showed that fluorescence resonance energy transfer could be used as a spectroscopic ruler, work that spawned a major branch of biophysics and cell biology. [After graduating, Haugland founded Molecular Probes Inc., a highly successful company specializing in reagents for fluorescence-based detection technologies.] In the late 1970s and early 1980s Lubert's lab worked out the biochemistry of signal transduction and amplification in vertebrate vision. In the late 1980s and 1990s, Lubert played a key role in the creation and development of Affymax Inc. and Affymetrix Inc., culminating in the development of massively parallel light-directed solid phase synthesis of DNA on a chip for use in hybridization analyses. This technology has profoundly changed molecular genetics research. Each of these research contributions is now described in every standard textbook of biochemistry – the ultimate accolade.

However, Lubert's influence has been far greater than his research and biotechnology contributions. While still in his mid 30s, he wrote – by himself – a superb textbook of biochemistry. In three subsequent editions – again, with no coauthors - he brought to a generation of students the beauty of biochemistry with lucid prose and spectacular figures. By the fourth edition, "Stryer", as it was known throughout the world, had been translated into a dozen languages and had sold over 1 million copies. This book has inspired not only a generation of students but also a generation of textbook writers and publishers. It set the gold standard for beautiful writing and beautiful figures, and its emphasis on molecular structure (especially protein structure) was a prescient theme.

Finally, Lubert has been a friend and supporter of young scientists. Here is a story that is typical. About 6 years ago, when Lubert and I were both on a grant committee for a private foundation, we were faced with a grant application from an assistant professor that fell just short of the funding cut-off, a cut-off set by the amount of money that the foundation made available to spend that cycle. We all knew that getting the grant would be a big boost for this young person, but there did not seem to be any way of making that happen. Then, Lubert simply said that he would pay for it from his royalty account. And that was it. No fanfare. Just an immediate reaction to do what was best for someone else.

Selecting Lubert Stryer for the Carl Brändén Award would bring honor to the award and to the Protein Society, and it would set a high standard for any future awardees.

Please feel free to contact me if I can be of further assistance.

Sincerely,

Jeremy Nathans

**Hope Jahren – July 2007**

Dr. Kristina Johnson
Provost
Johns Hopkins University

Re: Nominating Dr. Hope Jahren for the Biomedical Scholar's Awards Programs

Nominator: Jeremy Nathans

Dear Dr. Johnson,

First, welcome to Johns Hopkins. I am delighted that you have joined us as Provost.

I am nominating Dr. Hope Jahren, an associate professor of Geobiology at the Johns Hopkins University, to be the University's nominee for one of the Biomedical Scholars Awards. Dr. Jahren is a leader in the use of stable isotopes to study geobiology and paleoclimatology. She is now turning her sights to problems related to human health using stable isotope technology.

The research for which Dr. Jahren is most well known focuses on living and fossil terrestrial organisms, and how they are chemically linked to the global environment. Using measurements of the stable isotopes of carbon, hydrogen, and oxygen her research group has worked to elucidate the role of terrestrial biota in the Earth's history of climate change, including current climate change. Dr. Jahren's approach depends on the observation that biological processes are subtly but precisely biased with respect to the efficiency with which they utilize different isotopes of precursor compounds. For example, the isotope composition of the carbon-based compounds within plants reflects the bias introduced by photosynthesis, thus changing the carbon isotope ratio relative to that of the carbon dioxide precursor. Importantly, these isotope effects are further altered by various environmental conditions. The result is that the stable isotope ratios of various elements in plant fossils contain a chemical fingerprint of environmental conditions at the time that the plant was living. I note that the use of stable isotopes is distinct from the use of unstable isotopes (e.g. carbon-14) to date organic material by the change in isotope ratio. Dr. Jahren's research represents a beautiful synthesis of plant biology, microbiology, chemistry, geology, paleontology, and climatology.

Dr. Jahren earned a bachelor's degree in Geology at the University of Minnesota in 1991 and a Ph.D. in Soil Science at the University of California at Berkeley in 1996. Despite her relative youth, she has already made major advances in geobiology and has been the recipient of major awards within her field, including the Donath Medal/Young Scientist Award of the Geological Society of America and the MacElwane Medal/Young Scientist Award of the American Geophysical Union.

Dr. Jahren is coming from a field - or more accurately, the interface of multiple fields - that is somewhat unusual for a biomedical research award. However, I would consider this a strength of her application. Dr. Jahren's stable isotope approach will provide new insights not obtainable by other approaches to human metabolism and human disease. I believe it has great potential.

In summary, I think Dr. Jahren would be a superb choice as the Johns Hopkins nominee for any one of the three Biomedical Scholar Awards.

Sincerely,

Jeremy Nathans

**Letter to Roger Kornberg about his father, Arthur Kornberg – February 2008**

**Roger Kornberg is a Professor of Cell Biology at Stanford Medical School. His father, Arthur Kornberg, founded the Department of Biochemistry at Stanford Medical School.**

Dear Roger,

I very much enjoyed seeing you and having the chance to talk on Tuesday evening. I wanted to add a couple of thoughts that I did not fully convey regarding Arthur. I greatly admired and respected Arthur both as a person and a scientist. I have many fond memories of our interactions and more generally of my time in the Biochemistry Department – it was really like being part of a big family. Of course, there were funny moments like the one I described when Arthur - with a twinkle in his eye and knowing full well what my answer was going to be - set me up with the question of whether I had purified an enzyme. But what really resonated was Arthur's loyalty to people, his seriousness of purpose, and his wisdom. Over the years, I had several extended conversations with Arthur – the last one in Baltimore when he visited Johns Hopkins about 15 years ago – and these were some of the most important conversations of my life.

With warm regards,

Jeremy

Jeremy Nathans
Molecular Biology and Genetics

**Peter Kim – October 2013**

Dr. Suzanne Pfeffer
Chair, Department of Biochemistry
Stanford Medical School
Stanford, CA 94305

Dear Suzanne,

I am writing in response to your letter regarding the appointment of Dr. Peter Kim as Professor in the Department of Biochemistry and the Chemical Biology Institute at Stanford Medical School. I am honored to write and to give my strongest endorsement to that appointment.

By way of background, I might note that I can give you an assessment with a long historical sweep. I have known Peter since 1979, when we entered Stanford Medical School as classmates in the M.D.-Ph.D. program. We worked within fifty feet of each other for the next six years, and although I couldn't always see Peter, I always knew when he was there. Anyone who has heard Peter's signature laugh will know what I mean. In the years when Peter was at MIT, I enjoyed following his work on protein structure, especially alpha helical structure. This wasn't because it was in my immediate field (it wasn't), but because it was so beautiful and important. Over the past six years, I have had the opportunity as a member of the Scientific Advisory Board at Merck Research Laboratories (MRL) to renew my association with Peter and to work with him in a very different context.

No letter could be easier to write than this one. Peter is one of the most creative and accomplished biophysicists of his generation. His work on protein folding and the central roles played by alpha helical structure and dynamics is now in every biochemistry textbook. If one were to compile a list of the most important 50 papers of all time on protein structure, more than one would be Peter's. What really sets

Peter's work apart is the elegance and ultimate simplicity of the experimental insights, as seen for example in the concept of parallel helical dimerization of bZIP transcription factors and the coil-to-helix transition that drives conformational changes in viral capsid proteins that act as membrane fusogens.

Peter's move to Merck surprised me. He was at the top of his game scientifically, but I think he wanted a new challenge. He certainly got it. The breadth and depth of scientific, medical, financial, regulatory, and engineering knowledge needed to succeed as the President of MRL is staggering. Last year MRL had a budget of ~$8 billion, with major programs in vaccines, oncology, cardiovascular medicine, neuroscience, infectious disease, respiratory medicine, immunology, and endocrinology. The merger between Merck and Schering-Plough nearly doubled the size of the R and D portfolio, and required the integration of two large and different enterprises. Merck's research and manufacturing is conducted in multiple countries and with multiple partners, and the strengths, weaknesses, and sensitivities of those partners need to be understood. At MRL, Peter has been, by any objective measure, an extraordinarily successful leader. He assumed his responsibilities at a time when the R and D pipeline was at a low ebb, a major product (Vioxx) was soon to run into serious trouble, and the leadership was intellectually thin. Ten years later, he leaves MRL with a very impressive pipeline and an extraordinary team.

Watching Peter in action at MRL provided a priceless education in how to effectively build an organization. Peter is a master at asking incisive questions and bringing out constructive, candid, and thoughtful comments from those around him. On multiple occasions, he had to make difficult decisions, such as withdrawing Vioxx, halting clinical trials, and replacing people who were not performing well or who, through no fault of their own, were simply caught in the restructuring that follows any merger of large companies. Through ups and downs, Peter retained his cool, his modesty, his integrity, and his sense of humor.

Stanford is very lucky to have attracted Peter. He is a remarkable scientist and a remarkable human being.

With warm regards,

Jeremy Nathans, M.D., Ph.D.
Professor
Molecular Biology and Genetics, Neuroscience, Ophthalmology
Investigator
Howard Hughes Medical Institute

# Eulogies

**Daniel Nathans (1928-1999)**

**Letter from Arthur Kornberg – November 1999**

Dear Jeremy,

I was terribly shocked and saddened when I picked up the NY Times this morning; I didn't know Dan was ill.

Although I didn't know Dan well, I felt him to be a kindred spirit in so many ways and I felt a sense of friendship and mutual regard. I feel his loss, an irreplaceable loss of part of my treasured circle.

Please convey to your Mom, brothers, and family my deepest sympathy. Having suffered such losses, I can convey particularly to your Mom that time does allay the sharpness of the pain, and we humans do have astonishing resilience to carry on for many reasons.

With warm regards,

Arthur

**Daniel Nathans (1928-1999; family memorial service) – November 1999**

We are here to mark the passing and to reflect on the life of Daniel Nathans, a person who was very dear to all of us. Pop always considered himself lucky; he remarked on more than one occasion that he had led what he called a 'charmed life'. By this he meant - in part - that by accident of birth he lived in a place and time of opportunity. But more than that, he meant that he was born into a loving family, that his parents and older siblings had taken care of him and sheltered him from the hardships that swirled around them, and that he had the incredible good fortune to have met and married Joanne. Joanne's mother was fond of saying "You're a lucky boy, Dan" - by which, of course, she meant lucky to have married her only daughter - and Pop could not have agreed more. I should add that she also said with equal frequency to Joanne "You're a lucky girl". This was a marriage that was truly made in heaven and it beautifully united two kindred spirits.

But life is more than a role of the dice - in other words, good luck is not enough. Pop will be long remembered for what he did and how he did it. I am not referring only to his accomplishments as a scientist, although those accomplishments were highly original and laid the foundation for a revolution in the biomedical sciences. What leaves the most lasting impression is the special dignity that Pop brought to everything he did. He treated other people well, regardless of their station in life. He was modest and he remained unchanged by his increasing fame. He was loyal to his family, his friends, his colleagues, his students, and to the institutions with which he was associated. He was a wonderful son, husband, father, grandfather, brother, and uncle - and any other categories that I may have missed. He had a very light touch, and he taught principally by example. He saw the best in people and he encouraged them to bring out the best in themselves.

Pop had extraordinary judgment. This went far beyond simply being able to size up a complex situation or form an accurate judgment about someone. Pop had real wisdom. I cannot define wisdom - but you

know it when you see it. Denis Baylor, a very distinguished neuroscientist, told me a few years ago that he had served some years earlier on a committee with Pop. From this brief time together, Baylor was full of admiration and affection for Pop. He said simply "Dan is so wise". Last year, I heard Dan DiMiao, who worked in Pop's lab in the 1970s and is now a professor at Yale, describe one of the lasting effects of Pop's influence. When DiMiao has an especially difficult decision to make he asks himself "What would Dan Nathans do in this situation?". I couldn't help laughing when I first heard this because I use this method myself, and I strongly suspect that many others do as well. Besides generally clarifying the important issues, the question "What would Dan Nathans do in this situation?" makes it crystal clear that the correct decision is the one that takes the highest road.

With Pop's death, we and many others have lost a special person. Despite the sadness of this moment, I know that we all count ourselves lucky for having joined our lives with his, and for sharing in that special grace that Pop created and which we now treasure.

**Nupur Thekdi (1977-2001; Johns Hopkins memorial service) - March 2001**

We are here today to honor the memory of our friend and colleague, Nupur Thekdi. Nupur was a student in the combined M.D.-Ph.D. program. He was in his fifth year at Johns Hopkins and was working on his Ph.D. thesis in my laboratory. Nupur was working on a knockout mouse in which a gene encoding one of the Wnt receptors had been deleted. Over the past 6 months he had made a number of very significant observations that had begun to reveal the developmental defects associated with this gene deletion. Both Nupur and I were excited by this work and - as every graduate student in the audience will appreciate - we were also grateful that the Good Lord had seen fit to make this into a viable Ph.D. thesis project by giving these mice an interesting phenotype.

Let me say some things about Nupur. Nupur was the eldest of three children. He grew up in a small town in Ohio and excelled academically. He studied biochemistry as an undergraduate at Harvard where he worked in the laboratories of Mark Ptashne and Steve Harrison. What was Nupur like as a person? Nupur was, by nature, modest and soft-spoken. He was extraordinarily considerate of others - that rare sort of gentleman who invariably thought of others first. He was a very patient teacher and was generous with his time and expertise. He had broad interests in politics and culture. Like me, he was an avid reader of the New Yorker magazine.

Nupur had a wry sense of humor - you usually had to listen carefully to get the joke. Partly because his sense of humor contrasted with his otherwise sober demeanor, Nupur's jokes were especially funny. Here's one example: a few weeks ago I was standing with Phil Smallwood, a technician in the lab, discussing a Southern blot that hadn't come out as we had expected. I held the film up to the light and wondered out loud "What might be going on?". At that moment, Nupur happened to be standing behind me so that Phil could clearly see him but I could not, and he silently mouthed "Phil screwed up!". Needless to say, this got the expected rise out of Phil, and then a good laugh all around.

The events of March 15 defy comprehension. It is one thing for someone to depart this world after a long and full life - we mourn the loss but feel that this is the inevitable end that we will all face someday. But for someone to die at the threshold of adult life - with so much to live for, with so much yet to experience, and with so much talent and promise - this is the greatest imaginable tragedy. The older I get the more I appreciate how precious and fragile life is.

I can almost imagine, as children do, that by simply closing my eyes tightly and then opening them, Nupur will somehow be magically returned to us. But we all know that what has happened cannot be undone. Nupur will live on in our memories and I know that we can honor that memory by emulating the gentleness that was his hallmark.

**Robert Nathans (1927-2010; family memorial service) – June 2010**

**Robert Nathans was the older brother of JN's father, Daniel Nathans.**

Uncle Bobby, or Bobby, as I came to call him when I reached adulthood, made a strong impression. He valued substance, and he let you know it. By "substance" I don't mean just knowing the facts. What he valued was really thinking about things. In other words, questioning one's assumptions.

This could be intimidating. But it was also exhilarating. Bobby was liberated in a way that few people are. He said what he thought. And he had some pretty strong opinions. But he also had a big heart and a big appetite for new ideas.

One thing that left an especially strong impression is how Bobby would talk to and listen to children as if they were adults – that is, he gave you his full attention in a way that let you know that your opinion was important. While this meant that you really had to step up to the plate, it also gave you a chance to test out your ideas on someone who was going to give you his unvarnished opinion. It was an invigorating experience.

Bobby had an especially close relationship with my father Dan. They were only one year apart, and their mother Sarah freely admitted that they had both started out as unplanned pregnancies. Although Bobby's and Dan's personalities were different in many ways, their enormous mutual affection and respect was obvious. I often wondered what they were like as children and teen-agers, and how the unique bond between them had developed during those long-ago years.

I last saw Bobby a few months ago, shortly after the big snowstorm. I drove down to his apartment and we had a long talk over his kitchen table. We talked about science, politics, and our family. Bobby talked about Barbara, his soul mate. As always, he gave me a lot to think about.

In the end Bobby has left all of us with the greatest gift anyone can give, the experience of being together and talking from the heart about the things in life that matter the most.

# Howard Hughes Medical Institute

**Letter to David Clayton – November 2005**

**At the time of this letter, David Clayton was the Chief Scientific Officer of the Howard Hughes Medical Institute.**

Dear David,

As I am sure you know, Larry Katz has advanced metastatic melanoma. I've been in touch with Larry and with a former graduate student from my lab, Wenqin Luo, who is now a postdoc with him.

Wenqin tells me that everyone in the lab has a strong sense of loyalty to Larry and they are not looking to leave. However, Larry has already written letters for everyone anticipating the day when he will no longer be able to help them. The part of this story that I think you might want to mull over is this: Wenqin tells me that there is considerable uncertainty on the part of lab members as to what HHMI or Duke University will do after Larry dies. For obvious reasons, they don't want to bring this up directly with Larry, but they are wondering whether they will need to scramble to find new positions. For young scientists with high aspirations and, in some cases, with projects in which they are heavily invested, this uncertainty is pretty stressful. I wonder whether HHMI has or should have a publicly known policy regarding the duration and level of support for personnel in labs in which an HHMI investigator becomes incapacitated or dies. If such a policy already exists or is put into place, I hope that it will provide sufficient flexibility so that trainees can land on their feet.

All the best,

Jeremy

**Comments on the Janelia Research Campus – November 2009**

**HHMI's Janelia Research Campus opened its doors in 2006 with an emphasis on technology development, neuroscience, and imaging of biological structure. Gerry Rubin is the director of the Janelia Research Campus and, at the time of this letter, Robert ("Tij") Tjian was President of the Howard Hughes Medical Institute.**

Dear Gerry and Tij,

You will probably have many letters with comments regarding Janelia's scientific direction. My brief comment is more general: stick with the original vision of creating the kind of scientific enterprise that would attract the best young talent out there - the next 30 year old Sydney Brenner. If Janelia can attract the most creative and driven young scientists, great things will follow.

All the best,

Jeremy

**Letter to the HHMI International Early Career Scientist competition team – October 2011**

**HHMI supports young scientists from multiple countries outside of the United States via its International Early Career Scientist program. The final event in the competition for funding brings all of the candidates together for a symposium in which each candidate delivers a scientific lecture before the HHMI staff and a group of outside advisors.**

Ed McCleskey , Ph.D., Scientific Officer
Jean Schroeder, Ph.D., Senior Program Officer
Birgit An der Lan, Ph.D., Program Officer
Laura Kinkead, M.B .A., Program Officer
Chuck Schultz, Ph.D., Program Officer
Mary Bonds, Competition Program Administrator

Dear Ed, Jean, Birgit, Laura, Chuck, and Mary,

Here's a thought that is probably better said than left unsaid.

When the international scholar candidates attend the HHMI review in November, the experience has the potential to be quite stressful for them. There are many factors combining in this direction: the applicants are relatively junior scientists, they are coming from countries that are less well off financially than the US, they will be seeing HHMI at its most materially impressive (Janelia), they will be subjected to a rigorous review by senior scientists in a language that for most of them is not their native tongue, and they will be jet-lagged. Whatever the outcome for any individual candidate, we want all of them to look back on the experience and feel that they were treated like honored guests and that HHMI is a terrific organization. I know that the hospitality that the HHMI staff shows to our guests has always been and will continue to be top notch, but I think it may be useful to remind the outside reviewers that we are all ambassadors for HHMI (and for the United States) and that small kindnesses can make all the difference. For example, when each applicant first enters the room, each of the reviewers should shake hands with the applicant, introduce him/herself, and make the candidate feel welcome. Similarly, at the end of the interview, there should be a round of handshakes and a warm "thank you" from each reviewer.

Perhaps Tij could say a few words along these lines to all of the reviewers before the reviews get underway.

All the best,

Jeremy

**Letter to Jack Dixon requesting additional funds – May 2012**

**At the time of this letter, Jack Dixon was the Chief Scientific Officer of the Howard Hughes Medical Institute.**

May 14, 2012

Dr. Jack Dixon
Chief Scientific Officer
HHMI

Dear Jack,

I am writing to you at the suggestion of Dennis McKearin. That suggestion and this letter began with a conversation that Dennis and I had about one month ago regarding the challenges of running a lab with a relatively flat operating budget and a set of rising costs for salaries, animal services, and equipment maintenance fees. To cut to the chase, Denis suggested that it would not be out of line for me to request a modest increase in my lab's supply budget to keep up with these rising costs.

The challenge that we are facing is probably familiar to you. For example, I have one R01 grant, and it was renewed this January for another five years (after scoring in the top 2%). However, my request for a budget increase of 15% above the budget of the previous 4 years was rejected. Although we are grateful to have the grant, we have to plan for a budget in actual dollars that will be nearly constant over nine years. A similar situation attends the two relatively modest grants that we have from private foundations. As noted above, many costs have been steadily rising. Even those items for which the unit cost is falling - like DNA sequencing and computing – have actually seen an increase in overall cost because the lower unit cost has opened up the possibility of using these technologies on a substantially larger scale.

We have taken a number of cost-cutting measures in response to the financial squeeze. For example, we now buy some equipment items on the used equipment market, which we find to be cost-effective. For some large pieces of equipment we have not purchased comprehensive service contracts, gambling that the equipment won't have any major breaks during its first few years of use, a gamble that has thus far paid off. We have also avoided all but the most minimal expenditures on renovations and furniture.

What I would like to request is an annual supply budget increase of somewhere between $40,000 and $60,000. To show that I am willing to "put some skin in the game", I would be happy to simultaneously take a $10,000 annual salary cut to partially offset the cost to HHMI of a supply budget increase. I presume that the salary cut could easily be arranged on the Johns Hopkins side, although I have not looked into what that would involve.

I appreciate your considering this request. Given our close professional relationship, returning a negative answer to a request such as this one has the potential to be a bit awkward. Therefore, let me close by saying that you should feel completely at ease if the decision is negative.

With warm regards,

Jeremy

**Comments on the Drosophila Olympiad Project at the Janelia Research Campus – June 2012**

**JN served with Leslie Vosshall, Professor at Rockefeller University, on a 2012 committee that assessed scientific programs at HHMI's Janelia Research Campus.**

Dear Leslie,

Thank you for that very astute write-up. With respect to the sections titled "Team project vs. individual science" and "Lessons learned from the Fly Olympiad", I'd like to air what I think is a minority view - perhaps it can be included in the write-up and labeled as such. When we were discussing this on Wednesday, my view was still gelling so I didn't try to articulate it. Here it is:

The Olympiad is a large and evolving experiment – both scientifically and socially. It represents a different way to tackle behavior and neurobiology. Socially, it asks whether large numbers of people with diverse interests and skills can work together synergistically. It is risky because it is moving ahead rapidly on multiple fronts, each of which has many unknowns: developing automated and quantitative behavioral tests, developing neuronal inactivation lines, and developing a wiring diagram. The screen is unprecedented in concept: it isn't knocking out genes, it is knocking out cell function and attempting to do this on a nervous system-wide scale. With respect to behaviors, the screen is unprecedented in scale – one could view this as either a strength or a weakness, but it is an intrinsic part of the experiment. Thus, the Olympiad has a lot of moving parts and we should expect growing pains.

I note that many ambitious biological screens have tried seemingly improbable or naive strategies and hit major bumps in the road. A few examples will illustrate the point. In the 1970s, Seymour Benzer identified many behavioral mutants, like *per*, without any clear path to turning that early investment into biological insight. In 1980, one could easily have said of the Benzer lab that it hadn't contributed much to the field of neurobiology in the preceding decade. Similarly, in 1980, one could say that Lee Hartwell hadn't learned all that much about the cell cycle in the previous decade. In fact, Hartwell spent much of the 1970s going through hundreds of lines with mutations that affected mundane functions on his way to finding the master regulators of the cell cycle – and he still didn't know what they were molecularly until the 1980s. Finally, Nusslein-Volhard and Weischaus started with the seemingly improbable strategy that they would simply collect all embryonic lethal mutations, look for those with distinctive cuticle patterns, and then try to make some sense of the collection. And, voila, it worked!

The lesson that I take from the examples in the preceding paragraph is that we should not be too quick to judge a large and complex screen. The Janelia scientists have shown that they are flexible in their thinking, and the screen is evolving as it hits the inevitable bumps. A second lesson is that new technologies can be game changers – as recombinant DNA technology was for each of the three examples cited above. We can't predict what new technology will be incorporated into the Janelia toolkit, but it is clear that they have a keen interest in using whatever is out there or developing what they need as they go along.

All the best,

Jeremy

# Johns Hopkins

**Comments on the inauguration of the Daniel Nathans Professorship – December 2003**

On behalf of the Nathans family I would like to thank Drs. Brody and Miller for making the Daniel Nathans professorship a reality. It is certainly a fitting tribute to Dan, and it is fitting that Carol Greider - an exemplary colleague and scientist - will be the first holder of this chair. Naming professorships, lecture halls, and buildings after distinguished faculty members is a long-standing and cherished tradition at Hopkins. In a very tangible way it helps connect the current generation with those who came before us, and it connects us with those who will follow.

Let me say a few words about Dan's background, especially as it relates to Johns Hopkins. Dan was born in 1928 and grew up in Wilmington Delaware. He was the last of eight children, and, as he described it, he was his parents' last hope for a doctor in the family - by the time he entered college it was pretty clear that none of his seven older siblings was going to go to medical school. Dan was a stellar student. At Washington University Medical School he was the top student in his class. Henry Brem, the chair of neurosurgery here, told me the following story: one of Dan's classmates at Washington University told Henry that Dan's medical school class was quite competitive - as evidenced by the fact that many students were competing for the number two spot. At Washington University, Dan had his first taste of laboratory research, with Oliver Lowry, the chair of Pharmacology. The Lowry name may be familiar to some in this audience from the Lowry assay for determining the concentration of proteins in solution.

Dan did a residency in internal medicine at Columbia/Presbyterian Hospital and a fellowship in oncology at the NIH. He then made an important and - given his training up to that point - unusual career decision. He decided not to practice medicine, but to become a researcher. To get the training that he needed, he joined the laboratory of Fritz Lipmann at the Rockefeller University as a postdoctoral fellow. Lipmann was one of the great biochemists of the 20th century. Among other contributions, he was the person who figured out that the energy currency in all living organisms was the high energy phosphate bond. In Lipmann's lab, Dan worked on in vitro protein synthesis. He identified and purified elongation factor G, with Norton Zinder he showed that one could translate natural mRNAs in vitro, and he worked out the mechanism of action of puromycin, an antibiotic that causes premature release of the growing polypeptide chain.

As a medical student, Dan had gotten to know Barry Wood, then the Chairman of Medicine at Washington University. The Wood Basic Science Building in which we now sit is named for Barry Wood. In addition to serving as the Chairman of Medicine at Washington University (a post he accepted at age 32), he was an all-American quarterback in college, a Johns Hopkins medical student and house officer, and, beginning in the 1950s, Vice- President and then chair of Microbiology at Hopkins. Barry Wood had a remarkable instinct for identifying and nurturing young scientific talent. In 1962 he hired Dan as an assistant professor and shortly thereafter he hired Ham Smith. He also hired Ken Berns and Bernie Weiss, who have both had outstanding careers in virology and microbial genetics and biochemistry, respectively. If you have a close look at the photographic exhibit about Barry Wood that is just upstairs on the first floor of this building you will see a charming picture of Dr. Wood sitting in front of a chalkboard. On the chalkboard under the heading "main function of a university" there is the following list: “(1) to teach, (2) to engage in research, (3) to play football". Next to the list, in handwriting that I strongly suspect is Dan's, there is an arrow indicating that item 3 (football) should be moved to the top of the list with the admonition: "Please, let's get the order of importance right!"

During his first 6-8 years at Hopkins, Dan focused on protein synthesis and its regulation. He worked out the first example of feedback regulation of mRNA translation - the binding of the coat protein from an E coli RNA phage to its own mRNA to shut down translation. In the late 1960s, Dan gave a lecture to medical students on tumorogenic viruses, and this piqued his interest in studying the mechanism of oncogenic transformation by studying the small DNA virus SV40. Thus in the late 1960s he switched his research program, and it was just at this time that Ham discovered the first restriction enzyme, and generously shared the news and the enzyme with Dan. The rest, as they say, is history. But I'd like to point out the larger lesson of that work, which was the wonderfully collegial relationship between Ham and Dan that made possible the experiments that applied restriction enzyme cleavage to DNA analysis.

When Barry Wood died in 1970, Dan was appointed chair of Microbiology, which later changed its name to Molecular Biology and Genetics. A decade later he handed the chairmanship to Tom Kelly and became an investigator of the Howard Hughes Medical Institute. In the late 1990s he served for approximately one and one-half years as interim president of the University, and during that time he firmly guided the hospital and medical school through a period of fairly rough sailing.

Let me end with a word about the relationships that Dan had with those around him. Dan had a remarkable way of connecting with people. Had he chosen to practice medicine he would have been an extraordinary physician. He was straightforward and completely unpretentious; he had incredibly good judgment; and he put the larger good ahead of his own. Dan's relationships with those around him were built on a foundation of mutual respect. In my view, these kinds of relationships are our greatest asset at Johns Hopkins, and they are the defining feature of the Johns Hopkins culture. If there is one legacy that we can leave to our students, and that the Daniel Nathans Professorship represents, it is the legacy of working together and creating that special atmosphere of collegiality in which the whole is greater than the sum of the parts.

**Letter to Joe Coppola regarding the Johns Hopkins response to property crimes – May 2005**

**At the time of this letter, Joe Coppola was Director of Corporate Security at the Johns Hopkins Medical School and Phil Cole was Director of the Department of Pharmacology.**

Dear Joe,

Phil Cole mentioned to me that the employee responsible for stealing two Pharmacology Department laptops and suspected of stealing other items has been apprehended. Good work. If I understood Phil correctly, the University is considering pressing civil charges but not criminal charges. Is that correct? If so, I think it is a huge mistake not to aggressively press criminal charges. My reasoning is as follows. We need to have as clear a deterrent as possible against on-campus theft. For employees, the temptations to steal are everywhere: cameras, laptops, and many other small, valuable items can be found in every lab. In addition to the blow to morale and one's sense of security, losing a laptop or a piece of equipment can be a huge setback scientifically.

I would be grateful if you can let me know where this issue stands, both in the present case and in general. I would also be happy to discuss this with the general counsel's office.

With warm regards,

Jeremy

Jeremy Nathans
Molecular Biology and Genetics
Johns Hopkins Medical School

**Open letter to Johns Hopkins Medical School faculty – April 2006**

An open letter to the Johns Hopkins community regarding financial support for biomedical research

Dear colleagues,

This letter concerns the current and future state of biomedical research funding in the United States and the ways in which Johns Hopkins can best meet the challenges posed by an increasingly tight NIH budget. Many of us have been talking privately about these issues; I hope that this letter will help to stimulate a vigorous public discussion.

In the late 1990s and early 2000s, the NIH enjoyed a period of unprecedented growth, with a doubling of its annual budget from $15 billion to $30 billion in just five years. Not surprisingly, this period coincided exactly with the period of shrinking federal budget deficits and several years of federal budget surpluses. More NIH money meant more research and training grants, more research-oriented faculty, more graduate students, and more postdoctoral fellows. It also propelled ambitious plans for increases in research facilities at many universities and medical schools, including Johns Hopkins. Each of these expansions in the research enterprise has come with long-term expectations: faculty members want to continue getting grants and conducting research, students and postdoctoral fellows want to advance in their scientific careers, and university administrators want to fill research buildings with productive and well-funded scientists.

But fiscal times have changed, with the result that recent NIH budgets have barely kept pace with inflation. The bursting of the stock market bubble in 2001, the tax cuts enacted by the Bush administration, and vast new military and homeland security expenditures have driven the federal deficit to $400 billion per year for the past three years. In 1990, the national debt was $3 trillion. Today the national debt is more than $8 trillion, equivalent to nearly $30,000 per U.S. citizen. With the U.S. balance of trade deficit currently more than $600 billion per year, we can expect that with each passing year we will owe an ever-larger fraction of our debt-financing dollars to foreign lenders. Indeed, the fraction of the national debt that is owed to non-Americans is larger today than at any time in the preceding 70 years. These macroeconomic trends and their fiscal fallout – including minimal increases in NIH funding - are likely to be with us for decades.

Like two trains speeding toward each other, the trends outlined in the two preceding paragraphs – feeding an expanded scientific pipeline and the relatively sudden tightening of the NIH budget – are on an unavoidable collision course. What will the collision look like? At the level of the individual investigator, we are seeing it already. Most obviously, the competition for grant money has increased appreciably. Excellent scientists find that they must run faster just to stay in the same financial place; other excellent scientists are simply squeezed out of the system for lack of research funds. Whichever group one is in, the process is stressful and colossally inefficient. Increasingly, the individual investigator must focus on short-term goals: the experiment that is most likely to succeed, the next paper, and the next grant deadline.

Will the financial pressure-cooker foster highly original breakthrough science? Not likely. Original science requires a willingness to take risks, and as NIH funds tighten, scientific risk-taking will become one of the first victims. It is also likely that those who will be most affected by this pressure will be young scientists whose small laboratories are least able to weather the financial storm. It is a matter of simple mathematics that statistical fluctuations – here in the form of successes or failures in the grant application lottery – are relatively more severe for those laboratories with smaller budgets. For a small laboratory, having to resubmit an R01 that fell beyond the funding cut-off can make the difference between retaining or losing critical members of the research team.

In the present circumstances, what is the optimal strategy for a university like Johns Hopkins? The first step is to ask this question with an open mind, and to consider the consequences of various competing strategies – both in terms of the university's finances and in terms of our ability to attract and retain the very best biomedical scientists. We should be especially clear about the non-financial part of our goal: we do not want a research enterprise that is merely turning out publishable and fundable science. Johns Hopkins should be producing science that fundamentally changes biology and medicine. With this goal in mind, and without reviewing all of the strategic options, let me present what is, in my opinion, the optimal strategy.

The basic strategy is simple: the university needs to decrease the rate of expansion of laboratory space and increase financial support of its scientists and scientific programs. This means a renewed focus on quality rather than quantity. Almost without exception, the great breakthroughs in biomedical research come from individual investigators working in an environment that nurtures creative science. Creating and supporting this kind of environment should be the university's goal. Among other things, this means a rebalancing of the way we direct private donations. Instead of contributing to new research space, donors (both large and small) should be encouraged to support the very best research. The support could be in the form of a career development award, graduate or postdoctoral training, support of a core laboratory, or research in a specific area or on a specific disease. Properly directed, a relatively modest amount of flexible money from private sources can make the difference between success and failure in competing for NIH funds. Moreover, from a purely financial viewpoint, it makes no sense to invest heavily in a new faculty member and then pull the financial plug after a few years. Why not invest $100,000 today with the expectation that tomorrow the institution will enjoy $500,000 in indirect costs from a grant that would otherwise have been lost?

In the current fiscal reality, those institutions with sufficiently deep pockets and a willingness to support excellent science on a continuous basis are going to be able to attract and retain the best scientists and produce the best science. I hope that Johns Hopkins will be at the forefront of that group.

Sincerely,

Jeremy Nathans
Professor
Molecular Biology and Genetics
Neuroscience
Ophthalmology

**Letter to Chi Dang regarding core laboratory assessments - January 2009**

Dr. Chi Dang
Vice Dean for Research

Dear Chi,

I am writing to follow up a brief conversation that we had about six months ago regarding the evaluation of core labs and other services that JHMI has set up for researchers. These include: animal services, Pathology photography, the Welch library, the basic sciences network office, the microscopy, biopolymers, and micro-array cores, etc. I should start by noting that this letter is not being written because of any acute problems in need of immediate attention. Instead it reflects my observations over many years that there does not seem to be a uniform or objective manner in which core labs and services are evaluated, with the result that (1) performance issues go unnoticed or unaddressed far longer than they

should and (2) the central administration does not have an objective longitudinal record of performance to guide decisions related to resource allocation and personnel.

In observing how core labs and core services are run at JHMI, one is struck by the nearly complete absence of any system for formal customer feedback. In the "real" world where customers choose between competing service providers, a high premium is placed on getting and using customer feedback. The absence of that feedback here suggests that, as far as customer satisfaction is concerned, JHMI core labs and services are run like a monopoly: with no competition there is no incentive to consult the customer. Just to pre-empt a possible question, let me note that the assessments of oversight committees for each core or service are no substitute for direct customer feedback. The only way to find out about the performance of a core lab or service is to gather the data directly from the customers.

My over-all proposal is relatively simple, although details would need to be worked out. It is to create a central web-based system in which every faculty member who has used any core lab or core service is asked on an annual basis to rate the quality of that core or service and make constructive comments. As part of this system, each core lab or service would submit the annual billing record to the database: this would be used to determine which faculty used the service and how heavy or light that use was. The faculty feedback that is collected on the web site would be archived by the central administration, with the ratings and comments on each core or service made available to that entity. I suggest limiting participation to faculty members – I think this will keep the signal-to-noise ratio reasonably high. I also suggest that the participants be required to identify themselves on the evaluations; I don't think there is much to gain by doing this anonymously. Finally, while we don't want to burden this proposed database with day-to-day issues related to core labs and services, we might consider an option for faculty to enter comments into the formal database at times of the year other than during the annual review.

The proposed database would form part of an annual assessment of performance and an annual plan of action for each core lab or service. It might also be useful to make the results, at least in summary form, available to the wider JHMI community. One goal could be to use this system to publicly recognize excellence among our core labs and services. In addition to all of the positive reasons for setting up a system like this, another reason is that the alternative might well be that dissatisfied customers will pre-empt us and set up their own competing versions in the form of unregulated and less constructive blogs.

I would be happy to discuss this further if you would find that useful.

All the best,

Jeremy

**Letter to Ed Miller and Lloyd Minor regarding support for Carol Greider – October 2009**

**At the time of this letter, Ed Miller was Dean of the Johns Hopkins Medical School and CEO of Johns Hopkins Medicine, and Lloyd Minor was Provost of Johns Hopkins University**

Dear Ed and Lloyd,

Like everyone else here, I am delighted at Carol's selection for this year's Nobel Prize in Medicine.

I am writing to share a few thoughts, some or all of which may already have occurred to you. In the months and years ahead, Carol will be inundated with e-mails, phone calls, and demands on her time from every direction. She will also be offered opportunities at other universities, and they will be extremely attractive.

The question for us, Carol's colleagues, is what to offer her to best help her manage the deluge. Carol has two children to raise, a lab to run, a department to oversee, etc. It is already an 80 hour a week job.

First, let me suggest that Johns Hopkins offer Carol a top-notch administrator to process phone calls and e-mails and serve as a conduit to the outside world. As a department chair, Carol has a small administrative staff in place, but I would guess that she might benefit from a dedicated person to help her with this. At least she should know that this is an option.

Second, let me suggest that the University give Carol some additional discretionary funds. I know that her lab has experienced a financial squeeze over the past couple of years, although I do not know the current financial situation in detail. We should think pro-actively here. At the very least, Carol's endowed chair should be bumped up to ~$5 million so that there are funds available on a long-term basis to pay for some of her laboratory expenses beyond her salary. At present, I believe there is ~$2.5 million in the endowment.

Carol has been extraordinarily dedicated to Johns Hopkins, and I hope that we can say "thank you" by giving her a hand at this most critical juncture.

Please feel free to call on me if I can be helpful in this regard.

All the best,

Jeremy

**Thank you to a Johns Hopkins security officer – October 2009**

Mr. Harry Koffenberger
Corporate Security
Johns Hopkins Medical Institutions
Baltimore, MD 21205

Dear Mr. Koffenberger,

I am writing to let you know how grateful I am that one of your security guards, Mr. Bryan Hawthorne, took the time to assist a graduate student in my lab when her car had a flat tire. Mr. Hawthorne drove with her to the parking garage and then changed the tire for her. This was a few months ago, I only just now realized that I had not written to say “thank you”.

I would be grateful if you could pass this message of thanks to Mr. Hawthorne.

Sincerely,

Jeremy Nathans
Professor
Molecular Biology and Genetics
Neuroscience
Ophthalmology

**Letter regarding speakers at the Brain Sciences Institute symposium - July 2010**

**At the time of this letter, John ("Jack") Griffin was the Director of the Department of Neurology and Director of the Brain Sciences Institute (BSI), Richard Huganir was Director of the Department of Neuroscience, and Susan Magsamen was a member of the Science of Learning Institute.**

Dear Susan, Rick, and Jack,

Regarding the line-up for the BSI Neuro-Aesthetics Symposium, we really need to think hard about how to improve the gender ratio (something we discussed briefly) and also the racial make-up (something that we didn't discuss). If we include all of the people who are listed in the current schedule including MC's, facilitators, etc, we have a 28:4 ratio of men to women. The symposium closes with a panel that has 9 men and one woman, followed by remarks from two men. If we fill the currently empty musician/composer's slot with a woman and invite Michaela Gallagher to participate in the panel, we still have a 28:6 ratio. I think we need to figure out a way to get to a gender ratio that is not worse than 2:1.

With regard to racial composition, I don't know the racial/ethnic background of everyone on the list, but I would guess that there aren't many African-Americans. Since Baltimore is 60% African-American and this is a Hopkins event that reaches out to the community, we should do our best to make this inclusive. Aside from those considerations, any list of great musicians and dancers in the US would include many African-Americans. Susan's idea of trying to recruit Cyrus Chestnut sounds good to me. Other people to consider are Gary Thomas, the head of the Jazz Department at Peabody, and Mellasenah Morris, Dean of Peabody – both African American. Also, won't they feel that we should have consulted them in planning the symposium, since they are the local experts? Are there black female musicians (vocalists?) or other artists who we could consider?

In thinking about balancing the participants: How many more people can we add without over-crowding the event?

All the best,

Jeremy

**Letter to Ed Miller and Janice Clements regarding support for Carol Greider – August 2010**

**At the time of this letter, Ed Miller was Dean of the Johns Hopkins Medical School and CEO of Johns Hopkins Medicine, and Janice Clements was Dean for Faculty at the Johns Hopkins Medical School.**

Dear Janice and Ed,

I would like to share some thoughts regarding Carol Greider's future at JHMI. I have discussed these issues with Lloyd Minor, and I hope that JHMI and JHU leadership will give this a high priority. In what follows, I present my assessment of what I have seen. I am not speaking for Carol, who, I am sure, will have her own views.

First, the facts. Carol was recruited to the Department of Molecular Biology and Genetics at JHMI in 1997, promoted to full Professor in 1999, and to Department Chair in 2003. Incidentally, she had to turn down a Howard Hughes Medical Institute appointment to come here – which would have been worth about ~$1 million per year in research and salary support. From her first paper as a graduate student (the discovery of telomerase) to now she has been not just a super-star in her scientific accomplishments, but a

super-star in the deep and rigorous way she approaches science, in her soundness of judgment and integrity, in her collegiality and mentoring, and in her devotion to Johns Hopkins. Of course, she has also won a long list of awards including the Nobel Prize in Medicine. Currently, she is the youngest living female Nobel laureate, and one of the youngest living laureates of either gender. She has many years ahead of her in what is already a remarkable career.

As you know, faculty development and retention at JHMI is not always proactive. In Carol's case, it is easy to envision the "business-as-usual" approach, in which JHMI does little until a crisis happens, i.e. Carol considers leaving. The retention issue is especially challenging for basic science department chairs, since substantial resources are rarely forthcoming unless a new chair is being hired. To make matters worse, with the ultra-competitive NIH grant environment, being a department chair is a lot less enjoyable now than it used to be. Even in a relatively strong department like MBG, there are chronic financial headaches related to grants not getting funded – and these invariably land in the department chair's lap.

Obviously, someone of Carol's caliber as a scientist and a leader will have her choice of the most attractive positions in biomedical science. She has already gotten feelers for the directorship of one very major institute; I presume that such inquiries are arriving regularly. How long will Carol continue fighting in the trenches here when she can go somewhere else, increase her salary, and oversee a program or institute with substantial resources? The bottom line is: we need to be pro-active.

With these issues in mind, I have a very definite proposal. Carol and her close collaborator Mary Armanios are the world leaders in studying the relationship between telomeres, cancer, stem cells, and aging in both humans and mice. The proposal is for JHMI and JHU to give top priority to finding a donor who will endow a research program that focuses on these issues with Carol and Mary as its leaders. I can't think of a more attractive research area to sell to a donor, or a more compelling person than Carol.

Finally, let me note that beyond raising money for her own research area, Carol is literally worth many times her weight in gold to JHMI and to JHU – if the development office can work effectively with her. She should be meeting the top donors and telling them not just about telomeres, cancer, stem cells, and aging but about her vision for Johns Hopkins.

I would be happy to follow this up with a phone call or a face-to-face meeting if you think that would be helpful.

All the best,

Jeremy

**Letter to Carol Greider regarding downsizing glassware washers in MBG – January 2011**

**Carol Greider is the Director of the Department of Molecular Biology and Genetics at Johns Hopkins Medical School.**

Dear Carol,

Let's talk. My sense from your e-mail is that you are being too hard on yourself. The essential question is how much work the department has that is appropriate for the skill set of employees like Marie and Lakeychia. I think the answer is that there was not enough of that kind of work to go around. Under those circumstances, either hours need to be cut or the employees need to retool to do additional jobs - but the latter option is extremely challenging in a situation in which the minimal qualification in the lab is a college level science background.

I had a talk with Marie, and she and I sat down at my computer and we put together a resume for her (pdf enclosed) so that she can more effectively look for additional hours at Johns Hopkins. She hasn't seriously pounded the pavement yet - for example she has not made any inquiries at JHSPH. I am hopeful that she can find a second part-time position, and I told her that I would be happy to serve as a reference for her and help in any way that I can. I think that with some help from you, me, and Shirley something should materialize. Tangentially related to all this: although Marie is not wealthy, she isn't starving. She drives a big beautiful SUV that cost a lot more than my car. I joke with her about it occasionally because I know how much she loves it.

I also had a talk with Lakeychia. I'm more worried about her. Her health is not good (obesity and diabetes), and she is thinking about some sort of combination of independent business and some more schooling. That could be a tough row to hoe in the present economy. I told her I would be happy to serve as a reference and help her out in any way that I can.

Please don't lose sleep over this. Let's spend money carefully, but I hope that we are not at the point where we have to count pennies.

All the best,

Jeremy

**Letter to Sin Urban and Carolyn Machamer regarding graduate admissions – December 2011**

**Carolyn Machamer is the Director and Sin Urban is the Head of Admissions of the Biochemistry, Cell, and Molecular Biology Graduate Program at the Johns Hopkins Medical School.**

Dear Sin and Carolyn,

I have an idea that may already be happening or may have happened: we should do a retrospective analysis of BCMB admissions with the goal of trying to determine whether our criteria for selecting students can be improved. The argument against doing this is that it is intuitively obvious what criteria we should be applying – good grades, good exam scores, strong letters, lab experience, an engaging curiosity in the interview, maturity, emotional stability, etc. – and that any retrospective analysis that we might perform is unlikely to reveal anything new. Among the arguments in favor of doing this analysis is that almost every other profession performs these types of analyses, and since we are sitting on the data we would be foolish not to use it. One might also add as an argument in favor that we all appreciate the enormous benefits of getting better students and the enormous costs associated with getting poor students.

It would probably be best to focus only on students who have already graduated so that we don't run the risk of offending any current students. I suggest that the analysis focus on the extremes of student performance to enhance the signal-to-noise ratio, i.e. look at the applications and interview notes for students that went on to become the "top" and the "bottom" students. "Top" could be defined by asking faculty to indicate the best student(s) they have had in their labs, by Young Investigator Day awards, by publication record, etc. "Bottom" could be defined by analogous criteria.

The useful question is: are there attributes in the application, interview, and review process that can predict future performance more accurately than it is now being predicted? My guess is that this analysis might be most useful at the low end of the performance spectrum – i.e. there might be warning signs that we didn't read well at the outset. At the high end of the performance spectrum, I would guess that most students look pretty attractive at the point of application – but that is only a guess.

One possible outcome of the analysis might be that our predictive abilities are relatively poor with no

obvious way to improve them.

All the best,

Jeremy

**Letter to Paul Rothman regarding a proposal to advertise on the JHMI web site – November 2012**

Dr. Paul Rothman,
Dean and CEO
Johns Hopkins Medicine

Dear Paul,

I am writing to offer my opinion regarding the recent proposal to launch a JHMI medical information web site with paid advertising. Earlier this week, faculty members in the Department of Molecular Biology and Genetics were briefed on this proposal by our department director, Carol Greider. At present, that is the limit of my information on it. As I understand the proposal, the web site would be set up to attract traffic from non-physicians and it would generate revenue for JHMI by paid advertising, much of which would likely be direct-to-consumer medical product advertising. Other medical institutions, such as the Mayo Clinic, are already using this business model.

My view is pretty simple: this is not the right direction for JHMI. Indeed, I would characterize the proposal as fatally flawed from an ethical point of view. The JHMI name stands for quality and integrity, and it is our duty to build and maintain that reputation. The public will invariably associate advertising content on a JHMI web site with the JHMI name, and some customers will see it as an endorsement by us of the products being advertised. Of course, the lawyers will assure us that from a legal point of view we have not endorsed those products. But the reality is that the power of association is enormously influential in human behavior. Indeed, we can expect that advertisers would want to work with us in no small part because they recognize the value of being associated with the JHMI name.

In the court of public opinion, it will be impossible for JHMI to distance itself from the products that are advertised on our web site, and we will then find ourselves knee-deep in the ethically murky world of direct-to-consumer medical advertising. Among the problems that we would inevitably face is the risk of hosting ads for products that might later be shown to be ineffective or harmful.

There is no question that we can make money by trading on our reputation. In the short term that might seem like a clever idea, but in the long run we would be doing the institution a disservice.

My advice is to nip this proposal in the bud.

With warm regards,

Jeremy

**Letter to Ron Daniels and Jonathan Bagger regarding Bloomberg Professors – March 2013**

**In 2012, alumnus Michael Bloomberg made an extraordinary gift to Johns Hopkins that established 50 Bloomberg Distinguished Professorships. How best to identify candidates for these Professorships was a topic of much discussion.**

Ron Daniels, President
Jonathan Bagger, Provost and Senior Vice-President
Johns Hopkins University

Dear Ron and Jonathan,

I suspect that you are receiving more letters regarding the Bloomberg Professorships than you care to read. However, this letter is a bit different. It addresses issues of process and timing that will affect our ability to make the wisest choices for these appointments.

I understand from the JHMI leadership that this year's nominees for the Bloomberg Professorships must be submitted to your office by the end of March, that eight of the ten Bloomberg Professors to be appointed this year will be recruited from outside of the institution, that the candidates must be connected in some way with a series of predetermined initiatives, and that candidates whose work is strongly interdisciplinary will be given priority.

In my view, the use of multiple constraints – and most especially the very short time window for nominations - is going to severely impair our ability to identify and recruit the most talented candidates. Mr. Bloomberg has given Johns Hopkins an historic opportunity to go after the world's top talent in virtually any field. However, recruiting in the stratosphere of academic talent – which is where we want to be recruiting – cannot be rushed. In some fields, a game-changing candidate may appear only once every few years. Some candidates who appear outstanding on first inspection will lose some of their luster when they are carefully vetted. In some fields – and not necessarily the ones designated - we may find ourselves competing for an outstanding candidate with other institutions, and the Bloomberg Professorship will be a critical bargaining chip that we need to have in reserve.

All of these considerations argue for a flexible approach. In my view, the optimal approach would be to slowly ramp up the appointment process with an expectation of 3-5 appointments in the first year, 40-45 appointments over 8-10 years, and a reserve of 3-5 vacant Professorships at steady state so that there will always be an opportunity to move quickly if an extraordinary opportunity arises.

The message that we need to send to the JHU community, to Mr. Bloomberg, and to the wider world is that we are setting a very high bar. In more definite terms, ending the year with four outstanding appointees would be far better than ending it with four outstanding appointees and four almost outstanding appointees. A practical consideration related to this last point is that whatever faculty searches are already in progress this academic year are very unlikely to be geared toward candidates in the Bloomberg Professor league. I expect that this will change starting now, but it would take many months to conduct a new search with the goal of identifying candidates of this quality.

In sum, the challenge will be to identify from a broad field of outstanding candidates the very few who really are of Bloomberg Professorship quality. Let's not rush the process.

With warm regards,

Jeremy

Jeremy Nathans

**Letter to Paul Rothman regarding the Brain Sciences Institute – November 2013**

Dr. Paul Rothman
Dean and CEO
Johns Hopkins Medicine

Dear Paul,

I am writing to share some thoughts regarding the BSI situation and the future of neuroscience at JHMI. I would also like to meet privately with you for about 30 minutes to follow-up on the issues raised in this letter. In light of the still evolving fallout from BSI's plunge into insolvency, it would be best if we could schedule a meeting sooner rather than later.

First, you might be wondering why I have become involved in this issue, since I have no official role in the BSI and I have only a secondary appointment in the Neuroscience Department. Despite the lack of official connections with BSI, I consider myself primarily a neuroscientist, and as one of the more senior and more prominent neuroscientists at Johns Hopkins, I feel a responsibility to the neuroscience community here. I also feel a special responsibility to our younger colleagues - both neuroscientists and non-neuroscientists - whose careers depend in no small part on decisions made by the JHMI leadership.

My involvement grew out of my concern, starting a couple of years ago, that (1) the BSI was releasing virtually no financial information, (2) that this might be masking unwise decisions, and (3) that the looming fiscal belt-tightening at NIH made it imperative that we plan for lean times by directing substantial BSI resources into a research endowment fund. In the Fall of 2012, I met with Jeff Rothstein, Janice Clements, and Rick Huganir, to discuss these concerns and learned - to my alarm - that (1) the donor family had missed their annual payment, and (2) there was no endowment beyond a $5 million fund for the director. My talking points from that meeting are appended to this letter. I also discussed these issues in a separate meeting with Landon King early in 2013 and gave him a copy of those talking points. I should note that the nearly perfect wall of secrecy that surrounds BSI finances means that I have only a vague idea of what the numbers actually are - my guesses are probably within a factor of two at best. Senior neuroscience faculty members who are not part of the innermost circle are similarly in the dark.

While the events of the past few months have now made some of these issues moot (at least for the moment), we should realize that the public relations fallout within and beyond Johns Hopkins is just beginning. Five years ago, the BSI was anointed, with much fanfare, as the public face of neuroscience for the entire university, and the sight of it imploding is not going to instill confidence. We have recently lost two outstanding senior neuroscience faculty members: David Ginty to Harvard Medical School and Craig Montell to the University of California. Min Li will soon depart to become director of neuroscience at GlaxoSmithKline. The realization by our neuroscience faculty that JHMI may have blown a huge philanthropic opportunity, together with the possibility of further cuts in the NIH budget, will induce every faculty member worth his or her salt to start thinking about an exit strategy. In short, we are now at a tipping point.

Under these circumstances, the Dean and CEO must act quickly, vigorously, and publicly. Every neuroscience faculty member should be apprised of the situation. Attempting either to keep the problem secret or to sugar coat it is a recipe for disaster. Full transparency, including an overview of the financial data, together with a public pledge of continued transparency is essential. The message should be that we are all in this together and that we will work together to set it right. Part of setting it right will involve changes in BSI governance. There must be a written set of bylaws that codify the financial reporting and decision-making, and that limit the BSI director's power, and - to restore faith in the process - the bylaws should be made public. Central to the change in governance is transparency. Without getting mired in a

discussion of past events and who did or did not do what, I will simply note that if there had been even a modest level of financial transparency, it would not have taken very long for someone to point out (perhaps in late 2008?) that the stock market sometimes goes down and that ten year financial projections have a big element of uncertainty.

The response to the current crisis also needs to include an equitable approach to BSI's remaining financial commitments. Obviously we must honor our commitment regarding the start-up packages for our newly hired faculty, and Janice has told me that these are being covered in full. I am not sure where that money will ultimately come from, but I do not think it should come from the Neuroscience Department. As one idea, let me suggest that half of the annual income from the BSI director's $5 million endowment be directed to pay those start-up costs until the BSI raises new funds to pay back the JHMI administration. Such an arrangement would (1) show that the director has some skin in the game, and (2) incentivize him to raise new funds.

This letter would be incomplete if it did not address the Neuro-translation initiative, the BSI-sponsored small molecule drug development effort. This is a centerpiece of Jeff Rothstein's research and it is a reflection of Jeff's desire to help patients who are suffering from devastating neurologic diseases such as ALS. The practical question is: what are the chances that this initiative will deliver something meaningful? There are good reasons for skepticism. During the nine years that I served on the scientific advisory board at Merck Research Laboratories, which has an $8 billion annual budget, I was impressed with how difficult the drug development business is. This is especially true in the context of CNS drug development, where pathophysiology is complex, animal models are usually inadequate, and clinical trials are long and extremely expensive. Industry-wide, only 8% of compounds entering human clinical trials for CNS indications emerge at the end to win FDA approval. Put another way, 92% of CNS compounds that looked good in preclinical testing fail in humans, for one reason or another. This level of risk means that only those companies with very deep pockets and a willingness to burn through hundreds of millions of dollars are still in this area. Astra-Zeneca made a strategic decision two years ago to stop almost all in-house CNS R and D because it was considered too risky.

Because of BSI's financial secrecy, it is impossible for an outsider (me) to determine the level of BSI spending on the Neuro-translation initiative. Judging from the list of names and job titles on the BSI web site, it cannot be less than several million dollars per year, but perhaps some of the money comes from other sources. Janice has told me that the web site is out of date and there are now fewer people on the BSI payroll. The question before us now is whether scarce resources that could be used to support neuroscience at JHMI more broadly will be used to support a single initiative that has such a high degree of risk. In thinking about this, I note that a large part of the strategic thinking in the pharmaceutical R and D world involves weighing opportunity costs and deciding when to pull the plug on a program that is consuming resources that could be put to better use elsewhere.

In summary, if we fail to face up to the problems that got us here and that we can fix, and if we fail to wisely use what little resources remain for the support of the most important neuroscience priorities, then we will be consigning neuroscience at JHMI to a downward trajectory. On the other hand, if we all work together vigorously and openly, there is a very good chance that we can turn this around.

With warm regards,

Jeremy

Jeremy Nathans
Professor
Molecular Biology and Genetics
Neuroscience
Ophthalmology

**Letter to Hamilton Smith regarding an award in his name – January 2014**

**Hamilton ("Ham") Smith discovered restriction enzymes when he was a faculty member at Johns Hopkins Medical School. Starting in the mid-1990s, he partnered with Craig Venter to pioneer large scale genome sequencing and synthesis.**

Dear Ham,

I hope that this e-mail finds you well.

I am writing with an idea that I hope you will find attractive.

I would like to start an award in the basic science departments at Johns Hopkins that would carry your name and would recognize and encourage junior faculty members to pursue their most creative research. Having your name on it is important for many reasons. It is important because Johns Hopkins Medical School should be doing something substantial to honor you, because your curiosity-driven scientific style is exactly the style we want to encourage, and because having your name on the award would be enormously gratifying to the young faculty members who receive it.

The details are not entirely worked out, and I would be grateful for your advice on how to structure the award, assuming that you think it is a good idea. In a nutshell, here is what I am thinking. We would raise funds from various donors to create an endowment. The award would continue in perpetuity and each year its size would be determined by the income on the endowment. As many as three junior faculty members could be selected per year for the award, but in other years there might be one, two, or no awards. The award would go into a gift account for the recipient's lab to spend on research. A committee of JHMI scientists would select the awardees and initially I would chair the committee.

I very much hope that you will agree - and be pleased - to have this award carry your name. The full name might be "The Hamilton Smith Award for Innovative Research". If this sounds agreeable to you, I will then talk with the Dean to arrange the details so that the endowment fund can be set up.

With warm regards,

Jeremy

**Letter to Carol Greider regarding departmental reviews – February 2014**

Dear Carol,

Your description of the Biological Chemistry departmental review and Steve's description of the ICE review suggests that some written feedback about the process (to Antony Rosen, Landon King, and perhaps others) is in order. As chair of the review committee, you would be the logical person to deliver the feedback. Here are a few thoughts.

First, since we have distinguished outside reviewers participating, our reputation is going to be enhanced or degraded depending on how we execute the review. Whatever the outside reviewers may think of the substance of the department under review, they should go home with the impression that we know how to run things effectively.

Second, walking around and seeing every lab is critical, and it should be incorporated into every review. I suggest that you and the other internal committee members do this before submitting the report. You will observe some labs with antiquated equipment, rooms with multiple unused benches, labs in need of renovation, etc. Conducting a departmental review without a careful look at the facilities is like giving a patient a diagnosis without doing a physical exam.

Third, taking a chapter from Peter Pronovost's book, every review should be run based on a protocol and a checklist. This would include a time-table of events. For example, two months ahead of the review all of the members of the department to be reviewed should be notified of the date, given the schedule of events, given a standard CV form to guide their CV preparation, given written instruction regarding financial and other information that will be presented, etc. This point is so obvious that I am incredulous that it wasn't followed. One administrator of proven competence should be in charge of orchestrating the reviews.

Fourth, if this is not already the case, the written document should be structured in a standardized format so that it can be compared to reviews of other departments, and to past and future reviews. For example there should be a series of categories (faculty, finances, space, teaching, graduate students, etc) with both prose commentary and quantitative assessments. Quantitative assessment could be in the form of checked boxes, for categories such as comparison of the department to peer departments at other institutions, financial soundness, space needs, etc.

All the best,

Jeremy

**Letter to Steve Desiderio regarding a new Bloomberg Professor – April 2014**

**Steve Desiderio is Director of the Institute for Basic Biomedical Research at the Johns Hopkins Medical School.**

Dear Steve,

I would like to share a few thoughts in connection with the High Throughput (HiT) center and a Bloomberg Distinguished Professorship (BDP). These arose from a conversation that I had with Landon King, who had asked for my views on the subject.

As initially configured, the HiT center was very much a reflection of Jef (and then Min's) scientific strengths and interests. It was especially influential at JHMI on the genetics/genomics side but less so on the chemistry side. The genetics/genomics world has been substantially democratized over the past decade thanks to technologies like Next Generation sequencing, and the frontier has shifted increasingly from experimentation and physical methods to data analysis. Maybe the emphasis of the HiT center should also evolve in this direction. If it did, it would synergize with the university's initiative in big data analysis, and it would provide a core of expertise that would be widely valuable at JHMI. A shift in that direction would also suggest Steven Salzberg as a potential leader and BDP nominee.

If we want someone who is developing technology, we need to look hard at who is really creative and really having an impact. Many people are developing technologies, but only a few are really having an impact. If we want someone who is using technology creatively to address an important biological or medical question, then there are more candidates. But if we want someone who excels at both, then the field is very small. Locally, Bert Vogelstein and Ken Kinzler would be the exemplars.

Regarding high throughput screening and chemistry in general, I think this needs careful consideration. My view is that we are not in a position to make the large and long-term investment (tens of millions of dollars over a decade) required to do both the initial chemical screens and the medicinal chemistry follow-up that is required to realize the full value of this approach. As a member of Merck's SAB for over a decade, I have watched how lead identification and lead optimization are done in the pharmaceutical industry, and what I observed is that it requires very substantial resources.

I would be happy to discuss this in person, if you would find that helpful.

All the best,

Jeremy

**Letter to Carol Greider regarding financial transparency at Johns Hopkins – October 2014**

Dear Carol,

I'd like to raise an issue and also suggest a step that we, as a department, might take to move the current non-optimal situation in the right direction.

The basic issue is financial transparency, or, more precisely, the lack of it, at JHMI. Finances at JHMI are extremely complex, and it is not feasible or desirable to reveal all of the inner workings. But there is also a tradition of non-transparency that is detrimental to optimal decision-making, and in at least one current situation that I know about, is a major point of contention. Historic examples in which financial non-transparency has adversely affected decision-making include: (1) excessive spending of Physiology Department funds by a previous department director and (2) overspending of funds by the Brain Sciences Institute. Both of these problems would likely not have occurred if there had been public disclosure of basic financial information, for example in the form of an annual report.

Aside from the effect on decision-making, there is also a basic issue of fairness to those whose indirect cost dollars or personal contributions have gone into the system. Those who have put money into the system currently have some input into how the money is spent, so this is not a problem of "taxation without representation", but it is a problem of "taxation without transparency".

What I would like to propose is that each financial unit - individual departments, institutes (IBBS, BSI, IGM, etc), and support entities (core labs) – make a summary version of its annual financial statement available to the JHMI community. The summary financial statement would contain information such as major categories of expenditures, but not sensitive information such as individual salaries. For institutes, it would include funds raised and the various ways in which funds were spent. As far as I can determine, this type of information is not now being made publicly available.

There are various ways in which this idea could be implemented, but the one that I like best is for MBG and IBBS to lead by example. That would demonstrate that: (1) it can be done, (2) doing it does not produce any dire consequences, and (3) the response to greater transparency is positive (my prediction). A pre-emptive move would create an environment in which it will be easier for others to follow the lead.

I would be happy to discuss this in greater detail.

All the best,

Jeremy

**Letter from a first year medical student – December 2014**

Dr. Nathans,

Good evening.  My name is X, a first year in the School of Medicine and I recently took the Genetics course you taught with other professors.  The course was probably the toughest I took in Scientific Foundations of Medicine and I never really understood why we had the kinds of problems we had (and the methods of instruction employed) considering the considerable amount of thought and integrated thinking that went into them.  With the passage of time however, I can now see the wisdom in an approach to learning that has similar objectives.  I may not have done as well as I wanted to in the class, but the training I received from the course has served me well in the intervening courses we have had since then.  My educational goals have changed significantly since I took the course and I have noticed a marked change in the way I think about science.  I would almost certainly not have gravitated towards those ideals if I did not take the class and for that I am grateful.  I look forward to working with you in some capacity in the near future.

Happy holidays.

Best,

X

Dear X,

Thank you for your very nice note.  It sounds like you are learning a lot - and that is the goal.

With best wishes for the Holidays and New Year,

Jeremy Nathans

**Letter to Steve Desiderio regarding financial transparency at Johns Hopkins – February 2015**

Dear Steve,

I regret that I will not be able to attend the IBBS town meeting, as I have a conflicting thesis committee meeting. It will be a moment of triumph for IBBS and for you, and I wish I could be there.

Related to this topic, may I suggest a potentially important innovation that IBBS could spearhead? The idea is to take the lead in setting an example of financial and managerial transparency. As you know, transparency is not JHMI's strong suit, and our history shows that non-transparency can lead to non-optimal decision-making. For an organization that represents a broad academic constituency (as IBBS does) transparency is especially important.

The basic proposal is simple, and I hope that it would be adopted by all JHMI departments and institutes: every year each entity would publicly release a one page summary of finances and activities. It does not need to be so granular that sensitive information (such as individual salaries) is included, but the different categories of expenditures and sources of revenues should be enumerated. This is essentially what nonprofit organizations show in their annual reports.

For IBBS, the present moment is perfect for this first step, and it could encourage others to do the same.

All the best,

Jeremy

**Letter to Paul Worley and Shan Sockanathan – March 2015**

**Paul Worley and Shan Sockanathan are Professors in the Department of Neuroscience at Johns Hopkins Medical School.**

Paul and Shan,

I heard from Rick that the University of Arizona is interested in the two of you. While I salute their good taste, I very much hope that the courtship doesn't come to fruition. If there is anything I can do to improve your environment here, please let me know. Needless to say, I think the world of both of you, both personally and scientifically. It would be a huge loss for me personally and JHMI generally if you were to leave.

All the best,

Jeremy

**Letter to Steve Desiderio regarding the distribution of endowed professorships – April 2015**

Dear Steve,

I am delighted to see that Geraldine is being honored with an endowed chair. Very well deserved.

In the spirit of being pro-active, I thought I'd send you this e-mail with a prediction that there may be some push-back from other basic science departments around the general issue of endowed chairs. As you may know, Peter McDonnell has put together an endowed chair for me (in Ophthalmology) that will

probably be rolled out in June. That would bring the score-card for the past couple of years for chairs awarded to basic science faculty to: Molecular Biology and Genetics, 4; all other basic science departments, 1. I'm counting here Se-Jin's chair, Carol's Bloomberg Chair, these latest two for Geraldine and me, and Mike Caterina's chair (the only non-MBG chair). Unless I'm missing something, I think that is the total. Hopefully, there are one or more chairs in the pipeline for basic science faculty in departments other than Molecular Biology and Genetics.

All the best,

Jeremy

**Letters regarding microscope thefts – September 2014 – April 2015**

9-30-14

Dr. Robert Siliciano, Director MD-PhD program
Dr. James Weiss, Director of Admissions
Dr. Tom Koenig, Dean of Students

Dear Bob, Jim, and Tom,

By now you have probably learned that X, an MD-PhD student, was arrested in connection with multiple thefts of laboratory equipment, most especially microscopes and microscope parts, from JHMI labs and from the Armstrong Building. My lab was one of many that were victimized. X is currently free on bail and waiting indictment.

I saw the collection of stolen items that was recovered from X's home. It was truly incredible. He was a kleptomaniac. Power tools, microscopes, microscope parts, micro-manipulators, chemistry glassware, and lab equipment of all kinds. I would guess that most of it will never find its way back to the rightful owners. The thefts must have required dozens of trips.

I would like to strongly suggest that now is the time for a formal review of X's record at JHMI to see what we could have done differently. This should start with his application for admission and include his classroom, lab, and clinical rotation career. It should also include an assessment of how we should deal with a student who had failed to match for a residency. The review should include an assessment by corporate security. It might best be conducted by the JHMI office of research integrity, which has substantial experience in these matters. It might also benefit from the input of a forensic psychologist. The final written report should be circulated to individuals associated with admissions, student advising, and security.

Finally, I note that in addition to the damage done internally by these events – both in terms of material, lost time, and morale – there is a substantial risk to the reputation of JHMI if individuals with these behaviors emerge with a degree (especially an M.D.) from Johns Hopkins.

All the best,

Jeremy

Jeremy Nathans
Molecular Biology and Genetics
Johns Hopkins Medical School

April 14, 2015

Statement regarding the theft of microscope equipment from the laboratory of Jeremy Nathans at Johns Hopkins Medical School in September 2014 – to be read at the trial of X.

I am a professor in the Departments of Molecular Biology and Genetics, Neuroscience, and Ophthalmology at the Johns Hopkins Medical School. I have been a faculty member at Johns Hopkins for 27 years. My laboratory consists of 11 researchers – a mix of senior researchers, technicians, graduate students, and postdoctoral fellows. We work on scientific questions related to vision and ophthalmologic disease: how the eye develops and functions, the molecular and cellular basis of eye diseases, and potential treatments for eye diseases. This work depends on specialized, delicate, and expensive equipment, including microscopes (typical purchase price: $250,000). In late September 2014, our lab and other labs were targeted by a thief who stole a large number of expensive and essential microscope components. The individual was clearly knowledgeable, as many of the components were removed in a way that indicated a high level of familiarity with the equipment. The thefts completely disabled the microscope from which the components were stolen and disrupted those research projects that depended on this microscope. A theft like this casts a dark cloud of suspicion over virtually everyone, since it appeared to be an inside job and the thief and/or the thief's accomplices were therefore assumed to be a member of the Johns Hopkins community. In addition to disrupting ongoing research, the requirement for heightened security creates substantial expense and inefficiency. For example, as a defensive measure, we have redesigned one microscope room to add an additional wall and door at a cost of $5,000. However, the most damaging long-term effect is a loss of trust within a scientific community that is built on trust.

Jeremy Nathans

# Trying to move mountains

**Problems with the International Office at Johns Hopkins Medical School – July 1991**

Dr. David Blake
Office of the Dean
Johns Hopkins University School of Medicine

Dear David,

I am writing to request your assistance in improving the quality of the International Student Office. This office is under the direction of X and is responsible for processing visa paperwork.

I am writing to you because my two encounters with this office have not been good. The first involved a request for a change of visa status for an incoming graduate student. The paperwork for this change was initially withheld by the International Student Office despite telephone and in-person appeals by myself and a telephone appeal by a department chairman. The papers were subsequently released after the Office of the Dean became involved. The change in status was approved shortly thereafter by the Immigration and Naturalization Service. In the second episode, which is still ongoing, the International Office submitted an incomplete visa application form, with the result that a postdoctoral fellow has needlessly lost her funding pending correction of the error. At this writing, one month after the error was detected and funding cut off, and despite numerous entreaties, the International Office has yet to resubmit a corrected version of the application. I estimate that this episode will cost in excess of five thousand dollars in lost laboratory funds.

I am soliciting written comments from other faculty members to ascertain the extent of this pattern of poor performance. An efficient International Office is important in providing for the well-being of foreign students, postdocs, and scientists. I hope that you will vigorously pursue a permanent solution to the present problem.

Yours sincerely,

Jeremy Nathans
Assistant Professor

**Design and construction – November 2015**

**E-mail to Jack Grinnalds, head of Design and Construction at the Johns Hopkins Medical Institutions. A major renovation of all of the bathrooms on the fifth-tenth floors of a research building [The Preclinical Teaching Building (PCTB)] was undertaken in the Fall of 2015 at a cost of $65,000 per bathroom. These twelve bathrooms were the most recently constructed bathrooms in the basic science complex. The explanation given for the renovation was that the wheelchair accessible stall in each bathroom was no longer compliant with the most recent version of the Americans with Disabilities Act.**

Dear Mr. Grinnalds,

Steve Desiderio shared his and your recent e-mail exchange with me. I am a faculty member with a lab

on 8 PCTB. I have worked on this floor for the past 28 years. I understand that there have been occasional issues related to bathroom cleanliness (housekeeping issues) and plumbing/minor maintenance (facilities issues), but none of those problems seemed to rise to a point that required a total gutting and reconstruction. As regards the Americans with Disabilities Act (ADA), each PCTB bathroom had a wheel chair accessible stall of the type that is standard in ADA-compliant bathrooms throughout JHMI buildings (large stall, large door, and a hand-rail along the length of the wall).

More generally, I was surprised to see that JHMI would proceed with a major renovation without advance consultation with the faculty whose labs are immediately adjacent to the site and who would presumably have the greatest interest in the plan.

Finally, I am concerned by the substantial cost of the renovation. In this era of fiscal belt-tightening, we can reasonably expect that the central administration will factor in the $780,000 spent on this project when considering any future requests from the departments that occupy PCTB.

If you can fit in a 10-15 minute phone call this coming week, I would be interested in hearing more about the factors that went into the decision.

Thank you.

Sincerely,

Jeremy

Jeremy Nathans
Professor
Molecular Biology and Genetics
Neuroscience
Theobald Professor of Ophthalmology
Investigator, Howard Hughes Medical Institute

**Fighting the plague of Material Transfer Agreements – November 2015 – September 2016**

November 2015

Dear X,

The MTA. This is a form of welfare for under-employed lawyers. In >30 years of giving out mice, DNA, antibodies, etc I have never once asked anyone to fill out an MTA. The lawyers here know what I think of MTAs and they have stopped asking me to use them.

All the best,

Jeremy

September 2016

Dear Megan,

I am Hao Chang's postdoctoral advisor. As you know, Hao is trying to transfer his mouse colony from Johns Hopkins to the University of Wisconsin.

At Johns Hopkins MTAs are optional for mouse transfers. Because our mouse lines have no commercial value, I have been giving out our genetically engineered mice to any scientist who requests them for >25 years and have never used an MTA as part of that process. Moreover, all of our mouse lines are freely available from JAX with no MTA required.

Unless you have a blanket MTA that covers all of the mice and can be processed quickly, the requirement for an MTA will simply slow the process without providing any benefit to either party. I would be happy to discuss this by phone with you and/or your department chair if that would be helpful.

Sincerely,

Jeremy Nathans
Professor
Molecular Biology and Genetics
Neuroscience
Theobald Professor of Ophthalmology
Investigator, Howard Hughes Medical Institute

**Unsuccessfully requesting published materials – October 2015 to February 2016**

October 15, 2015

Dr. Charlotte Bevan
Imperial College
London, UK

Dear Dr. Bevan,

I enjoyed reading your paper on the androgen reporter mouse line (Dart et al "Visualizing Androgen Receptor Activity…" PLOS One, 2013). Would you be willing to share the luciferase reporter plasmid that corresponds to the reporter used in the transgenic mouse (SC1.2ARE-luciferase)? Also, do you have the sequence of the plasmid, or at least the ARE and promoter region?

If I understood your paper correctly, the luciferase reporter plasmid has only one copy of the ARE. Was there a reason that you did not use a multimerized set of of AREs? That seems to be a common design for luciferase reporters to increase the signal-to-noise ratio. For example, the standard ERE luciferase reporter has three tandem sites.

Thank you for considering this request. We can provide a Federal Express number for the plasmid shipment.

Sincerely,

Jeremy

Jeremy Nathans
Professor
Molecular Biology and Genetics
Neuroscience
Theobald Professor of Ophthalmology
Investigator, Howard Hughes Medical Institute

November, 2015

e-mail from Charlotte Bevan:

Hi, in case it needs an MTA, could you give the answers to these questions? Apart from the ones that are obviously for me. Cheers

1. What are the materials? Are you free to transfer the materials (no third party obligations)?
2. Are these human samples? If so, could your provide a more detailed description of the samples you are transferring? Are they relevant materials as defined by the Human Tissue Act?
3. If human samples, please provide ethics approval number.
4. What will the recipients be using the materials for?
5. What is the quantity of materials being sent to?
6. Who originally obtained/ developed the material?
7. Who funded the activity – to ensure no one else has rights to the material?
8. Who actually owns the material?
9. Is the material of commercial value/commercially exploitable?
10. The project title for which the material would be used (this needs to go in the MTA, e.g. project name)?
11. A brief description of what the work will involve (this will also need to go into the MTA). Maybe a summary of the proposed research plan would be helpful. At least a paragraph or two to sufficiently describe what the requesting Scientist will do with the materials.
12. The Principal Investigator/Requesting Scientist is:
13. The organisation that the requesting Scientist works for:
14. Who should the MTA be sent to – contact details?

February 19, 2016

(To multiple recipients)
Imperial College
London, UK

Dear all,

This letter signifies that I am officially terminating my request for a reporter plasmid from Dr. Charlotte Bevan (original request e-mail from October 15, 2015 is reproduced below). Dr. Bevan has very kindly provided the nucleotide sequence of the relevant region of the plasmid, and we will resynthesize it chemically. The Imperial College MTA has numerous stipulations, which would make compliance difficult (see the e-mail below from HHMI attorney Ms. Beysselance).

I include below an example of a similar request to my lab and my response to that request. Note the dates on the e-mails: the requesting investigator had the sequences and protocol on the same day and the plasmid within two days. No MTA or other paperwork was involved.

Sincerely,

Jeremy Nathans
Professor
Molecular Biology and Genetics
Neuroscience
Theobald Professor of Ophthalmology

Feb 9, 2016, at 10:29 AM

Dear Jeremy,

I wanted to ask you whether you can please send me the sequence (and if you have also a plasmid with the DNA) of Sun1-sfGFP-myc, as you published it last year in Neuron for profiling of neuronal populations? We would like to make a flexed AAV with it for specific injections. And if you happen to have a lab style protocol handy for purification etc, this would also be great. If there is someone in your lab I should contact about these questions, please just redirect me.

Thanks a lot for your help and best wishes,

Silvia

Prof. Dr. Silvia Arber
Biozentrum
University of Basel
Department of Cell Biology
Klingelbergstrasse 70
CH-4056 Basel
Switzerland
&
Friedrich Miescher Institute
Maulbeerstrasse 66
CH-4058 Basel
Switzerland

Feb 9, 2016 at 11:51 AM

Dear Silvia,

The sequence of the SUN1-sfGFP-6xmyc cassette is enclosed. I'll send you the plasmid today. Our protocol is enclosed. The Neuron paper (Mo et al) also has a detailed protocol - essentially identical to the one here. Alisa Mo's contact: amo4@jhmi.edu

All the best,

Jeremy

**Correspondence with the Johns Hopkins finance office – February 2014 to December 2016**

**The e-mail trail below represents a subset of e-mails related to JN's creation of an endowment to support the research of junior faculty in the basic science departments at the Johns Hopkins Medical School. The Hamilton Smith Award for Innovative Research was created in 2014 and over the next several years ~$380,000 was raised from several dozen individual and corporate donors.**

February 2014

(Jim Erickson, Senior Finance officer; later Director of Finance)

Jim,

We need the formal document as the first step. I want to go to potential donors and say the fund exists and these are its ground rules. When the checks come in they need to go to an existing fund with rules already in place - most especially, the school's guarantee that this fund will be managed as an endowment in perpetuity. And I need that document to be signed by someone at a level of authority (either Rich Grossi or Paul Rothman) so that 20 years from now there is no backtracking on it.

All the best,

Jeremy

February 12, 2015

Dear (Development officer),

Thank you very much for that detailed reply. That is very helpful.

Let me ask one more question. Dr. Rothman has told me that he will arrange for JHM to reimburse our endowment for that fraction of the 15% tax that goes to JHUSOM (see two e-mails below). Can you tell me what amount that would be? I have heard that it is 11% to SOM and 4% to JHU = 15% total. Is that correct?

All the best,

Jeremy

Hi, Dr. Nathans.

I confirmed this with our Sr. Director of Finance, and you are correct: 11% to SOM and 4% to JHU = 15% total.

If you have any other questions, please let us know.

Have a good night,

(Development officer)

June 10, 2015

Dear (Finance officer #1),

To follow-up our phone call, here are two items.

First, as shown in the e-mails below, Dean and CEO Paul Rothman agreed that the 11% JHMI tax would not be applied to the Ham Smith Fund unless it grows extremely large. That leaves only the JHU 4% tax. Therefore, the fund keeps 96% of donations.

Second, Gem Johnson's contact is below. She is managing the development side and can give you an update on donations.

Sincerely,

Jeremy Nathans

September 10, 2015

Dear (Finance officer #1),

I am writing to check on the status of the Hamilton Smith Endowment Fund. We have money in an account that was raised over the past 15 months and is earmarked for this endowment. The amount is somewhere between $250,000 and $300,000. My understanding is that it is in the pipeline for approval as an endowment. Can you give me an update on its current status and expected approval date? Earlier e-mails are below.

Thank you.

Sincerely,

Jeremy Nathans
Professor
Molecular Biology and Genetics
Neuroscience
Theobald Professor of Ophthalmology

September 15, 2015

This is complicated by our current cash situation. The funds that were originally raised and then the donors were notified of the desire to create a permanent endowment will have to be treated differently and subject to yearly approval to transfer from current use funds to endowment.

However, for the donors that were made aware before the gifts that the funds would be used for an endowment, an endowment can be created.

Please provide a list and amounts of the gifts in which the donors were made aware of the endowment beforehand. I will then submit for approval.

Once that is complete we can go through the process of approvals for the current use funds.

Thank you.

(Finance officer #1)

September 15, 2015

Dear (Finance officer #1),

Thank you for the response. When I contacted the donors, all of them were told in advance that the funds would be used to create an endowment. One example of my communication is below.

I am cc'ing Gem Johnson (gjohns45@jhmi.edu), the development officer who has worked with me on fundraising. She can forward to you the current spreadsheet listing all donors and the amounts donated.

Sincerely,

Jeremy Nathans
Professor
Molecular Biology and Genetics
Neuroscience
Theobald Professor of Ophthalmology

September 6, 2015

Dear (potential donor),

I am writing to explore the possibility that your foundation might be interested in partnering with me and my colleagues at Johns Hopkins to support a new endowment that we have recently created to support the most innovative biomedical research by young faculty members here. The endowment is named in honor of Hamilton ("Ham") Smith, a remarkable physician-scientist who revolutionized biomedicine as a young faculty member at Johns Hopkins 45 years ago. Thus far, we have raised over $250,000 from individuals and biotech companies.

I enclose a formal description of the Hamilton Smith Award for Innovative Research and an article about this award that appeared recently.

A link to a video about Ham Smith and the award is below:
https://www.youtube.com/watch?v=fa2M8UbwhOw&list=UUATNzbTbfeoMhNonZGZmrhA

I would be grateful if you could find a few minutes for us to discuss this further by phone or for me to meet with you in person.

With warm regards,

Jeremy

Jeremy Nathans
Professor
Molecular Biology and Genetics
Neuroscience
Theobald Professor of Ophthalmology

Investigator, Howard Hughes Medical Institute

September 15, 2015

Please see the email below. Jim Erickson mentioned that the gifts were current use. There is a long list of current use funds that have been requested for endowments and currently none of them are being approved.

(Finance officer #1)

July 27, 2015

Good morning, (Finance officer #2).

I have attached a packet of materials for Mr. Erickson's review re: the Hamilton Smith Award. Donors were originally solicited for a current use gift in honor of Dr. Hamilton Smith, but the Institute for Basic Biomedical Sciences would like to use those donations for a permanent endowment. All donors have been contacted and none have opted out of the endowment.

The attached materials include the gift agreement signed by Dr. Desiderio (Director of IBBS) and (Finance officer), the opt-out email sent to donors, the purpose of the endowed fund, and an accounting of the gifts. Please let me know if your office needs anything further.

Thank you!

(Development officer)

September 15, 2015

Dear (Finance officer #1),

Today is the first time that I have been informed of the current use vs. endowment issue. I am surprised that there was no attempt made to inform me of this issue earlier or to check with me regarding the facts related to what the donors were or were not told. The highlighted sentence in the e-mail from (Development officer) is incorrect. I personally contacted every donor, and I told them that this was to be an endowment. The donors gave the money with that expectation.

Sincerely,

Jeremy Nathans
Professor
Molecular Biology and Genetics
Neuroscience
Theobald Professor of Ophthalmology

September 15, 2015

Good morning, all.

The majority of the funds for the Hamilton Smith endowment are sitting in a current use account, so we will need Business Office approval to establish the endowment. I have attached the original packet of supporting documents sent to the Business Office. It includes a copy of the letter that was sent to donors asking that their gifts be used for a permanent endowment. The attached also includes correspondence about the need for donor and Business Office approval. As you will see in the attached Gift Summary, $250,200.00 of the funds intended for the endowment are currently sitting in a current use account. ($24,200.00 of the funds are restricted funds.)

Sincerely,

(Development officer)

September 15, 2015

Good afternoon, everyone.

I wanted to clarify (after checking with a colleague who is no longer at Hopkins who was more involved in this endowment than I was) that we sent the second letter to donors (included in the packet of supporting documents I sent earlier today), informing them that their funds would be held in a permanent endowment, on the advice of General Accounting. Because the original solicitation letter did not include the words "permanent" or "in perpetuity," General Accounting thought it best to cover our bases and send the opt-out letter with the "permanent" language. As Dr. Nathans said, the intent was that Hamilton Smith would be a permanent endowment, but the majority of the funds were put into a current use account. I know the Business Office is very reticent to change unrestricted funds to restricted, but I hope that because the original solicitation was done with the intent of creating an endowment that we will be able to set up the Hamilton Smith Endowment soon.

Please let me know if I can provide any additional information to move things forward.

Thank you,

(Development officer)

September 15, 2015

Dear all,

Reproduced below is an e-mail exchange from February 2014 between me and Jim Erickson (Senior Finance Officer; and starting in 2015 Director of Finance) that is relevant to the current situation.

Sincerely,

Jeremy Nathans
Professor
Molecular Biology and Genetics
Neuroscience
Theobald Professor of Ophthalmology

September 16, 2015

If the original solicitation included the correct wording to establish a permanent endowment and the funds were placed in a restricted account then as Jim stated below, the school would not put it to another use.

I am not in the department that would give you the advice for the permanent endowment process so I am not 100% sure what needed to be done originally to avoid the gifts from being placed in an unrestricted account.

I only can assist in putting together the information for a request to use unrestricted funds to establish an endowment. I apologize that this process has been frustrating for you. I have a packet of information ready to present for approval and this one will be first to discuss once the determination is made that we can move forward with these requests.

In the meantime ensure that any additional gifts are being placed in the restricted account to avoid the need for approval.

Thank you.

(Finance officer #1)

October 2, 2015 and repeat e-mail October 10, 2015

Dear (Finance officer #1),

I am writing to see how things are progressing with the Hamilton Smith endowment fund. Could you give me an update? Thank you.

Sincerely,

Jeremy Nathans

October 12, 2015

I have a meeting with Jim scheduled for the 19th. I should have an update for you at the conclusion of that meeting. Thank you.

(Finance officer #1)

October 19, 2016

Unfortunately the meeting with Jim today was cancelled. I am working to get the meeting rescheduled and will keep you updated. Thank you.

(Finance officer #1)

October 19, 2015

Dear (Finance officer #1),

Thank you for the update. I trust that a meeting can be rescheduled in the near future.

Sincerely,

Jeremy Nathans

October 28, 2016

Dear (Finance officer #1),

Are things on track with the Ham Smith endowment fund? I would like to get this moved into endowment status sooner rather than later.

Sincerely,

Jeremy Nathans

October 29, 2015

The meeting was rescheduled for next Tuesday. Thank you.

(Finance officer #1)

November 5, 2015

Dear (Finance officer #1),

Can you give me an update on the results of the meeting regarding the Ham Smith endowment fund? Thank you.

Sincerely,

Jeremy Nathans

November 14, 2015

Dear (Finance officer #1),

Since I have not heard from you regarding the 11/10/2015 meeting, I am taking this opportunity to inquire as to its outcome.

Sincerely,

Jeremy Nathans

December 2015

Good Morning,

Due to delays within The Fund for JH Medicine, Dean Rothman just signed the approval yesterday. The Fund is currently finalizing everything and sending to General Accounting this afternoon. Vincent Shaughnessy is aware and awaiting the endowment documentation and will have this completed for December close. I apologize for the delay, please let me know if you have any questions. Thank you.

(Finance officer #1)

December 2015

Dear (Finance officer #1),

Thank you for that update, although as per our phone call it sounds like the signing has not yet happened. I would like to archive a copy of the signed approval regarding the endowment status of the Hamilton Smith Fund. When you get it, please send me a pdf of that document.

Sincerely,

Jeremy

Jeremy Nathans
Molecular Biology and Genetics
Neuroscience
Theobald Professor of Ophthalmology

December 2015

Dr. Nathans,

The information that I received this morning was incorrect. Shortly after sending the email I received a call from someone else within the Fund that stated the document was not yet signed but only sent to Dean Rothman today. I will follow up with The Fund and the Office of the Dean this evening before I leave to get an update. Also, once I have the signed approval I will email you a pdf copy. Thank you.

(Finance officer #1)

December 2015

Please see attached for the signed endowment memo. The endowment packet was sent to General Accounting today. I will call this afternoon to confirm receipt, this endowment is expected to be settled early next week. Thank you.

(Finance officer #1)

February 2016

Hi, (Finance officer #1),

Please see below. The funds are still in the current use and haven't been transferred to an endowment account. Would you please find out when we can expect this to be completed? Thank you.

(Institute of Basic Biomedical Sciences administrator #1)

February 2016

Hi (Finance officer #2),

Would you please be able to provide an update on the Ham Smith Endowment? Thank you.

(Finance officer #1)

March 2016

I made the transfer. I will put in a request to close the IO tomorrow. Thanks for bringing this to my attention.

(Finance officer #3)

September 30, 2016

(Institute of Basic Biomedical Sciences administrators #1 and #2),

Any news on recovering the JHMI tax for the Ham Smith Fund?

Thanks,

Jeremy

September 30, 2016

Hi Jeremy,

Thanks for checking in. I spoke with (Finance officer #4) in General Accounting a week or so ago and he was able to recover the tax on the Beckman Foundation award. He said we need to follow up with the SOM Business Office to recover the tax on all of the previous gifts, and I plan to do so this afternoon. I will circle back to you and (Institute of Basic Biomedical Sciences administrator #1) to let you know what I learn.

Thanks,

(Institute of Basic Biomedical Sciences administrator #2)

September 30, 2016

(Institute of Basic Biomedical Sciences administrator #2),

Thank you for that update. That is progress.

Jeremy

Oct 13, 2016

Hi Jeremy,

I heard back from the SOM business office on our Ham Smith Fund question. Would you please send me whatever documentation you have of your agreement with Dean Rothman vis a vis not applying the 11% SOM tax on gifts to this fund? The attached memo doesn't appear to address the tax issue.

I also checked with (Institute of Basic Biomedical Sciences administrator #1) on (Finance officer #4)'s statement that "the department is still on the hook" and she said that was not our agreement, so I will push back on that.

Thanks,

(Institute of Basic Biomedical Sciences administrator #2)

October 13, 2016

(Institute of Basic Biomedical Sciences administrator #2),

The critical e-mail is the one furthest down in the enclosed document. In addition, Paul Rothman told me verbally that the SOM tax would be forgiven for all donations to the Ham Smith Fund, with the proviso that if the Fund got very large this policy would be reconsidered. There is no departmental involvement - this is an agreement between donors and Dean Rothman. If (Finance officer #4) wants independent confirmation of this policy, she should contact Dean Rothman directly.

Jeremy

October 13, 2016

Thank you! I will follow up and keep you posted.

(Institute of Basic Biomedical Sciences administrator #2)

November 29, 2016

(Institute of Basic Biomedical Sciences administrator #2),

I am writing to follow-up your e-mail below (from October 13). Is there progress on the recovery of the Dean's tax funds for the Ham Smith award?

Jeremy

December 5, 2016

Jeremy,

Please forgive my delayed response. I haven't heard anything from (Finance officer #4) in the SOM Business Office since mid-October. I just sent another message and will let you know what I hear back. I'm afraid she may press the issue of the IBBS paying the tax in lieu of it being taken from the gifts, so I welcome your advice on how we push back. I will also consult with (Institute of Basic Biomedical Sciences administrator #1).

Thanks,

(Institute of Basic Biomedical Sciences administrator #2)

December 5, 2016

(Institute of Basic Biomedical Sciences administrator #2),

I am counting on you to pursue this energetically. Hearing that it has been sitting on the back burner since mid-October is not my idea of energetic.

Push back? The answer is simple, and you have it already: this is what the Dean agreed to.

Jeremy

December 14, 2016

Dear Jeremy,

I have been in touch with the SOM business office several times in the past week and I learned today that we have the necessary approvals for the gift assessment to be refunded without IBBS assuming the financial burden. We should see the recovered funds in the Ham Smith account in early January. Thank you for highlighting this issue and advising on its resolution.

Best,

(Institute of Basic Biomedical Sciences administrator #2)

December 14, 2016

(Institute of Basic Biomedical Sciences administrator #2),

Thank you for following-up on this. Please keep me informed.

All the best,

Jeremy

January 23, 2017

(Institute of Basic Biomedical Sciences administrator #2),

I wonder if the Ham Smith Fund financial adjustments have gone through.

All the best,

Jeremy

January 25, 2017

Hi Jeremy,

(Institute of Basic Biomedical Sciences administrator #1) and I are investigating and will follow up soon.

Best,

(Institute of Basic Biomedical Sciences administrator #2)

February 3, 2017

Hi Jeremy,

I heard from (Finance Officer #4) yesterday that the 11% tax has been credited back on all Ham Smith Fund gifts. The adjustment amounted to $30,954.00. There was some confusion because (Finance Officer #4) had refunded the tax on the Beckman Foundation gift in the fall but had not refunded the tax on the other gifts we had received previously. Going forward, we will provide (Finance Officer #4) with a quarterly update of gifts to the Ham Smith Fund and he will refund the tax on a quarterly basis. Thank you for bringing this issue to my attention and please let me know if you have further questions or concerns.

Best,

(Institute of Basic Biomedical Sciences administrator #2)

February 3, 2017

(Institute of Basic Biomedical Sciences administrator #2),

Thank you for that update. Can you forward a spreadsheet with the current financials so that I can confirm that addition?

Thank you,

Jeremy

February 9, 2017

(Institute of Basic Biomedical Sciences administrator #2),

I have attached the entry for the $30,954.00 being added back to 3517001467-80039200 which is the Principal Fund for the Hamilton Smith Award.

I have also included the NRS report for the endowment as of December 31, 2016.

Historic Book Value at 12/31/2016. $325,590
Amount to be bought in in 3rd quarter $30,954 (Refund of Tax)
Historic Book Value at March 31, 2017 $356,544

Amount of gifts received from donors $281,400
Amount of Award from Beckman Foundation $90,000 (The remaining $10,000 went to current use)

Total amount of money in endowment before CAF $371,400.
Amount of CAF ($371,400.04) ($14,856)

Historic Book at March 31, 2017. $356,544

This illustration assumes how new money is designated to the endowment during the 3rd of 2017.

Hope this is helpful.

Best,

(Finance officer #4)

February 10, 2017

(Institute of Basic Biomedical Sciences administrator #2),

Thank you. That looks good.

When the next quarterly financial report arrives (March 31, 2017, I presume), I would be grateful if you could forward it to me so that I can see that this refund actually happened.

All the best,

Jeremy

# Support for Scientists, Especially Young Scientists

**Letter to Michael Bloomberg regarding support for young scientists – August 2013**

**Michael Bloomberg, a Johns Hopkins University alumnus, has made multiple major donations to Johns Hopkins, including the establishment of 50 Bloomberg Distinguished Professorships beginning in 2013.**

The Honorable Michael R. Bloomberg
Mayor, New York City
City Hall
New York, NY 10007

Dear Mr. Bloomberg,

I am writing with a few observations and ideas related to our shared interest in promoting ground-breaking scholarship at Johns Hopkins. By way of introduction, I have been a faculty member at the Johns Hopkins University School of Medicine and an investigator of the Howard Hughes Medical Institute for over 25 years. I am also a member of the National Academy of Sciences and the Institute of Medicine.

First, let me tell you how grateful I am for your generous support of Johns Hopkins over many years. It has made an enormous difference in the lives of faculty, staff, students, and patients. It has also raised the bar in terms of our ambitions for the university.

My comments relate largely to the sciences, the area that I know best. My basic observation is that we have many truly outstanding young scientists at Johns Hopkins. For example, in my primary department (Molecular Biology and Genetics), the most recent addition to the faculty is a young British cell biologist, Andrew Holland, who we ranked #1 among more than 200 applicants.

In terms of the impact that Johns Hopkins will have on the world, I would like to suggest that support of our young faculty is at least as important as attracting more established faculty from other institutions. One reason that I hold this view is because I believe that the university's role is to find and nurture talent before that talent has fully blossomed. The history of scientific discovery supports this approach. For example, if one examines the research that led to the four Nobel Prizes awarded to Johns Hopkins School of Medicine faculty (Dan Nathans, Ham Smith, Peter Agre, and Carol Greider) and the two Nobel Prizes won by Johns Hopkins University astrophycisists (Adam Riess and Ricardo Giacconi), that research began in each case when the scientist was under the age of forty. For three of the six scientists (Carol Greider, Adam Riess and Ricardo Giacconi) that research began at or before age thirty. Only one of the six scientists (Dan Nathans) had been promoted to the rank of Professor at the time that his or her Nobel Prize winning work was initiated.

To fully realize their creative potential, our younger colleagues need a modest level of unrestricted financial support. Therefore, what I would like to suggest is a partial realignment of your financial support from senior faculty toward young faculty. For example, one could envision a series of Bloomberg Career Development Chairs to be held by junior faculty of extraordinary promise. Each chair might provide $500,000 support over a period of five years.

Let me close with some hard evidence that in those areas in which Johns Hopkins excels – for example, neuroscience - our junior faculty are as good as those of any university. Each year the Society for Neuroscience, which represents the neuroscience research community worldwide, confers the Young Investigator Award on one or two scientists who have received their M.D. or Ph.D. degrees within the past ten years. Since 1990, six of thirty-five winners have been junior faculty at Johns Hopkins. Stanford has also had six winners during this time, but all other universities are further down the list. My point is simply that we have extraordinary talent among our young faculty at Hopkins. It is up to the rest of us to create an environment in which that talent can be fully realized.

With warm regards,

Jeremy Nathans, M.D., Ph.D.
Professor
Molecular Biology and Genetics, Neuroscience, Ophthalmology
Investigator
Howard Hughes Medical Institute

**Letter to Art Levinson regarding the Breakthrough Prize – September 2013**

**Art Levinson was CEO of Genentech and is currently Chairman of the Board of Directors of Apple. He is also the Director of the Life Science Breakthrough Prize Foundation, which awards annual scientific prizes of $3 million per recipient. He was a staff scientist at Genentech when JN was a postdoctoral fellow there in the late 1980s.**

Dr. Art Levinson
Chairman
Life Science Breakthrough Prize Foundation

Dear Art,

I hope that this letter finds you well. It has been more than 25 years since our paths crossed at Genentech.

I am writing now with a few thoughts about the Life Sciences Breakthrough Prizes. First, let me say that raising the public profile of life science and life scientists is a terrific idea. With that goal in mind, here is a question: can the Breakthrough Prizes be configured to achieve that goal, and at the same time have maximal impact toward catalyzing the next big breakthroughs? Directing the prize money exclusively to scientists who have already made major advances does not seem optimal for achieving the latter goal. I note that at the time of the 2012 awards, the average age of the eleven winners was 58 (range: 50 to 70). To have maximal impact on future science, we need to give a boost to scientists who are in their 20s, 30s, and 40s.

Here's one idea for doing this. Divide each $3 million prize between the main winner, who gets $1.5 million, and 5 younger scientists – to be chosen by that winner, without nominations – who each get $300,000. On the day that the 5 main winners are announced, the 25 younger scientists are also announced – with the result that one has 30 instead of 5 surprised and happy people and a far larger bang for the buck in terms of publicity. The effect on a young scientist of being selected for one of these prizes would be electrifying: imagine being a 35-year old cancer researcher and learning that Bert Vogelstein had picked you as one of the 5 young awardees. In terms of raising awareness for the Breakthrough Prizes, it is a safe bet that every young scientist in the world will be up early on the day of the announcement. Finally, this arrangement would also send the message that more established scientists have a strong interest in helping their younger colleagues. A related idea: the Foundation should stipulate that all of the prize money must go to support research or education or some other science-related cause,

rather than potentially going into the pockets of the recipients. In these days of tight funding, the most creative science is getting squeezed most severely, and $15 million per year – if it is directed to the most creative science - will have a major impact.

I hope that you and your colleagues will consider some variation along these general lines. Twenty years from now, the Breakthrough Prizes should be famous not just for recognizing great work but also for catalyzing it.

With warm regards,

Jeremy Nathans, M.D., Ph.D.
Professor
Molecular Biology and Genetics, Neuroscience, Ophthalmology
Investigator
Howard Hughes Medical Institute
e-mail: jnathans@jhmi.edu

# Advice for Students and Colleagues

**Notes on First Year Medical Student Teaching for the Curriculum Committee – December 2003**

1. In addition to imparting a basic fund of knowledge in human biology, the emphasis should be on mechanistic underpinnings and on critical thinking.

Re: fund of knowledge. I tell students that if they know a subject they should be able to give a 3-5 minute chalk talk on it at a level appropriate for a bright high school student.

Re: critical thinking. Evaluating primary data, seeing the incisive experiments (which are almost always conceptually simple), testing hypotheses, thinking about causality, not taking interpretations on faith. These principles can be equally applied in all aspects of the first year curriculum - from anatomy to genetics.

Examples of causality. (1) Causality in genetics (working backwards): a patient with chest pain, a myocardial infarction, atherosclerosis in coronary arteries, hypercholesterolemia, LDL receptor defect, LDL receptor gene mutation. (2) Causality in trauma care (working backwards): a toddler with head lacerations, a fall down the stairs, no child guard on the stairs, problems with parenting. In both cases if we focus only on treating the immediate problem and do not follow the chain of causality, at least part of the way, we are not going to prevent problems in the future.

2. The content of the first year curriculum is basically on target. The knowledge that first year students need – like knowing how the kidney works – isn't going to become obsolete anytime soon.

3. The mix of 50:50 lectures : small group instruction works well. My prediction is that going to more small group instruction is going to result, on average, in lower quality teaching. Small group instructors, with few exceptions, do not have the fund of knowledge to match the lecturers on every topic. There are inherent inefficiencies in small group learning related to heterogeneity across students. Only one-on-one tutoring (as at Oxford) solves that. Lecturing does not need to be a passive learning experience – students should be engaged by a good lecturer (more on this later).

4. What the students say they want vs. what is best for them. Student comments should be taken with a healthy skepticism.

For example, the desire for all-encompassing lecture notes largely reflects the desire to avoid buying textbooks to save a few hundred dollars. Every student should have a collection of 20 outstanding well-thumbed textbooks after 4 years of medical school. These will serve as a basic reference core for at least a decade, and many for longer (note: many books now have a web component and a clinical correlation component – Berg et al Biochemistry has both). We would do the students a favor by increasing tuition in the first two years by $500 and using it to buy textbooks for them. The signal-to-noise ratio is higher in a textbook than in lecture notes, and it is higher in lecture notes than in the lecture itself.

The desire for pointing and clicking as opposed to turning pages confuses the relative importance of the medium vs. the message. The power of electronic learning is in the ability to rapidly link to related topics and to search and access a far vaster set of data - this is extremely useful but not intellectually profound. The students will do this naturally; but the core first year material and the ability to think critically require little in the way of database analysis, literature searches, etc.

The current trend towards total reliance on lecture notes creates a system of spoon-feeding that will not serve the students well in the future. At the other extreme, reliance on web sites is risky because the quality is variable, the sites must be carefully vetted by the instructor first, and they are subject to unanticipated changes. Textbooks (or pdfs of them) represent a happy medium of quality and comprehensive coverage.

5. How to present information. Electronic information is processed by the brain in the same basic way as traditional non-electronic information (i.e. spoken language or written text with diagrams and pictures) with one exception: movies and manipulation of multidimensional data (e.g. rotating 3-D images) are possible with electronic teaching. This is valuable for visualizing inherently multidimensional material - e.g. anatomy. Many PowerPoint presentations suffer from excessive clutter because it is easy for lecturers to download complex images from the web. But the brain doesn't store complex data sets: it extracts the essentials, the "take-home" lesson. This is why a pencil sketch so effectively captures the essential features of a person's face and is almost always "better" than a color photograph. This is also why teaching with a whiteboard is so effective - it delivers information in a way that matches a simple memory trace, and it also has a temporal flow which is a good match to the rate at which we can assimilate new information. Example: enzymatic DNA synthesis.

6. Teaching teachers how to teach well. There is room for diverse lecturing styles, but a few traits shared by the best lecturers are worth keeping in mind. Have a plan. Know the customer, i.e. pitch the material at the right level. Speak clearly and in complete sentences. Don't speak in generalities too much - get specific. Give the students something to chew on. Engage the students by selective question-and-answer interludes. Make it clinically relevant. Describe the incisive observations or experiments. An example from the LDL receptor story: cells from patients with familial hypercholesterolemia (who were later shown to lack functional LDL receptors) have extremely high HMG-coA reductase when grown in serum (which has a lot of LDL). Hypothesis: Is it defective feedback regulation? Answer: No, because cholesterol delivered by passive diffusion lowers HMG-coA reductase to basal level. Therefore the defect is in uptake of LDL particles.

An example of a great teacher: Richard Feynman. His teaching is characterized by (1) originality, (2) complete mastery of the subject, and (3) clarity, eloquence, and humor.

**Wilmer Research Meeting – July 2004**

My remarks will focus on laboratory rather than clinical research, because this is what I know best.

Many of the issues I would like to discuss - all of which are centered around how to effectively nurture top-notch biomedical science - are not unique to ophthalmology. They affect all clinical departments to varying extents. However, the current and projected financial climate in medicine and in research funding has made dealing with these issues more important than ever. I'll start with a series of sociological observations.

1. Training. The clinical and basic science worlds are getting increasingly complex and training is getting more specialized. But to get the best research done we need to have people who know enough about both worlds to make connections. MD-PhD training is one way to bridge the gap but the time involved is formidable if one also does postgraduate clinical training: college, MD-PhD, residency, fellowship (clinical and/or research). One won't become a principal investigator (PI) until age 35 or older.

2. Career paths. The research world is a pyramid (or less generously, a pyramid sales scheme). Simple math shows that most trainees cannot do what their mentors did - there simply is not enough NIH money. NEI funding: let's assume that NEI spends -$300,000,000/year on laboratory research ($200,000,000 direct costs) - that would support about 500 labs at $400,000 per lab per year of direct costs. If each PI

has a 25 year career as a grantee, that means only 20 new PIs per year can enter vision research each year. Given the current federal deficit, we can assume flat or nearly-flat funding for many years. An additional factor: everything (especially personnel) is getting more costly.

3. Lab size and fluctuations. The gambler/casino analogy – the casino will eventually win in a one-dimensional random walk because it has deeper pockets. PIs need a critical mass of expertise in the lab and a critical mass of projects so that fluctuations don't sink the lab (at least 5 full-time students, techs, or postdocs, plus the PI = >$250,000 personnel costs). Having a hedge against fluctuations enables a PI to take risks. Not having it can lead to conservative science. This is a completely rational response, and it is reinforced by the group-think and conventionality of grant and manuscript reviewers.

4. Cultural differences between scientists and clinicians. Scientists need the freedom to be a bit eccentric, to think differently, and to try the "what if" experiment that has only a 1 in 10 chance of working. The mentality in the clinical world is different. In general, patients don't want their physician thinking "what if" ideas when it comes to their treatment - they want competence and the very best current standard of care. The two cultures have to recognize and respect their differences, and try to make them work synergistically.

5. The labor market in science. The US biomedical research community now draws on a base population that approximates the entire world. The competition among trainees for limited positions at the next step in their career has gotten more intense. Many of our top trainees are not US born and will need extra coaching in language and the ins and outs of American scientific culture. This is an opportunity: the pool of talented trainees and young researchers has never been deeper than now. But this is also a challenge: does the US system have the ability to absorb this new talent in the long-term? As the first wave of foreign-born trainees emerges from graduate school and postdoctoral fellowships the results have been mixed.

6. Being outstanding as both a clinician and a laboratory scientist is now much more difficult than in the past. Science is moving very quickly, and it involves a more complex set of tools and base of knowledge. Competition from basic scientists who have found that they can tackle clinically relevant problems means that there is only a small niche of research problems that are the exclusive reserve of clinician-scientists. Clinicians need to work ever harder just to stay in the same place financially.

7. The grant and publication system is a nearly perfect Darwinian system – it is a great deal for the taxpayer because it gets talented people to work extremely hard, but brutally competitive for the biomedical researcher. The Darwinian system inevitably drives people to be excellent in one area rather than excellent in multiple areas. In other words, being an outstanding clinician counts for very little on an R0l application or when trying to get a paper accepted. How can we create breathing room within this Darwinian environment to nurture the best biomedical science?

8. Ideas to discuss:

A. Accommodate increased specialization by moving away from the triple threat model. M.D.s who mostly do clinical research and treat patients, and Ph.D.s and M.D./Ph.D.s (many without residencies) who mostly do laboratory research. We now train tri-athletes and expect them to win the 100-meter dash against sprinters.

B. Narrow the research pyramid at an earlier point in the research careers of young academic biomedical scientists. Not every K08 awardee can go on to get an ROl (simple math), and by letting all of them try to take this route we spread out our resources (money and space), decrease everyone's chances of ultimately making it, and create an enormous amount of stress. This will mean that we (senior faculty, division directors, and the department chair) have to make carefully considered decisions early rather than simply letting the Darwinian system take its toll. We need to create an environment where we honor and

encourage doing research intensively for a few years as a trainee, followed by a career as a full-time or nearly full-time clinician. There is an analogous path for PhD scientists to the pharmaceutical industry, teaching, etc. In my view the quality that counts most in any career is excellence - whether in the lab, the clinic, the classroom, or elsewhere.

C. Basic scientists and clinicians need to talk more with each other and to constantly nurture a culture of mutual respect. They need to be genuinely interested in each other's work - in particular, the clinicians need to bring good clinical problems to the scientists. One example: genetics provides a good meeting ground because it starts with patients and goes to molecular mechanism. Every scientist at Wilmer who hasn't done an ophthalmology residency should read a textbook of ophthalmology cover-to-cover to be fluent. PhD scientists are fully capable of learning enough clinical ophthalmology to tackle any clinically oriented problem - they should be encouraged to do this. The collaborative arrangements that NIH is encouraging are perfectly suited to a department like Wilmer that is strong both clinically and in research.

D. All new tenure track research-oriented faculty members should be hired through national searches in a highly public process. This is the way basic science departments do it. We should abandon the idea that our trainees are the best and that we don 't need to look any further. However, there may be real advantages to working with and seeing at first hand a clinician before hiring that person. The evaluation of clinical excellence is less publicly accessible than it is for research excellence where publications and a research seminar are usually a good indicator. More eggs in fewer baskets: we need to invest more resources (money, space, and free time) in fewer young research faculty members so that they have what they need to be successful. In Darwinian terms this means increasingly taking the elephant approach to child rearing (one gestation takes 18 months) as compared to the frog approach (hundreds of eggs).

E. In any given year, one or at most a few top-notch ophthalmology researchers come to the job market. This talent pool is small compared to what a basic research department sees because the basic research fields are now so broad. Wilmer needs to be flexible and patient in terms of area for hiring in any given year - each division should realize that it could take several years for the best candidate to appear in that area.

F. Wilmer should stay strong in every area - research, clinical, teaching. We should encourage diverse career paths, including private practice, among our trainees. The bottom line is excellence.

**Advice for a biomedical engineering graduate student - October 2005**

Dear Dr. Nathans,

I'm X, a BME student in your discussion group. It's great experience to be in your group. I feel sorry that I did not make the most of it and I failed in the genetics exam (I got 69+1 points). It's a shock to me, because I worked hard for it. But it's a pity I did not memorize every knowledge point very clearly. I understand that my performance in discussion section is awful too. Still, could I ask whether there is another chance for me to make up for the course? I'll try my best and make things better.

Thank you very much.

Regards,

X

Dear X,

Do not worry. First, a 69 means you got 2/3 of the answers correct – that is pretty good. You also did fine in the discussion section. If, at the end of the Molecules and Cells block, it looks like your grade isn't high enough (which means to us that you need to learn a few more things) we will simply ask you to write a short paper or work on a problem set in those areas that need more work. I've been running this course for 9 years, and we always figure out a way to give every graduate student either an A or a B as their final grade.

In summary: (1) do not worry, and (2) enjoy the material and learn as much as you can.

Sincerely,

Jeremy Nathans

**Johns Hopkins Medical School White Coat Ceremony – May 2006**

**The White Coat Ceremony marks the transition from the preclinical phase to the clinical phase of medical school. This address was delivered to Johns Hopkins medical students and their instructors, mentors, family members, and other supporters.**

It is an honor and a pleasure to have the opportunity to say a few words on the occasion of this year's White Coat Ceremony. I understand from Rob Shochet that this talk really should be only a few words, and that if I exceed my allotted time of exactly 8 minutes, a trap door will open beneath the podium.

First let me say how much I've enjoyed teaching and interacting with you, the members of the first year class. You are driven, curious, and delightful – all at the same time. That's a good combination.

Second, let me say on behalf of the Nathans family that we are delighted to see that one of the colleges is being named in honor of Daniel Nathans. Dan was a remarkable person and a remarkable scientist. His application of restriction enzymes – discovered by his colleague Hamilton Smith – revolutionized genetics and ushered in the biotechnology era. At Hopkins, where he spent his entire professional career, Dan is especially remembered for a quiet leadership style that consisted principally of seeing the best in other people.

In keeping with the brevity of this talk, the theme will be "the importance of the little things in life". To explain what I mean by "little things", I'll start, somewhat obliquely with a thought that I had when I was about ten years old. When I was a child, I used to walk to the local elementary school, and this took about 30 minutes. On those days when I didn't walk with my older brother or my classmates, I had plenty of time to think, and one question that I chewed on was what my goals in life ought to be. I suspect that each of you has also pondered this "meaning of life" question. As Socrates reminded the Athenians, this is a good - if not always comfortable - thing to do every now and again. Thinking about this question seems to come naturally to young people because for them the future is seen as a world of infinite possibilities. As an aside, it seems to me that this sense of infinite possibilities is one of the greatest things about being young – even later in life one should try to retain some of it.

In thinking about this "meaning of life" question, it seemed reasonable to me, at age ten, to consider all possible outcomes, even those that now seem rather grandiose. First, in surveying what little I then knew about history, it seemed that people ended up in one of two categories: in the first category, there was the very small fraction of people who were remembered by posterity, to greater or lesser extents; and in the second category, there was almost everyone else, entirely forgotten. How many peasant farmers from the Middle Ages do we individually remember today? None. From this perspective, it seemed pretty clear in

which of these two categories one wanted to end up. At the top of the list for category #1 would be those people whose enduring influence has touched millions of lives – Jesus and Buddha, for example. A little further down, we would have Mozart and Newton. And so on, down the list.

So, this got me to thinking: is the goal simply to make the biggest impact? The more I thought about this conclusion, the less I liked it; and not just because of the unpleasant possibility that I might end up in category #2 despite my best efforts to end up otherwise. It seemed that there was something in this argument that was missing the boat; that this view constituted a rather shallow reckoning-up of life. So here's the conclusion that I reached: in the end, it isn't a numbers game. That is, what counts isn't the number of people whose lives you touch, but the way you touch them. And more generally, it isn't quantity that counts so much as quality.

How does this relate to medicine? It suggests that your contribution as a medical student and as a physician largely comes down to helping one patient at a time, or helping one colleague at a time, or teaching one student at a time, and in each of these endeavors doing the best job that you can. These are the kind of contributions that are not generally in the public eye, but they are the ones that count the most. In medicine, the ultimate reward is the satisfaction of knowing that you did the best for your patients, your colleagues, and your students. In this sense, medicine is one of the most satisfying of all professions. Although this general view is not unique to medicine compared to many other professions, the stakes are higher in medicine because the impact on people's lives is greater. Of course, I should note that making a contribution that has a wider impact is also great – for example, identifying the mechanism of a disease, developing a drug, or devising a procedure - but such contributions are not really so different because they are also typically built on many incremental steps that involve mentors, colleagues, and students.

So my advice – for medicine and for life – is to plan for and take pleasure in each little contribution. This is something that you can do as effectively when you are a medical student as you can when you are an attending physician. If you have taken a careful history and done a careful physical – that is good. If you have spent an extra few minutes helping a patient by writing down exactly what their medications are and how to take them – that is good. If you are in the lab and have run a pretty gel with the right controls on it – that is good. Like a picture that is produced by the sum of many pixels, all of these little acts combine to produce the portrait that is your life and your career.

I wish you all the best in the years ahead.

**Advice for a biomedical engineering graduate student - December 2006**

Dear Prof. Nathans,

My name is X, graduate student of BME. Maybe you still remember me. I talked to you last time when I didn't do well in your genetics block. As you know I am sorry that I didn't do well in the later blocks, part of the reason is big pressure, since I never did so bad in my courses before. Anyways, thanks for give me the chance to do extra work on the course. I'll try my best. I just wonder when shall me meet and discuss about the work. I also emailed Dr. Yang and Dr. Pederson and cc to you.

Thanks and happy holidays!

X

Dear X,

First, don't worry. We are going to give you a little bit of extra work, you will learn a few new things, and then it will be done. We also know that these courses are difficult for BME students who have not been studying biology, and that this difficulty is made greater by the fact that the course is delivered in a language that is not your native one. So, relax and learn as much as you can! For Molecular Biology and Genetics, the assignment is simple: write a 5-6 page paper (double spaced) on the genetics of cancer including implications for mechanism, cancer screening/detection, and cancer therapy. You can leave the paper copy in the IN box just outside my office door, 805 PCTB.

Any time in the next few months would be fine.

Sincerely,

Jeremy Nathans
Molecular Biology and Genetics

**Job interview advice for the teenage son of a member of the housekeeping staff – December 2006**

Dress well. Wear a good shirt, good shoes, and a tie.
Have a firm handshake and good eye contact.
Sit up straight.
Don't fidget.
Do your homework before the interview. Find out about the company on the internet, ask good questions, and show that you are interested in them.
Speak in complete sentences. No slang. ("yes" not "yea")
Be yourself. Don't brag and don't oversell yourself.
Show that you are ambitious and have a vision for yourself.
Thank the interviewer at the end of the interview

**Notes on teaching – August 2007**

General advice
- Have a plan. Know what you want to cover during that session. Tell the students at the beginning what you are going to cover, at least in outline.
- Know your audience (how much do they know already? How heterogeneous is it? Are there students who have difficulty with English?)
- Clarity. Speak clearly and in complete sentences. Write clearly on the board.
- If something is counter-intuitive or not explained by what you have said or what they know, or if something is too complicated to explain - just state this.
- Don't say something that you aren't sure of. Don't say "I think so" or "I'm pretty sure". Just say "I'm not sure" or "I don't know" and then tell the students you'll look it up and let them know the answer in the next session. (And make sure to look it up and report the answer next time.)
- Group dynamics: bring out comments from quiet students and titrate down the contributions from talkative students. Call on students either with specific questions, or a series of questions that lets you walk them through the logical process step-by-step. Stop and ask if they think something you have just said is reasonable.
- Control the discussion. Don't let a student spend much time saying things that are incorrect because this will confuse others. Steer the discussion towards the correct way of looking at things.
- Ask good questions.
- Blackboard technique. Keep it simple and make it neat.

- Create a visual image of things that are inherently visual (e.g. DNA replication).
- Don't use big fancy words when small plain ones will do just as well.
- In answering a question or covering a topic it is often good to start with a summary and then go into detail, rather than just diving into the details. This helps organize the details in the minds of the listeners.
- Encourage questions, especially "dumb" questions that students are embarrassed to ask. Inevitably other students will learn from them.
- Learn the students' names as soon as possible (photos help), and address students by name.
- Avoid doing math at the board unless you are a genius, you have written notes, or you have it memorized.
- A good test of whether you (or the students) really understand something: give a 2-3 minute explanation at the blackboard at a level that would be appropriate for a bright high school student.

Lecturing
-Rehearse the lecture and make sure it fits the allotted time. Start with an overview and end either with something appropriate and memorable or with a brief summary; don't just let the lecture wind down and die. Memorize the first sentence (at least). Make the delivery crisp. Remember that you know exactly what each figure shows but the audience is seeing each figure for the first time: therefore, walk the audience through each figure, define X- and Y-axis, etc. Interact with the audience, ask questions, stop and see if they are or are not confused. Humor is OK, especially if it illuminates a point that you want to make, but don't overdo it.
-The lecture should tell a story, or a few connected stories. Don't just recite disconnected facts or experiments. Show less data and talk more about the concepts. Connect what you are saying to other phenomena.
-Helpful examples: Richard Feynman's "Six Easy Pieces" and "Six Not So Easy Pieces". These are sets of classic physics lectures. Available in bookstores and at Amazon.com.

**Letter to Sin Urban – August 2008**

**At the time of this letter, Sin Urban was an Assistant Professor in the Department of Molecular Biology and Genetics at Johns Hopkins Medical School.**

Sin,

Thanks for the note. As regards that sinking feeling, after about 15 years one stops noticing it. I'll cc this note to Theo Karpovich who will throw you a book of lecture notes that you can use as a flotation device.

Jeremy

**Science Integrity – October 2008**

**Notes for a lecture and discussion with Johns Hopkins graduate students.**

Notes on "Scientific integrity: What it means to be a scientist"

Background reading: On Being a Scientist (National Academy of Sciences, 1989) (http://www.pnas.org/content/86/23/9053.full.pdf+html)

The purpose of this talk is to discuss some of the issues related to scientific conduct that you are going to encounter on more or less a daily basis. While the main theme is that common sense and honesty are the best guides, I hope to challenge you with examples in which the right path – if there is one – isn't so clear.

We won't spend much time discussing blatantly dishonest or fraudulent work. It is obviously wrong from an ethical point of view, and the only interesting question is how to spot it.

Issue 1: Ownership of ideas.

Suppose in a discussion with a grad student who works in the lab down the hall, she mentions her idea for a terrific experiment. The experiment fits perfectly with your thesis work – and in fact it is just the sort of idea you probably would have had a month or two from now when your work matured a bit more. But it was her idea. Can you go ahead and do the experiment? Do you have to ask her permission? What if she says she would prefer to do it herself? What if it is totally outside of her thesis work and came up in a discussion that the two of you had about your thesis work, does that make you a part owner of the idea? What if her idea isn't really the final version, but by building on it you think of the critical idea – does she have any ownership of that final idea? What if her idea turns out to be THE incisive experiment in a paper that you eventually publish – should she be a co-author?

More generally: what if you read an idea in a paper or hear an idea from a seminar speaker? Or from a poster at a meeting? Is it in the public domain at that point? (yes). What if you learn something from a talk or poster at a departmental or graduate program retreat? (maybe and maybe not) What if you are sitting at your desk and you overhear someone else's discussion that plants a seed of a good idea?

Finally, if you have an idea about an area that you want to investigate, are you allowed to sit on that idea with the expectation that others in the lab will not work on it? Obviously, the outside world is under no obligation to wait for you to do the experiment, but within a lab, or among labs at the same institution, there is generally (but not always) a feeling that one shouldn't step on other people's toes. I think there has to be some reasonable time frame - maybe 1 month, 3 months, or 6 months – after which the question of who gets to do what needs to be revisited.

In my own lab, I have generally tried to avoid issues of territoriality by having students and postdocs work on projects that are quite separate. The advantage is that everyone has a lot of elbow-room. The disadvantage is that we don't get as much synergy as we might, and projects tend to move more slowly since they are driven by just a single person. By contrast, when I was a postdoc at Genentech, projects moved along at amazing speed because they were done as collaborations between ten or more people.

I keep written notes of ideas, with attributions and dates, e.g. "Mary Smith's idea regarding photoreceptor development". Most people who contributed an idea are very appreciative of a general acknowledgment at the end of a paper. "We thank Mary Smith for helpful discussions during the course of this work."

Remember: in some fields, like math and theoretical physics, ideas are everything. Even in biology, which is largely driven by experimental data rather than ideas, ideas are critical.

One guiding principle in thinking about these issues: the right approach should be one that encourages openness and scientific exchange, i.e. it has to promote trust. Trust is not something you can see or touch, but it is absolutely critical. Talking openly with other people, who will have a different perspective and fund of knowledge, is essential to overcoming mental roadblocks and thinking about things in a new way. In laboratories or departments where trust has been eroded there is an unpleasant and unproductive air of secrecy.

Issue 2: The risk of self-deception

We all have some preconceptions about how we imagine our experiments will turn out. In many cases, whether we say so openly or not, we have a very definite idea of what it will look like if the experiment

"works". For example, we hope to see a beautiful immunostaining pattern in a wild type cell and some altered pattern in a mutant cell. The first big lesson in graduate school: most experiments don't work as planned. Most of the time the reason is simply technical: the antibody gives a high background, the cells are too heterogeneous, etc. How do you know when you've got an experimental result that gives the "real" answer? When it conforms to your expectations? (no)

Related to that, is it OK when you publish this work or show it in a talk to just show your best immunofluorescent picture? This is what is generally done, with the unspoken assumption that the best picture is closest to reality; the lesser ones presumably reflect technical artifacts. But that may not be true.

This is a very general and nontrivial problem. Consider an experiment in which you collect data in a series of runs and there is an initial period in which the data doesn't look "good" and then later on it looks "better". Can we discard the earlier data after the experiment is finished? We need objective criteria to do that, and when we publish it we need to state those criteria. For example, we could use signal-to-noise ratio, or we could a priori say that the first ten runs on any given day will be discarded. This is standard procedure in psychology when an animal or person has to acclimate to the apparatus and the testing situation.

Related to this, when preparing images for talks or for publication, what manipulations are permissible? Photoshop has a lot of options. Can we change intensity? Color balance? Contrast? I think you can change those parameters (which amounts to extracting what you think is the signal from what you think is the noise) as long as you do it identically for the control and experimental data and as long as you make it clear to the reader or viewer what you did.

Issue 3: collaboration and authorship

Pick your collaborators carefully. Make sure that they are people who you respect and trust. Many collaborations don't work out not because the collaborator isn't a good scientist, but because the project is not a high priority for one collaborator. Try to define who will do what as early as possible. The challenge: one doesn't want to be so rigid that the project can't evolve spontaneously. For some collaborations, one needs to discuss co-authorship pretty early on so that people are not unpleasantly surprised later. This can be awkward when the experiments have not even been done yet, but it can avoid the "I thought I was going to be first author" issues later on, which can leave some people very unhappy.

How much does one need to contribute to be an author on a paper? I think you need to make a substantial contribution, but different people put the bar at different levels. Some journals have a list at the end of each article indicating who did what.

If you have only contributed a reagent (e.g. a knockout mouse), but the other person has gathered the data, ask whether you should really be an author. What if the work turns out to be wrong, or just not up to your high standards, or the paper is poorly written? Despite what you may think, if it is wrong or poorly done you will be tainted by the association. In particular, if a paper has to be retracted, all of the authors are associated with that fact. I prefer to make reagents available without being an author, and I have let my students collaborate with other labs and be authors without my name being listed as an author. In my view, if a self-propagating reagent (e.g. plasmid, cell line, mutant organism) is already published, simply making it available should not be associated with authorship.

General advice:

Being a scientist is a great privilege. You are members of a community dedicated to discovery – it is the ultimate intellectual challenge and it provides incredible intellectual rewards. But it can also be very frustrating. Nature does not give up her secrets easily. It is extremely difficult to discover something new. Most experiments don't work. Savor the moments when something works, or when it is simply aesthetically pleasing. Even if it is something small – like a beautiful protein gel – pat yourself on the back.

Keep very good notes. Take the time to write carefully and neatly and to explain in your notebook what you are doing and why you are doing it, and then what you think the results mean. Writing forces you to think things through – a useful exercise. For example, whenever I order synthetic DNA, I type up an addendum explaining in detail what the DNA will be used for. I have ordered more than 3,000 oligos over the past 20 years and these write-ups have been very helpful, both days later and years later.

Keep thinking hard about what you are doing in the lab. Maybe the current approach is wrong or too narrow and there is a better way to get at the question. Consider whether there is a critical experiment that will make you abandon the current approach. Ed Scolnick, former head of research at Merck, regularly asked for the experiment that would terminate a research program – because getting the company to focus on the right research and development projects is largely a matter of not wasting time and money on projects that won't work. Write down your ideas and keep an archive. Read widely, skim lots of journals. Read catalogues – especially Molecular Probes, Pierce, New England BioLabs, Cell Signaling – they are the new textbooks. Cultivate a fund of knowledge that is distinctively your own.

Enjoy the thrill of the chase. Remain upbeat when times are tough. Be supportive of each other.

**Correcting errors in the lab – September 2009**

Dear X,

I want to follow-up our very brief discussion regarding what to say when you see someone doing something the wrong way.

First, there are degrees of error. At one extreme, if someone is doing something that is dangerous (for example pouring sodium hydroxide without wearing glasses or safety goggles), they must be told immediately that they need eye protection. At the other extreme, there are different ways to do things, some of which work better than others, and the difference is a matter of efficiency.

In between are examples like the one we witnessed yesterday: storing antibodies in a frost-free -20 isn't dangerous, it's just the wrong way to do it because it will lead to loss of antibody activity. What makes this situation a bit awkward for someone like you or me, who is offering advice, is that the person who as doing this very likely knows that this is not the right way to do it because I have said it publicly many times. The appropriate way to give advice in this case? Be polite, but be absolutely clear: there is a right way to do it (4 C for short-term storage, and -80 for long term storage) and a wrong way to do it (frost-free -20), and we need to do it the right way. When a situation like this arises, it is the responsibility of every senior scientist in the laboratory to make these points clearly to more junior scientists - both for the good of the junior person and for the over-all good of the lab.

Jeremy

**Advice for young scientists – May 2011**

1. JN's background.

Undergraduate at MIT; M.D. and Ph.D. (in Biochemsitry) at Stanford; postdoc at Genentech. Molecular Biology and Genetics at JHMI since 1988. PhD thesis: Trying to transform Drosophila; hearing about vision research in lectures from Denis Baylor (King Yau's postdoctoral work) and Lubert Stryer; reading Wald's Nobel lecture; overall plan for identifying cone pigment genes. Exciting moments: first homology alignment of a cone pigment sequence; first Southern blot with DNA from colorblind humans; first absorbance spectrum of recombinant rhodopsin.

2. What I have learned in 33 years of working in the lab.

A. Most of all, the incredible thrill of discovering something new - not necessarily something big and important, but something that no one knew before. Two aspects are beautiful: the thing that is discovered, and the act of discovery. Galileo: "I would rather discover a fact, even a small one, than debate the great issues at length without discovering anything at all."

B. Most experiments don't work (at least not as hoped). Design each experiment so that if it fails (and this is typically a technical rather than a biological failure) you can learn as much as possible. Include controls. Start with pilot experiments. Even differences between experimental and control samples that are real in one experiment may disappear in the next experiment – they were just statistical fluctuation.

Look at your data carefully and think about it critically. Don't try to see what you want to see. Don't fall in love with a favorite hypothesis. Try to do (or at least think about) the key experiment that will disprove your hypothesis or even make you drop the project. In my experience, many apparently interesting experimental outcomes are technical artifacts. Treat them as such until proven otherwise. At the very least, that is a valuable intellectual exercise – it forces you to think hard. Learn to diplomatically give and accept critical input. Don't just let something slide by if it looks wrong. When other people look at your work with a critical eye and give you their opinion, they are paying you the highest compliment: that your work is worth thinking about. If the critical questions ever stop, then you are in trouble.

No one except you will ever know how much work it took to achieve each small scientific advance that you make. One of the biggest shocks for any scientist – but especially for those just starting out - is how hard it is to find out something new, and how uncertain the journey is. One can work for months or years without making progress. Nothing in one's previous experience as a student is remotely like this. As an undergraduate you study and learn new things every day with nearly constant positive feedback. Lectures and textbooks are filled with an unbroken series of insights and successful experiments.

As a result, there are big psychological highs and lows in science. One naturally wonders whether the lows will be followed by highs - hopefully they will. After 30 years in science, I have seen enough that I know that lows will be followed by highs and highs will be followed by lows. Therefore, enjoy every little victory – a well-run protein gel, a nice immunofluorescent image, etc.

C. Mental toughness/endurance. Science is a marathon, not a sprint. Thomas Edison's comment: science is 99% perspiration, 1% inspiration. Edison's response regarding his 3,000th failure to find the best material for a light bulb filament: "I have successfully identified 3,000 materials that were not good enough". Keep a positive attitude. Support each other in good times and tough times.

Practical issues: it is difficult to get papers accepted, to get grants funded, to get a good job, etc. Keep trying, and remain confident that things will work out. It is a bit like boxing: you keep getting knocked down, but as long as you can get back up and continue swinging, then you are still in the game. In the

face of these challenges, it is important to realize that everyone is in the same boat, that random statistical fluctuations are part of the system (e.g. one negative review can lead to rejection of your paper), and there is no larger force operating either for or against you – it is just the system responding to the competing demands of thousands of scientists.

Be nice to journal editors and others who make decisions that affect you. They are just trying to do their jobs as best they can, and their jobs are not easy.

D. Importance of reading widely – each person has a unique fund of knowledge and can make a unique set of connections (in my case, vision research and molecular genetics). Reading the Molecular Probes, New England Biolabs, or Pierce catalogues is more valuable than reading the latest issue of Nature, in part because everyone else reads Nature. The danger of purely electronic scientific literature is that it too efficiently channels your searching into the narrow domain of your own area. Paul Talalay's comment: "the most important paper is the one next to the one you are looking for". Actively look for diamonds in the rough, away from the crowd. Life-long learning – classes are just the start. Read the classics, i.e. the works of the most original thinkers: Charles Darwin "Origin of Species"; Isaac Newton "Opticks"; Michael Faraday "The Chemical History of a Candle"; Jean Perrin "Atoms"; Erwin Schrodinger "What is Life?". The Journal of Biological Chemistry has a section with classic articles and accompanying commentaries.

E. Master the basics of chemistry, physics, and mathematics that relate to your experiments. For example, when you thaw a sample that has been stored in the freezer, you need to mix the liquid before taking an aliquot, because the freezing point depression of salty solutions leads to the selective concentration of salt at the bottom of the tube. Become skilled at using data analysis software. Excel is especially useful because it will be here in roughly its present form for the foreseeable future, and it has a good combination of user friendliness and mathematical power.

F. The importance of techniques. Ideas suggest experiments, and the experiments require the invention of new techniques; but the reverse also happens: new techniques permit new experiments, and new experimental results produce new ideas. Examples: DNA cloning and sequencing, PCR, monoclonal antibodies, x-ray crystallography, patch-clamping, electron microscopy, gene targeting, etc.

G. Respect technical excellence. Consider an Olympic gymnast, a great surgeon, or a violinist: every motion has a purpose, none are wasted. Master the techniques that you use and know how to get the most out of them. Cultivate "golden hands" at the bench. Observe carefully and take good notes when learning from others. Don't just listen, but watch what others do and write it down. My "vacuum cleaner" approach for writing down everything, e.g. learning how to synthesize peptides with Jonathan Rothbard.

H. Write down your ideas. I have generated 50-100 pages/year x 30 years – most pages have just a few sentences or a diagram. I keep a piece of paper and a pen handy at night because I can't get back to sleep if I have an idea and don't write it down. Of course, most ideas are relatively trivial, unoriginal, or impractical, but thinking about them and writing them down hones your creative powers. Really good ideas are rare and they will occur at the oddest moments; they generally do not occur in final form or all at once. Talk them over with other people to get a different perspective.

I. Take the extra time to keep a neat and thorough lab notebook (or the electronic equivalent, with paper printouts). Write down what the purpose of each experiment is, what the results are, and what they mean. I generally do all this in list form. Apply the same approach for ordering synthetic DNA, designing a construct, etc. Collect protocols.

J. Picking a good research question: balancing interest, originality, and feasibility. Example: One of the most exciting challenges in biology is finding life beyond our planet – but at present it is so technically daunting that I would not work on it.

Parallel pursuit of multiple projects until one project pans out. Knowing when to drop a project – try to do the incisive experiment as soon as possible. Don't just muddle along hoping that things will work out.

The classical approach: focus on one subject and dig deeply by probing it from different angles and following its implications, e.g. Carol Greider (telomerase) and Phil Beachy (Hedgehog). With luck and foresight, you will have chosen a problem that has depth and keeps yielding new insights. Note: some scientists pick very broad areas (e.g. Sol Snyder's work encompasses the vast field of signaling in the brain) or even multiple unrelated areas. The work of some scientists (e.g. electrophysiologists and crystallographers) is defined by their technical approach, or by technology development itself. Unfortunately, the granting system discourages switching to new areas – the NIH generally won't give you money unless you already have a track record in the area that you are proposing to study. This is short-sighted. The result is that ten or twenty years after starting their own labs, many PIs are still working on the same problem that they were working on as postdocs.

Choosing a good scientific question. This is not easy. There is a balancing act that can be visualized - in simplified form - by the following Venn diagram. Consider three partially overlapping circles in which the three-way overlap is relatively small, the pair-wise overlap is larger, and the region within each circle that has no overlap with the other two circles is far larger. The first circle represents the set of all scientific questions that are interesting or significant. The second circle represents the set of all scientific question that are experimentally tractable (i.e. they can be tackled with techniques/technology that exists or will soon exist or that can be developed to address the question). The third circle represents those questions that are non-obvious, or at least are under-populated by other scientists - i.e. these fields are not too crowded. The sweet spot is the (small) territory represented by the intersection of the three circles. Two out of three overlap in this Venn diagram space is not good enough: that space represents, for example, (1) questions that are interesting and non-obvious but not technically feasible (e.g., looking for life on exo-planets), (2) interesting and technically feasible but obvious and already crowded (we all know many areas like this), or (3) technically feasible and not obvious, but not interesting or significant.

One approach to the challenge of finding the sweet spot is to try to enlarge it by modifying the Venn diagram. For example, developing a novel technique, modifying or perfecting an existing technique, or bringing together a distinct combination of techniques all result in an expansion of the space represented by the technically feasible circle. The advent of single particle cryo-EM is in this category. A more mundane instantiation would be the expanded technical possibilities that are made possible by the mastery of a surgical skill. Avram Hershko, who with his colleague Irwin Rose and his student Aharon Ciechanover discovered the role of ubiquitin in intracellular proteolysis, was especially attracted to the protein degradation question because when he started working on it in the late 1960s this area met the two criteria of being interesting/important and also non-obvious or at least not very populated (as opposed to protein synthesis, which was a hot topic at that time). However, it took Hershko and his co-workers almost ten years to solve the technical feasibility challenge.

K. Data is sacred. Don't lose it. Back-up your electronic data. There is no such thing as being too organized or too neat when it comes to archiving materials or data. For example, in my lab we number our plasmid constructs, and I keep a back-up collection of current and past plasmids. With a few minutes of looking around, I can generally find any of the ~3,000 plasmids that we have constructed over the past 20 years.

L. Don't let a good experiment or publishable figure get away – do it right or repeat it until it is publication quality and then you don't have to go back and do it later. An experiment done perfectly with all the controls in place so that it nails the result is far more valuable and enduring than one that comes

close but doesn't quite get there. When I review papers, if I see sloppy data, I reject the paper. If the authors can't do the experiment right, then they aren't ready to write-up the paper.

M. Think in terms of how the thing that you are doing today fits into the larger picture of your body of work. What is your goal for today? The most concrete version of this approach is to ask: what paper am I going to write that incorporates what I am doing today? What figure in that paper is going to emerge from what I am doing today?

3. Observations on the scientific enterprise and the sociology of science.

A. In the United States, we have a finely honed Darwinian system for funding, hiring, publishing, etc. It is great for the taxpayer – they get top talent and hard work at a very reasonable price. Older scientists and mentors should protect younger scientists from the harsh realities of scientific life (looking for money, excessive competition, the push to publish too soon, etc.)

B. Academia vs. industry. Working individually or in small groups vs. working as part of a large team. In industry there is some loss of autonomy, but there is also the excitement of being part of something big and important. Suppose that you were part of the team that put the first person on the moon or built the Hubble space telescope? That would feel pretty good.

C. Scientific training as currently practiced has a built-in paradox. It exhibits exponential population growth, but exponential growth is unsustainable. This is obvious based on our nearly flat government funding. For a steady state with no growth, each research-focused professor would train one replacement over a 30-year career. The inference is that most trainees cannot become research-focused professors. Therefore, one needs to look broadly regarding one's career. Industry, teaching, academic science, research institutes (like NIH), business, law, medicine, public policy. Scientific training is superb training for all of these because the scientific method of skeptical inquiry and hypothesis testing is the only successful method for learning the truth about the world.

Question: If I get a PhD and do not become a professor is that OK? YES! In your professional life, as in your personal life, the journey is unpredictable. Hopefully you will find a path that is right for you – it should be satisfying and the right fit for your talents. If you do scientific research (at taxpayer's expense) for 5 years and then go on to something else, consider it a great experience and part of your life journey. Despite its faults, I have come to view the current system as perhaps the best and certainly the only fair way to train scientists: it is as close to a meritocracy as anything our society has been able to create, and just about everyone has an opportunity to participate.

D. Competition and priority in publishing. My general advice: try to pick an area that is not too competitive. You don't want to open up or click on the next issue of some journal and see an article that has exactly the same experiments as the ones that you are doing. The way the system works, it is hard to publish work that confirms previously published work – or at least it is hard to publish it in a good journal. How did this system of priority publishing get started? In the 1600s: scientists circulated engrams with answers to establish priority, and Newton sparred with Leibniz over who deserved credit for the invention of calculus. To put an end to this problem, the Royal Society of London decided that whoever publishes first gets the credit for the discovery.

My own research interests have shifted over the years, and the shifts were driven partly by my desire to move further from what other scientists were doing.

General advice regarding competition: it is nice to be first, but it is better to be right. The most important question: how you and others will look at the paper in 5 or 10 years. Related to this, try not to be swept up in the nearly universal striving to publish in the most competitive/prestigious/high profile journals; this has reached the proportions of a biblical plague. I would rather have a complete story published as a 12

page paper in a somewhat lower profile journal than have our work compressed into 4 pages in a higher profile journal with a lot of beautiful figures and important text relegated to supplementary material.

E. The importance of NOT comparing yourself to other people, or your accomplishments to those of others. This cannot be completely ignored because virtually everything that one needs so that one can do science – getting into a good lab, getting a fellowship, a good job, money, space, etc. – is determined in a competitive fashion. But psychologically the comparison game is a hard one to win – there will always be someone else who is better. Segre's and Fermi's joke: Fermi jokes that all of Segre's papers aren't as good as one of Dirac's; Segre's come-back is that all of Fermi's aren't as good as one of Einstein's. It is psychologically healthier and more productive to see every scientist as bringing a different set of talents and approaches with the only true challenge being to discover one of Nature's secrets.

One of the pleasures associated with reading about the greatest scientific discoveries is not only that they are incredibly beautiful but they also put one's own work in an appropriately humble perspective. Newton's quote about what he did in 1665 (at age 22): "In November (1665), I had the direct method of fluxions (differential calculus) and the next year in January had the theory of colours, and in May I had entrance to the inverse method of fluxions (integral calculus). And in the same year, I began thinking of gravity extending to the Moon, and from Kepler's rule … I deduced that the forces which keep the planets in their orbits must be reciprocally as the squares of their distances from the centers about which they revolve… "

4. General advice for success in science

A. Nonscientific challenges for PIs: administration, finance, and personnel. Maintaining equilibrium; keeping one's cool. Andrew Murray's advice: learn how to deal with someone who is crying in your office – especially if that person is you. Remember, tomorrow you may need the help of a person who today is being a thorn in your side. If you can possibly avoid it, don't publicly embarrass another person. Management advice: set high standards/expectations. Teach by example, be consistent, and be nicer than you have to be. This also goes for raising children.

B. Keeping one's mental balance/perspective; importance of life outside of science. Read lots of books (novels, history, biography, etc), paint, dance, go to the gym, volunteer in the community. Develop friendships. All of this takes time and effort.

C. Time management. Self-discipline does NOT mean driving yourself to work all the time. It means strategically investing your time to develop your talents and to accomplish your goals. Don't waste your time or other people's time – time is a precious and finite resource.

Time management is especially challenging if you have children. Children are wonderful, but if you are a parent you have to be prepared for significant constraints on your time, and typically at a point in your career when working very hard is part of the job. When my children were young, I found that I could jettison many inessential activities, like going to the movies. We also never bought a television, and we never missed it. Spending time with my children was my main form of relaxation for over a decade. Now that they are older, I've added a few more activities.

D. How many hours should one work per week? Experimental science is very labor intensive. Unless you are a genius, 40 hours per week is not going to suffice. 60 or 70 hours per week is more realistic. As noted above, use your time wisely. Leave time for reading, thinking, and talking with people.

E. Michael Faraday's advice to a young scientist: "work, finish, publish". Books on this topic: Peter Medawar "Advice to a Young Scientist"; Ramon y Cajal "Advice for a Young Investigator".

F. Skills. The skills you need in later life (i.e. when you have a "real" job) are not exactly the same as the ones you need for success as a student or postdoc. Learn to write and speak clearly. Answer e-mails on time – the response can be brief, e.g. "done" or "got it". Bring a note pad and take notes at meetings: the message to yourself and others is "What is being said is sufficiently valuable that it is worth recording." For example, I always take notes at my students' thesis committee meetings. Write notes and lists for yourself. Use a weekly calendar book. It organizes your thinking. Read clear writing, e.g. well written textbooks. Lubert Stryer's (now Berg's) Biochemistry. For non-English speakers there are people who, for a fee, can go over your written English and correct it.

G. Three general factors for success: (1) hard work/motivation, (2) mental ability (intelligence/curiosity/originality), and (3) luck. The first is under your control, and the second can be honed but is only partly under your control. All three interact in a complex way. As noted by Pasteur: "Luck favors the prepared mind".

5. Motivations for being a scientist

A. Putting a brick in the Great Wall – scientific accomplishment as a form of immortality. The incredible satisfaction of being part of something grander than oneself. This is the psychological basis of all great religions.

B. Science gives one the freedom to develop an individual style. You also have the freedom to develop an eclectic body of knowledge and an eclectic perspective – after the first year of graduate school course work you are free to learn whatever you want for the next 50 years. Contrast this with law, medicine, or most other professions.

C. Doing some practical good.

D. Satisfying one's curiosity. Geographic exploration was the great frontier before 1800. The new frontiers are scientific ones and the new explorers are scientists.

E. Aesthetics – Nature is beautiful, and the scientist has a special window on that beauty. An example: Newton's explanation of the rainbow.

**JHMI Dean's Lecture on mentoring – November 2012**

General items.
Mentoring relationships occur at every level. Postdocs mentor graduate students. Senior residents mentor interns. Deans mentor department chairs. Professors mentor lab members. Clinicians mentor medical students. Senior administrators mentor faculty and junior administrators. The list goes on… For a mentor, the people you help are your living legacy, and their success is a source of great satisfaction.

Getting input from others is generally easy. All it takes is asking someone "Could I get your advice?"

In medicine, mentoring of trainees is generally spread out over many mentors. In biomedical science, the principal investigator/lab head is the principal mentor to a small number of postdoctoral fellows, students, and technicians, and with each one this relationship continues for many years. Advice for students and postdocs: choose your mentors carefully. Do your homework – talk to all of his or her lab members. Advice for faculty: choose your students and postdocs carefully. Conduct structured interviews. Talk to all references. Be prepared to turn applicants away (politely, of course).

Scientific style. The mentor imparts many things by example or in the course of working together without explicitly saying how things are done. These could be called "scientific style" and would

include: how to choose an interesting field or scientific question, how to design experiments, how to analyze data, how to write a paper or grant, how to present research in a seminar. In the clinical world this would include "clinical judgment".

One of a mentor's responsibilities is serving as a reference. Letters of reference should be specific and honest. State how well you (the letter writer) know the person. Offer to follow up with a phone call, if that is appropriate.

Specific issues.

Career direction/advancement.
Cultivating ideas.
Time management.
Money (essential, but not discussed much here).
Data management.
Risk management.
Competition.
Publishing.
Interacting with others.
Stress.
Keeping a perspective.

Career direction/advancement.

Each faculty member has been selected to be good at just one thing or a narrow range of things. Faculty experience outside of academia varies from none to some, with most faculty clustered at the "none" end of the spectrum. But we are training most of our graduate students and postdocs for careers outside academia. The challenge for the students and postdocs is how to get good advice about career opportunities in the wider world.

Biomedical research is a big and complex enterprise. Like the internet, no one person or set of people really control it. It has a logic all its own – mostly Darwinian logic. Nobody sat down and planned it this way. It developed over decades as a result of many competing interests.

The career pyramid problem. In biomedical research, job security is good but not great. In academia, there is a Darwinian narrowing of the pyramid at every step in one's career path. In industry, the vagaries of the economy produce substantial uncertainty. Let's do a back-of-the-envelope calculation to estimate the number of academic biomedical research labs running on NIH grants. NIH budget: $30 billion per year. Let's assume that half goes to laboratory research, half to clinical research. Assume that it takes ~$350,000 in annual direct costs to run a lab, or about ~$500,000 in total costs (direct + indirect). $15 billion divided by $500,000 = 30,000 labs. If the average PI runs a lab for 20 years (not everyone gets their grants renewed) then there will be on average about 1,500 PIs exiting the field each year and, therefore, at steady state, 1,500 new PIs each year. How many graduate students get PhDs in the biomedical sciences in the U.S. each year? Answer: 9,000 (2009 data). With the addition of PhD trainees from other countries, the total number of postdoctoral fellows in biomedical research in the U.S. is ~50,000, which equates to ~10,000 for each yearly cohort of postdocs, assuming a ~5 year mean fellowship time. This calculation implies that only 15% of postdocs can be accommodated in an NIH-funded academic researcher track. The percent may actually be lower, since many labs consume more than $500,000 per year and the mean duration of individual labs may be greater than 20 years.

In medicine, job security is excellent, and the pyramid has a different shape. It is relatively hard to get into medical school, but once in, one's future as a physician is virtually assured. However, particular

paths within medicine have their own sub-pyramids, and in academic medicine the pyramid continues to narrow as it does in biomedical science.

Cultivating ideas.

Encourage independent thinking among your colleagues and students. Never denigrate an original idea, no matter how dumb it sounds. Maybe it sounds dumb because it takes a while to "get it". My most negative comment in response to someone else's idea is a noncommittal "that could be interesting" or "let me think about that". Good ideas – like plants - don't germinate and grow unless they are in an environment that is conducive to growth. In general, one must generate many mediocre ideas before hitting on a really good one.

Thinking together. The whole is greater than the sum of the parts. In academia, the "functional unit" is the individual investigator (student, postdoc, or PI) or a small team of investigators. In industry, the talents of a large and diverse group are focused on each project, and successful companies have cultivated the process of analyzing projects in a group setting. This requires effective and open communication.

Exchange ideas and criticism without bruising anyone's ego. Be polite, but be honest. Don't make the issue personal. Try to look at the question from all sides. Louis Brandeis [1856-1941; American Supreme Court Justice 1916-1939] was described by one of his colleagues as being completely unburdened by psychological baggage. That is a very useful trait, and it probably accounts in part for his extraordinary success.

Write down your ideas. The act of writing clarifies your thinking. It also gives you a longitudinal record, and helps you modify the ideas as they evolve. Share your ideas. Get the input of other people - their thinking will be orthogonal to yours and in a few seconds they may give you an insight that you would never have had on your own.

Time management.

Make efficient use of your time and other people's time. Take notes at meetings. It shows that you are taking the meeting seriously and it makes clear that your expectation is that what will be said will be worth noting. I always take notes at my students' thesis committee meetings – these are once yearly 2 hour meetings in which 3-4 outside faculty members advise the student on his or her thesis project. (The student is usually busy presenting, so it is better not to also burden the student with note-taking.) After 25 years as a faculty member, I am still surprised to see how many other faculty members do not take notes at their students' thesis committee meetings.

For those with young children, time management issues are acute. Children need time and attention. One partial solution: older colleagues can do more community service, such as administration and teaching, to relieve younger ones.

Money (essential, but not discussed here).

Data management.

Data is sacred, and the interpretation can only be as good as the data. The interpretation might evolve with additional data or new conceptual insights, but high quality data lives forever. The mentor and student should together go over how data is collected, recorded, and interpreted. [An example of immortal data: the Michaelson-Morley experiment showed in 1887 that a single beam of light appeared to have the same velocity in the reference frames of two observers who were themselves moving at different velocities. The correct explanation wasn't forthcoming until 1905 (Einstein's theory of special relativity).]

Avoid suggestive or leading questions in discussion of future experimental outcomes. Do not show disappointment or elation when the data negates or supports your favorite hypothesis. The goal is to get THE truth. When I talk with my students about an experiment or data analysis, I am careful not to suggest that there is a desired outcome. My mantra is: "The data is what it is." Whenever possible, design the incisive experiment in a blinded fashion. I would guess that inadvertent self-deception is the most common form of scientific deception.

Writing that suggests bias. Original version: "To confirm the …hypothesis that osteopenia…" (2012 paper in J. Cell Biol.) Correct version: "To test the … hypothesis that osteopenia…" Very rare: "In an attempt to disprove our hypothesis…" Experiments can strengthen hypotheses, but they cannot prove them. They can, however, disprove hypotheses. Proofs apply only to mathematics.

Risk management.

Prioritizing projects. In industry, there are regular assessments of probability of success (POS), benefits and costs, and, as a result, there are regular and formal re-prioritizations of projects. In academia, we generally don't do this in a formal way. However, it would be useful if each project was subjected to the question: is there a single incisive experiment that, depending on the outcome, could kill this project?

Some projects are risky. The non-risky ones generally have low rewards or are so technically accessible that it is likely that others are doing them already. Taking on a risky project means taking on a psychological risk. This can be (will be) stressful. Re-evaluate the strategy and the project at regular intervals.

Competition.

Scientific competition within your field. The problem comes down to the risk of getting scooped. This is stressful, but don't rush to publish an incomplete story. Quality trumps speed. It is nice to be first, but it is better to be right. Consider moving out of a crowded field.

Incorrect work from other investigators. This is a big problem. Be skeptical of data that looks too good to be true. There is also a sociological effect at work that is hard to control: if 20 investigators look for effect X, which occurs at random, then one in 20 will find it with a P value of 0.05. If only that group publishes their data – not unlikely since a failure to see an effect isn't generally considered publication-worthy – then the one paper in the literature on effect X will honestly report that X was observed and is statistically significant at P=0.05. But the larger conclusion is exactly wrong.

Publishing.

The "prestige factor" among journals. This issue has been given far too much attention. It is now at a level that can only be characterized as toxic. Whose fault is it? Ours (with a little help from some journal publishers). Try to resist, remembering that quality trumps everything else. But we all recognize that one student or postdoc cannot single-handedly change the system.

Don't be disheartened by harsh comments from reviewers. There are other journals. Pick yourself up off the mat, improve the manuscript if possible, reformat it, and send it out to the next journal. The first manuscript on the scanning tunneling microscope (later awarded the Nobel Prize in physics) received the following comment from one reviewer: "This is not of general interest."

Interacting with others.

Collaborations.  Choose your scientific collaborations very carefully.  If work from another lab will be part of a paper on which you are an author, you need to have confidence in the quality of the work from that lab.  There is a potential for a mismatch of expectations and effort.  If the project is important to you, it needs to also be important to your collaborators.

Talk to the people who help you out but don't have glamorous jobs – the security guards, the housekeeping staff, the people who change the linens, wheel patients around, and take care of laboratory animals, etc.  Ask them how they are doing, listen to what they have to say, and thank them for their help.

Learn people's names and address them by name.  For some people (me included) remembering names is not easy. I have lists of names and I carry them around in a little book.

Answer your e-mails on time (within 24 hours).

Stress.

Cultivate the art of thinking things through in a systematic way.  That helps.  Write down the challenges, the potential outcomes, the approaches, the risks, the benefits, and the various unknowns.  Treat each problem like a chess game: define the goal and the optimal strategy to achieve that goal.  This works for scientific problems, and it is useful for a surprisingly diverse array of other problems.

Stress is a part of this business and it is a part of life.  You cannot eliminate it, but you can recognize it and manage it.  Be alert to signs of stress in yourself and in others that suggest that it is getting excessive.  A sense of humor helps.

Keeping a perspective.

Try to keep things in perspective. Life is short.  The grant is important and the paper is important, but some things are more important.  Discipline yourself to think about other things for at least part of each day.  One of the insights one gets as a parent is how psychologically healthy it is to focus completely on others (i.e. your children).  Also, children, especially young children, have way of making you appreciate what is really important in life.

Take pleasure in every little triumph.  A beautiful gel.  A nice immunostaining image.  A Kaplan-Meier curve that is informative.  A correct diagnosis.  Share the joy with others.  Happiness, like knowledge, is not diminished when it is shared.

Be supportive of others.  A kind word goes a long way.

Useful web resources and free pdfs.
- https://www.grad.washington.edu/mentoring/
- "Entering Mentoring" (free pdf from HHMI)
http://www.hhmi.org/catalog/main?action=product&itemId=272
- "Advisor, teacher, Role Model, Friend: on Being a Mentor to Students in Science and Engineering" (free pdf from the National Academy of Sciences) http://www.nap.edu/openbook.php?record_id=5789

**Letter to Hao Wu – August 2014**

**Hao Wu was a postdoctoral fellow in JN's lab from 2009 to 2014.**

Hao,

Our final conversation was too brief, so I would like to add a few thoughts here.

First, working with you was a real privilege. You set a high standard, both as a scientist and a gentleman. Your presence had (and will continue to have) an enormously positive influence on the lab.

Second, I am very proud of the science that you did. It was original, important, and beautiful.

Third, only the person who is actually doing the experiments really knows how much work it all is, how many false leads were pursued, how many hopes went unrealized. In short, how difficult the journey was. From what I have seen, every great scientific journey is a challenge, and the final result is a bit like an iceberg. Only the tip sticks up above the ocean. But if the rest of it were not beneath the surface, then there would be nothing to hold the tip above the water. As someone who watched your scientific journey from close range, I know how big the submerged part of that iceberg is.

Let's stay in touch. We will be just an e-mail or a phone call away.

With warm regards,

Jeremy

**Letter to Chris Potter – January 2015**

**At the time of this letter, Chris Potter was an Assistant Professor in the Department of Neuroscience at the Johns Hopkins Medical School.**

Hi, Jeremy,

I wanted to get your advice. I remember that you are still able to work at the bench? I'd love to do the same, but each recent attempt has failed (due to all the other commitments that end up taking priority). I was wondering what system you worked out? Do you schedule bench time into your week? Or set aside mornings? Or only give yourself projects that can be completed with small amounts of time? Or count on a technician to finish certain projects? I'm missing the bench work, but can't quite figure out the best way to have my cake and eat it too.

Thanks for any wise words!

Cheers,

Chris

Chris,

I do less lab work now than I used to, but I still help out. I'm sort of a super-technician, available to do things that need to get done. It is useful for the lab and it keeps my edge.

How to do it? You need to be pretty intent on time management. Don't get roped into things that are a waste of time, or that can be done just as efficiently without you. Choose your committees very carefully. Let people who you are talking to you know that the conversation needs to be focused and efficient. Come in to lab early and on weekends before other people have arrived to distract you. Politely excuse yourself if you have an experiment going - that explanation usually trumps everything else. Do your reading and writing at home in the evenings and on weekends. Answer your e-mails once or twice per day only and answer them quickly. Don't carry a cell phone. Politely let people know that e-mail would be more convenient than a phone call or a face-to-face meeting.

Good luck,

Jeremy

**Commencement Remarks, Biology Department, JHU – May 2015**

Congratulations to graduates, and their mentors, lab-mates, family, and friends. It is a long journey of discovery – including self-discovery – and it is not made alone.

Challenges:
Nature does not readily give up her secrets
Most experiments don't work
Competition, getting your work published, dealing with the diverse personalities around you.

Excitement and aesthetic rewards:
Being an explorer. Science is the new frontier. The thrill of discovery.
Part of a larger and noble endeavor – science is one of mankind's greatest group effort.
Aesthetic beauty of the experiments and of the way that nature works. Newton's explanation of the rainbow.

Larger societal issues:
Rational thinking and the scientific method. You are the carriers of the sacred flame.
Scientific thinking is needed in all areas of human affairs. [An example. Recent FBI reassessment of forensic evidence related to hair analysis: evidence was flawed in >90% of cases. Serious questions about many other types of classic forensic evidence, e.g. ballistics. DNA testing has set a gold standard for statistically rigorous evidence.]
In business and government: what is the data? how reliable is it? What inferences can be drawn from it?
In the United States congress: 435 members of the House of Representatives + 100 Senators = 535 total. Only one (Bill Foster) has a Ph.D. Almost all of the others come from law or business. We need engineers and scientists. People who can rigorously analyze a problem and come up with practical solutions.

Larger theme:
The capacity for wonder and creative thinking. The similarities between creative thinking and jokes. Conveying that capacity to others.
Newton's quote: "I do not know what I may appear to the world, but to myself I seem to have been only like a boy playing on the sea-shore, and diverting myself in now and then finding a smoother pebble or a prettier shell than ordinary, whilst the great ocean of truth lay all undiscovered before me."

**Letter to Lucas Hua – September 2015**

**Lucas Hua conducted his Ph.D. thesis research in JN's laboratory. After receiving his Ph.D. in mid-2015, he started postdoctoral training in Elaine Fuchs' laboratory at the Rockefeller University. In 2016, he joined Seattle Genetics as a staff scientist.**

Lucas,

Thank you for writing. To get right to the point: I am 100% supportive of whatever you decide is the best path for you, and I would be honored to serve as a reference. You have enormous ability and potential. The challenge is to find the career path that is right for you.

Let me add a few thoughts that are more or less related to the issues that you raised.

The challenges that you are wrestling with are what everyone should wrestle with at some point in their lives. Anyone who has not wrestled with them is either very lucky or has been gliding through life without thinking hard about the important questions.

Fellowships. I can appreciate the pressure to get an independent fellowship. Perhaps the pressure is largely internal, but it is almost unavoidable given the talented postdocs all around you. From what I have seen, applying from a very well funded lab makes it more difficult to get a fellowship, since the committees often take lab finances into account.

Publishing in the most visible journals. You know what I think about that.

Vacation. You definitely need a vacation. I suspect that you would be feeling better if you had taken a few months off between graduate school and starting your postdoc to recharge your batteries. When you make the next transition (or maybe before that time) take at least a few weeks to do some traveling. [My experience: traveling with a group is a plus. With a group, the details of travel, meals, and lodging are pre-arranged and there is instant companionship, which makes it more interesting and relaxing.]

Ambition, etc. I know exactly what you mean. But this can be a double-edged sword. On the plus side, ambition is part of the essential fuel for doing good (or great) science. I don't mean just crass ambition, like a desire for fame and glory - although, if one is being completely honest, that is generally a part of it. But the best ambition reflects a desire to discover something profound and beautiful, and perhaps also to change the world. The down side is that if one sets the bar too high then it is a set-up for disappointment. Also, a high bar can take the fun out of the process of science if all of the emphasis is on reaching a predetermined goal rather than on the step-by-step journey and the pleasure that should accompany each little victory in the lab. To me, science is a craft and I am a craftsman. If a day arrives when I don't enjoy the craft, I'll do something else.

Related to the above, can a scientist really know the value of the experiment that he or she is doing? In many cases, the value only becomes apparent years later when others build on the work. One among many examples is Melvin Simpson's discovery of the ATP requirement for intracellular proteolysis in the mid-1950s. Twenty years later, this relatively obscure observation became the cornerstone and inspiration for Hershko's and Ciechanover's discovery of ubiquitin-dependent proteolysis, which requires ATP.

Larger issues. What makes for a fulfilling life? Doing something that you really care about. Also, finding the right person to share your life. Although both involve an element of luck, a happy outcome in both arenas is substantially under one's own control.

Let's stay in touch.

All the best,

Jeremy

**Letter to a student who was not accepted at Johns Hopkins for graduate school – March 2010**

Dear Dr. Nathans.

I sadly will not be attending Johns Hopkins next year. I believe CMM and BCMB made incorrect decisions, but once decisions are made, I cannot argue. I greatly respect both programs and the school, and certainly - I'm sure this was obvious - your research. I will greatly enjoy keeping up with the research of your lab in future PubMed searches, and I wish you the best of luck in your research. I really regret whatever mistakes I may have made that have now inhibited me from participating in this, but as a mathematician, I can only hope that everything happens for some indefinitely uncertain reason.

Most sincerely,

X

Dear X,

I am sorry to hear that Johns Hopkins did not work out. I hope that you have other options for graduate school for this coming year. I don't think that you should dwell on the possibility that you made any mistakes. There is a big element of chance in this business. All anyone can do is simply be true to one's self.

I wish you all the best in the adventures ahead.

Jeremy Nathans
Department of Molecular Biology and Genetics
Johns Hopkins Medical School

# Publishing, Apportioning Credit, and Other Sociological Issues

**Letter to Al Lazen, National Research Council – April 1997**

Dr. Al Lazen
National Research Council
National Academy of Sciences
2101 Constitution Avenue NW
Washington, DC 20418

Dear Al,

I have read the "Crisis in Expectations" draft that you sent me last week, and I am writing to give you my views on it. First, it is a well-written and extremely timely report. In abbreviated form it should be required reading for all life science undergraduates. The issues that this report lay out have been on my mind (and the minds of my colleagues) for years, and it makes compelling reading for those of us who have been training graduate students and postdocs. Below are some thoughts that you might find helpful:

1. Many of the trends at work here are demographic. Beginning 10-12 years ago, the global "economy" for life science trainees changed because artificial barriers to movement of people across borders were lowered. In particular, students from China and the former Soviet block have been allowed greater freedom to study (and eventually remain) abroad. In essence, there has been a globalization of the life sciences labor market. U.S. training and postdoctoral programs can now draw on a pool of talented undergraduates and PhD candidates from a population base that far exceeds the population base of the U.S. itself. My impression is that the selection process for bringing talented, highly motivated foreign nationals to the US for training is very efficient - i.e. the ones who come here fall on the right side of the bell curve of talent, motivation, work ethic, etc. From the point of view of those who are further to the left on that curve this makes the competition far tougher than the numbers alone would indicate. This trend towards market globalization mirrors a similar trend that is already well advanced in manufacturing. For many prospective students, a $16,000 graduate student stipend, long years of training, and a reasonably good chance of becoming a permanent resident of the U.S. look like a pretty good career path.

2. The effect of abolishing mandatory retirement at academic institutions was only briefly noted. The lack of mandatory retirement is a potentially major problem as the bolus of academics hired in the late 60's and onward reach retirement age. Universities may have to buy out these faculty members with generous retirement plans, an expensive option that will leave less flexible money for jump-starting the careers of younger scientists. In many cases the older faculty members will remain in place and the rate of appearance of new slots will be correspondingly diminished. Even a modest 3-5 year increase in age to retirement (68 or 70 instead of 65) will mean an approximate increase of 10-15% in the mean duration of a faculty career, and an equivalent decrease in the number of individuals who can enter that career, all other things being equal.

3. The U.S. funding system is about as efficient a Darwinian system as one can imagine. In the present competitive atmosphere, it is unlikely that any individual principal investigator is going to consider the larger issues of excess postdocs and students when the success or failure of his or her research program depends entirely on the ability to attract those postdocs and students. To use a familiar microeconomic model, the individual farmer cannot boost the price of corn by voluntarily growing less corn on his or her

farm. Each farmer is too small a player to influence the market. The federal government recognized this problem in the 1930s and ever since has been stabilizing the price of agricultural commodities by paying farmers to not grow crops. Collective action is required to alter the market forces in the life sciences, and only the federal government has the power to provide the incentives that produce such action.

4. Little was said in the report about the quality of trainees, perhaps because this is harder to measure than quantity. Creativity, drive, analytical ability, etc., vary widely, can evolve over time, and are hard to predict. At the outset of a career, even the best student may be unsure that he or she made the correct choice or has the requisite talent or temperament. Therefore, from the point of view of the U.S. taxpayer (the consumer), the system needs flexibility to allow the best scientists to emerge. As noted in the report there is probably an optimal level for operation of the training system's Darwinian mechanisms - a system that is too Draconian will discourage good people at the outset.

Thank you for letting me review this report.

Yours sincerely,

Jeremy

**Letter to Robert Simoni (Editor, Journal of Biological Chemistry) – November 2003**

Dear Bob,

I hope this letter finds you well.

I have debated about whether or not to write this letter, but all things considered I believe it is better to write it than not. I hope that you will share this with the members of the editorial board at the Journal of Biological Chemistry. The subject matter concerns the varying degrees of candor with which scientists describe the work of others in their publications. This issue comes up frequently as we write and read: in writing, we decide how much to credit others and, reciprocally, others decide how much to credit us. What prompted this letter is the following paper: Qu Z, Wei RW, Mann W, Hartzell HC. (2003) Two bestrophins cloned from Xenopus laevis Oocytes express Ca-activated Cl currents. J. Biol. Chem. 278: 49563-49572. The paper by Qu et al was published one and one-half years after a closely related paper from my laboratory: Sun H, Tsunenari T, Yau KW, Nathans J. (2002) The vitelliform macular dystrophy protein defines a new family of chloride channels Proc Natl Acad Sci USA 99:4008-13.

If you download both papers and compare them, you will be struck by their similarity. Both papers study bestrophin channel behavior in transfected 293 cells, the relative permeability of the channels, the calcium activation of the channels, and the effect of point mutations associated with vitelliform macular dystrophy on channel activity. Indeed, the two point mutations studied by Qu et al are among the 15 mutations studied by Sun et al. [For the purpose of this discussion, let's assume that all of the experimental data presented in Qu et al is correct and correctly described.] Although Qu et al studied Xenopus bestrophin and Sun et al studied human bestrophin, the two sequences are highly homologous and the data show the behavior of the channels to be essentially indistinguishable.

Now here's the rub: the only mention of the Sun et al paper made by Qu et al is the following sentence in the Introduction: "… more recently it has been shown that human bestrophin-1 expressed in heterologous systems induces a chloride current." As no further mention is made of the nearly identical experiments published one and half years earlier, the naïve reader – and I presume the naïve reviewer - would be led to believe that Qu et al were the first scientists to determine the ionic selectivity, calcium sensitivity, and mutational defects associated with bestrophin channels. Indeed, with the exception of the one sentence

above, the entire Qu et al paper is written as if the Sun et al work had simply never occurred. “Brazen” is perhaps the kindest word that comes to mind.

At this point I should indicate emphatically that the purpose of this letter is NOT to try to arrange for more credit for myself or my colleagues. I am content to let history judge those matters. I also do not want this letter to have any negative fallout for Qu et al. The purpose is simply to raise this issue, both as it relates to reviewing papers and to informing (or misinforming) the readership of the JBC. As regards reviewing, clearly a paper has a better chance of getting accepted if it purports to show novel findings. The problem is that the fields encompassed by the JBC are now so vast that reviewers, even expert reviewers, are often unaware of relevant work. Requesting that competitors not be among the chosen reviewers compounds the problem. This problem becomes even greater in the case of the diverse readers of the JBC, many of whom are in no position to recognize an unbalanced or inaccurate account of relevant experiments in the field.

My modest proposal is that in the Instructions to Authors, the JBC editorial board explicitly state that authors are expected to give a fair and balanced account in describing their work and its relationship to that of others. This is not fundamentally different from the expectation by the editorial board that authors give an accurate description of experimental procedures and results.

With warm regards,

Jeremy

**Letter to Nick Cozzarelli (Editor-in Chief) and Diane Sullenberger (Managing Editor) (<u>Proceedings of the National Academy of Sciences</u>) – June 2005**

Dear Nick and Diane,

I've just read David Politzer's Nobel lecture in the May 31, 2005 issue of PNAS. I applaud the idea of publishing these lectures - I recall that <u>Science</u> used to publish some of them but hasn't in recent years. But there is one aspect of this lecture that I find bizarre, and which I suggest we edit out of any future Nobel lectures. I am referring to the repeated reference to who did and who did not win a Nobel Prize.

Indeed, the name of every person who is a Nobel laureate is flagged throughout the article by a little superscript N. Is this to indicate that those who are anointed by the Nobel committee should be considered a separate species? There are also text references to who did or did not win a Nobel Prize. For example, on page 7790, John Ward is introduced with the comment "he is not a Nobel Laureate”. One could argue that this sort of Nobel fetishism is hardly worth dignifying with a letter like this one. But I think we should recognize that this mind set is insidious and destructive - it implies that getting credit and getting public recognition is and should be THE goal for scientists. It implicitly degrades the purest and most admirable motivations: the pursuit of beauty and truth, and the pleasure of working with and helping our students and colleagues.

As a corrective for the future, I would be happy to look over any Nobel lectures that are being considered for publication and gently edit them. Of course, the authors would need to approve and <u>PNAS</u> would need to note that the text was edited because the lectures are copyrighted by the Nobel Foundation.

It might be appropriate to communicate this note to Dr. Politzer. I hope that in the future he will use his renown in a way that fosters the highest of scientific motivations.

Sincerely,

Jeremy

Jeremy Nathans
Member, Editorial Board, PNAS

**Letters to Peter Lawrence and Makoto Kuro-o regarding scientific credit – November 2008**

**Peter Lawrence, a geneticist at Cambridge University and an astute observer of the scientific scene, wrote an open letter in late 2008 to raise questions about the fair apportionment of credit for scientific discoveries. JN's response refers to Kurosu et al (2006) Regulation of fibroblast growth factor-23 signaling by klotho. J. Biol. Chem. 281: 6120-6123 and Urakawa et al (2006) Klotho converts canonical FGF receptor into a specific receptor for FGF23. Nature 444: 770-774. Two of several e-mails with Lawrence and Makato Kuro-o, the senior author of Kurosu et al, are reproduced here.**

Dear Peter,

You raise (as usual) a point that is on everyone's mind but is not being addressed head on.

A couple of comments. First, I would lay the blame for this squarely at the feet of journal editors, whose shameless drive to promote "hot" science is distorting the publishing enterprise. Second, so as not to appear self-serving I would suggest that you consider dissecting an example that does not involve your own area and your own publications. And I have the perfect example for you. Have a look at the two papers listed below. Both are extremely well done experimentally and address fundamental questions in receptor signaling and renal physiology. They also present substantially overlapping data and come to identical conclusions. One (Kurosu et al) was published electronically in the Journal of Biological Chemistry (JBC) on January 25 2006 and in paper form on March 10, 2006. The second paper (Urakawa et al) was received by Nature on April 12, 2006 and published electronically on October 29, 2006. Amazingly, the Nature paper does not refer to the JBC paper - it is as if the earlier discoveries didn't exist. This is especially surprising since some of the experiments are nearly identical. I think that this is one of the more egregious examples of the phenomenon that you describe. I doubt that it reflects collusion on the part of the Nature editors, but it represents a failure of the scientific publishing enterprise to respect the truth of the historical record just as we respect the truth of the scientific data.

All the best,

Jeremy

Dear Makoto,

Even though the papers appeared over two years ago, it seems to me that it would help somewhat if Nature were to publish a correction. They should be willing to make an effort to set the historical record straight. Is it worth writing to them to raise this possibility?

Rest assured that many people - not just me - have read and admired your JBC paper, and appreciated its profound significance. I can imagine how incredibly exciting it must have been to have made that discovery.

All the best,

Jeremy

**Letter to the editors of Cell regarding our manuscript – January 2009**

**Publishing papers in the more competitive journals can require an extra level of engagement with the editors. The letter below and a follow-up phone call convinced the editors to send the manuscript out for review. It was eventually accepted.**

Drs. Angela Anderson and Patrick Hannon
Cell
600 Technology Square, 5th Floor
Cambridge, MA 02139

Re: Ye et al "Norrin, Frizzled4, and Lrp5 signaling controls a genetic program for endothelial cell development"
CELL-D-08-01662

Dear Angela and Patrick,

Andrea Dulberger suggested that I write a brief note in preparation for a phone call regarding our manuscript.

Your (Angela's) comments are below:
We have read the manuscript with interest, but would like to suggest that publication would be as appropriate in another journal. Previously you showed that the Norrin-Fz4 signaling system functions in vascular development in the eye and ear. The current work extends these findings, and provides a very thorough analysis of Fz4 conditional knockout mice and cells, and provides evidence that Norrin/Fz4/Lrp signaling relevant to vascular development occurs in endothelial cells and controls a complex transcriptional program. Although these findings will be of interest to the field, in our view they fall short of providing the level of conceptual advance that would be required for the paper to be a strong candidate for Cell.

My response follows:
Our earlier work showed biochemically that Norrin, Fz4, and Lrp function together as ligand, receptor, and co-receptor, respectively. Our and other groups' published work has also provided a descriptive picture of the vascular phenotypes associated with loss of function mutations in each of these genes. But until now there has been a huge gap in this story at the cellular level. In particular, it was not known in which cell type (s) signaling occurs, and at the cellular and molecular levels what the consequences of that signaling might be. For example, both neurons and astrocytes play a critical role in retinal (and brain) vascular development and were plausible candidates for the cells in which Fz4 signaling is required. In the present manuscript we have incisively addressed these questions by (1) constructing a conditional Fz4 knockout allele and eliminating Fz4 from a variety of predetermined cell types, (2) studying the vascular defects associated with genetically-directed ectopic expression of Fz4, and (3) creating and studying the behavior of WT and Fz4 knockout endothelial cells. These experiments show that the fundamental role for Fz4 signaling is in endothelial cells (with a minor contribution from mural cells), that Fz4 signaling controls the competence of endothelial cells to form vascular structures, that Fz4 signaling controls a distinctive transcriptional program, and therefore that all of the diseases that involve mutations in this pathway are - at the cellular level - diseases of endothelial cell development and function. Interestingly, our behavioral and single cell electrophysiology of light-dependent responses in the retina argue that chronic but localized hypoxia in the CNS can be compatible with long-term neuronal survival and eventual rescue - a provocative and hopeful message for those working on or afflicted with CNS vascular diseases. Finally, our observation of Fz4 signaling throughout the vasculature strongly suggests that Fz4 signaling controls a wide variety of vascular processes beyond the retina.

Let me add that at every step we have made this work as definitive and as comprehensive as possible. For example, using our highly efficient immuno-affinity purification method, we determined for the first time the transcriptome of retinal vascular cells (in any species and in any context) - despite decades of work and thousands of papers on this vasculature. We didn't just make a conditional Fz4 KO, but we made one in which the gene deletion is accompanied by the simultaneous activation of a reporter so that we can monitor at single-cell resolution the behavior of mutant cells in genetic mosaic experiments. We didn't just monitor the electro-retinogram to analyze the functional consequences of Fz4 deletion and the resulting vascular deficiency, but we also analyzed live animal optokinetic and pupil responses and recorded the light responses of single retinal ganglion cells. I could go on...

In sum, the present work reveals the Norrin-Fz4 -Lrp system as a central regulator of endothelial cell development, on par with the Notch, Angiopoetin, and Ephrin systems in terms of its profound effects on endothelial cell behavior. I am confident that if this manuscript goes out to the experts in the vascular biology field that the response will be enthusiastic. I am also confident that this work will endure as a seminal contribution to vascular biology.

I look forward to discussing this with you by phone.

All the best,

Jeremy

Jeremy Nathans
Molecular Biology and Genetics
Johns Hopkins Medical School

**Letter to Sol Snyder (Editor, Proceedings of the National Academy of Sciences) - April 2010**

**Below is one of many e-mails that address the relative merits of a manuscript submitted to the Proceedings of the National Academy of Sciences (PNAS). JN is a member of the editorial board.**

Dear Sol,

I am a bit out of my depth on this one, since the assessment largely relies on mouse behavioral assays. First, I like the experiment: it is a bit "out there" but it isn't completely crazy, and, if there is anything to it, there would be real public health implications. Second, the methods look pretty straightforward.

But I agree with your skepticism on basic physical principles. If the paper's conclusion is wrong, it will take quite a while for the right answer to emerge and in the meantime there will be a long trail of media hype. On the other hand, if it is right and we reject it out of hand, we will be appropriately accused of committing the sin of editorial small-mindedness. Maybe we can ask X or Y to look at it.

All the best,

Jeremy

**Letter to King-wai Yau – June 2011**

**King-wai Yau is a Professor in the Department of Neuroscience at the Johns Hopkins Medical School.**

Dear King,

I am delighted to see your paper on visual pigment spectral sensitivity in the latest issue of Science. The data look beautiful.

Jeremy

Dear Jeremy:

Thank you very much for your kind words. The redeeming value of the long painful review process (aside from the fact that we have indeed encountered more than one reviewer who truly did not know what he/she was talking about) is that it has pushed us to really try to communicate our ideas clearly to the reader. One group of readers that we especially would like to communicate the paper to are the ion-channel biophysicists, who apply the Boltzmann distribution all the time to their ion-channel work (gating kinetics, etc.), and let them know that Boltzmann statistics may not be appropriate. Chris Miller (whom I greatly respect) already wrote back and said that he loves the work. David Clapham is also complimentary. Already, this makes all our efforts worthwhile.

Best,

King

Dear King,

I have heard that there is a curious amnesia that causes the pain of childbirth to be partially suppressed. It seems that the pleasure of having a baby tends to erase the memory, which makes good sense from a Darwinian point of view. So it is with publications...

All the best,

Jeremy

**Letter to Susan Wessler (National Academy of Sciences Home Secretary) - March 2013**

Dr. Susan Wessler
Home Secretary
National Academy of Sciences

Dear Dr. Wessler,

I would like to bring to your attention an issue that I think would be worth at least a brief discussion.

In the background materials provided with the 2013 preference ballot for election of new NAS members, one nomination stood out stylistically: that of X. Have a close look at the text of the nomination. It stands out for both the modest amount of substantive content and the detailed listing of number of papers

published, numbers of citations garnered by those papers, the candidate's h-factor, and a list of the candidate's awards and honors (including, in one case, the cash value of the award). Indeed, most of the text in the one-paragraph write-up is devoted to the latter items. With this style of write-up, we can imagine what a nomination for Albert Einstein would have looked like in 1907: the candidate has fewer than a dozen publications, a low h-factor, and no awards.

In my view, the emphasis on previous awards and honors is a red flag - it suggests that NAS membership decisions should be substantially influenced by judgments that have been made by other groups. At the very least, whoever wrote the nomination should have been aware that any mention of awards and honors in this paragraph is redundant with the list provided in the brief biosketch one paragraph above. More importantly, this style of nomination tends to move the criteria for election to the NAS one small step toward appearance and away from substance. The NAS leadership might consider taking this opportunity to remind both the nominators and the committees that vet the nominations that each write-up should be a substantive and scholarly summary of the candidate's accomplishments. The corollary to this message is that, at every step of the process, judgments regarding candidate rankings should be based on substantive criteria.

Finally, I note that a poor write-up does a disservice to the candidate. In the present case, I think the candidate would have been better served by a write-up that emphasized her substantive accomplishments.

With warm regards,

Jeremy Nathans
Professor
Molecular Biology and Genetics, Neuroscience, Ophthalmology

**Letter to Science regarding the Chinese Academy of Sciences – April 2013**

Dr. Bai Chunli
President
Chinese Academy of Sciences

Dr. Alan Leshner
Executive Publisher
Science

Dear Drs. Bai and Leshner,

I enjoyed reading the supplemental booklet "Science in the Chinese Academy of Sciences" produced in 2012 as a collaboration between Science and the Chinese Academy of Sciences (CAS) and distributed to Science subscribers. The booklet provides an excellent overview of the CAS and the many impressive research programs in which it is engaged.

Perhaps inadvertently, the supplement also highlights a major challenge in Chinese science: a dearth of women at the most senior levels. In the booklet, photographs and names are presented for 53 individual scientists, including 28 CAS scientists and 14 recipients of international cooperation awards. All are male. Among photographs of small groups of researchers who are not named, >95% are male. This impression that the CAS institutes and programs are dominated by male scientists seems at odds with information on the CAS web site, which states: "At the end of 2008, CAS has 50,300 regular staff. Among them, female staff amounted to 16,100, accounting for 32%...". The CAS web site also notes that as of 2008 40/692 (5.8%) CAS members were female. The inference is that in China, as in the United States, there are more women in junior positions and fewer in senior positions.

Returning to the booklet, there is one place in which a significant female presence is seen: on the second to last page in a group portrait of CAS graduate students, of whom roughly a third are female. This photograph suggests that the future may be different.

With warm regards,

Jeremy Nathans, M.D., Ph.D.
Professor
Molecular Biology and Genetics, Neuroscience, Ophthalmology
Investigator
Howard Hughes Medical Institute

**Letter to Thomas Wälchli – July 2015**

Dear Dr. Wälchli,

I am writing to tell you how much I enjoyed reading your review that just appeared in Neuron ("Wiring the vascular network with neural cues: a CNS perspective", July 15, 2015). The review is very informative and it is beautifully written. I especially enjoyed the section at the end that discusses major unanswered questions.

Another motivation for writing is that I cannot resist mentioning two recent papers - one from my lab and one from Brad St. Croix's lab - that substantially clarify the role of Gpr124 by showing that it functions as a Wnt7a- and Wnt7b-specific co-activator of canonical Wnt signaling in conjunction with a Frizzled receptor and an Lrp co-receptor (see enclosed pdfs). A third paper, also enclosed, adds the GPI-anchored protein RECK as part of the Gpr124 co-activation complex. Additionally, the Zhou and Nathans (2014) paper reveals a greater role for Norrin/Fz4 signaling in CNS angiogenesis and BBB maintenance than had previously been appreciated, and it shows that an explanation for the CNS region-selective Wnt7a/Wnt7b KO, Gpr124 KO, and Frizzled4 KO phenotypes is the partial redundancy between Wnt7a/Wnt7b/Gpr124 signaling and Norrin/Frizzled4 signaling combined with region-selective expression of the various ligands.

Please do not take the above paragraph as a criticism of your review. Every review must necessarily represent a snapshot in time, and I imagine that you and your co-authors were writing the text before the appearance of the most recent papers on Gpr124. In fact, I found your description of Gpr124 and Wnt7a/Wnt7b to be especially interesting because it provides a clear picture of the field just before their unification, and also because it closely matches what we were thinking when we read the Gpr124 KO papers. In a nutshell, we thought that the near identity in location, timing, and severity of Wnt7a/Wnt7b KO and Gpr124 KO phenotypes was too striking to be a coincidence.

With warm regards,

Jeremy

Jeremy Nathans
Molecular Biology and Genetics
Johns Hopkins Medical School

**Letter to Richard Nakamura regarding grant review issues at NINDS – December 2015**

Dr. Walter Koroshetz
Director, NINDS
koroshetzw@ninds.nih.gov

Dr. Richard Nakamura
Director, CSR.
rnakamur@csr.nih.gov

National Institutes of Health
Bethesda, MD

Dear Drs. Koroshetz and Nakamura,

I am writing to apprise you of a problem with grant reviewing that I suspect will not be news to either of you. I decided to write to you in part because I believe that objective documentation of a problem is the first step toward its resolution.

By way of introduction, I am a Professor of Molecular Biology and Genetics, Neuroscience, and Ophthalmology at the Johns Hopkins Medical School, and an Investigator of the Howard Hughes Medical Institute. I am also a member of the National Academy of Science and the National Academy of Medicine (formerly the Institute of Medicine).

First, a few preliminaries. The issues that I raise are based on my experience with a single study section (Brain Injury and Neurovascular Pathologies; BINP). I do not know whether or to what extent these issues generalize to other study sections. Also, I will note at the outset that part of the impetus for writing is that in two rounds of review, an R01 that I submitted and that I think is outstanding was give extremely poor scores (triaged on the first round and not discussed on the second round; reviews are enclosed as pdfs). Perhaps those scores reflect the fact that my lab is well funded by HHMI. If so, I will be the first to say that I am sympathetic to the view that, in an era of tight funding, submissions from HHMI investigators (and other well-funded investigators) should be scrutinized more carefully. But I would add that if, in fact, this is how the system operates, it would only be fair to declare it publicly so that we all understand the rules of the game.

The main point of this letter relates to the quality of the review process and the quality of the reviewers. It is independent of the actual funding decision as related to my grant submission. When I read both sets of reviews I was struck by the nearly complete lack of emphasis on whether the proposed research would lead to a major advance or whether the proposed experiments were important, novel, or decisive. Substantial attention focused on details: for example, an insistence on power calculations for the number of mice to be used in analyzing knockout phenotypes, despite that fact that the proposed knockout experiments were several years in the future with no clear way to know at present how subtle or severe the phenotype might be. The result was a hodge-podge of marginally relevant criticisms with little or no discussion of substantive issues and little acknowledgement that my laboratory already had made major advances in the area of blood-brain barrier (BBB) development and homeostasis. There also seemed to be little or no appreciation for the process of scientific discovery; instead, the emphasis was on the need for extensive preliminary data that would allow a certain path to collecting more data.

In light of these reviews, I decided to conduct a simple scientific experiment. The BINP study section is the principle study section overseeing research related to the CNS vasculature and the BBB. To assess the contributions of the 31 members of the BINP study section to the BBB field, both basic and disease-related, I chose two current review articles on this topic (pdfs enclosed). These articles were chosen because they were published in prestigious journals (<u>Cell</u> and <u>Cold Spring Harbor Perspectives</u>) and were

authored by distinguished scientists who are leaders in the BBB field. I used the references cited in each article to compare my laboratory's impact on the BBB field with that of all study section members combined. The result is below.

Daneman R, Prat A. (2015) The blood-brain barrier. Cold Spring Harbor Perspectives on Biology 7(1):a020412. (with 113 references). For 31 study section members: 1 citation for a review article, no citations for primary research articles. For Jeremy Nathans: 3 citations for primary research articles.
Zhao Z, Nelson AR, Betsholtz C, Zlokovic BV. (2015) Establishment and Dysfunction of the Blood-Brain Barrier. Cell 163(5):1064-1078. (with 114 references). For 31 study section members: 1 citation for a review article, no citations for primary research articles. For Jeremy Nathans: 3 citations for primary research articles.
Total: For 31 study section members: 2 citations for review articles, no citations for primary research articles. For Jeremy Nathans: 6 citations for primary research articles.

This result is worrisome. Among 31 study section members charged with evaluating virtually the entire NIH portfolio on the BBB, not a single one has published a research paper that the authors of these reviews deemed worthy of citation. The most generous interpretation of this result is that the members of the BINP study section may be engaged in research that is not focused on discovery, but rather on the application of discoveries made by others.

I have discussed these concerns with Dr. Francesca Bosetti, the program officer associated with the BINP study section. She may be able to provide additional insight.

Sincerely,

Jeremy Nathans
Professor
Molecular Biology and Genetics
Neuroscience
Theobald Professor of Ophthalmology
Investigator, Howard Hughes Medical Institute
Johns Hopkins Medical School

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CC
Walter Koroshetz, MD
Director, NINDS
koroshetzw@ninds.nih.gov

Dear Dr. Nathans:

I am responding to your correspondence of December 26, 2015, to Dr. Koroshetz and me in which you apprised us of a problem with grant reviewing and with the hope of a step toward its resolution. The problem centers on the quality of the review process, particularly the quality of the reviewers, that in your

case resulted in a review outcome that you felt had little emphasis on whether the proposed research would lead to a major advance, contained marginally relevant criticisms, showed no appreciation for the process of scientific discovery, and appeared to emphasize the need for extensive preliminary data that would allow a certain path to collecting more data. Your application was reviewed by Brain Injury and Neurovascular Pathologies (BINP), a principal study section for the area of CNS vasculature and the BBB field. Your analysis of appropriate expertise and stature consisted of examination of two current reviews in which you were cited six times while only two BINP reviewers were cited at all and then only once each. In examination of another review article on BBB, N. Weiss et al., BBA 1788 (2009) 842-857, we note that multiple BINP reviewers were cited.

I apologize for the delay in responding. As you might imagine, your analysis and conclusions were unsettling and we have been trying to reconcile them with what we thought was an appropriate home for your application. Below I list some of our considerations.

BINP is a focal point for the BBB field and reviews more than 10% of all such proposals received by NIH. Of the 31 reviewers present for your review session October 15, 2015, 21 have research publications on BBB. The two cited in reviews you examined have publication numbers and h-indices similar to yours, as do two others.

With the tight money of a 10-year scientific recession for funding, many scientifically strong applications are going unfunded. In addition application numbers are up, which adds to the difficulty of recruiting top peer reviewers. Furthermore, reviewers are urged to distinguish the projects likely to have the most scientific impact from others and feel pressure to spread their scores. Although NIH policies put strong emphasis on projects that would result in major advances and on supporting basic research, reviewers operate under diverse pressures. We recognize this and try through annual new Chair orientations which I personally lead, and through SRO training of reviewers every round to provide guidance aimed to achieve what we all are striving for, i.e., identification of the best science.

As to a possible strategy of not supporting scientists with HHMI or other sources of ample research funds, that is not NIH policy as indicated by Dr. Koroshetz. Reviewers are charged with assessing the science. Budget matters are not part of scoring, and recommendations are only considered after scoring has been completed.

A specific comment concerning your review outcome and analyses: your application description does focus on “foundational studies” but also mentions “BBB breakdown in brain injury and disease.” Thus, the question by one reviewer of “translational impact” is not totally irrelevant. Furthermore, another reviewer did write that “such a basic mechanistic approach” is “no less important than more translational studies.”

In conclusion, I confess we have not reconciled conflicting priorities across the breadth of science that must be covered by NIH. On the one hand, the issues you raised about quality reviews and appropriate focus on likely impact and overemphasis on preliminary results resonate and are of concern. On the other hand, the BINP reviewers were well positioned to assess your application, as BBB expertise appears to have been extensive, and reviewers are instructed to use their own judgment in weighting the relevant review criteria.

What is the answer? We are hopeful that the return to growth in the NIH budget will bring relief after a decade of flat funding. Yet, I do not see a single, simple answer, and agree that we need to focus on quality review and quality reviewers. We need to continue to emphasize that what matters most is identifying the most promising science and providing well-reasoned, scientific feedback to applicants. On a personal note, I would urge you to not lose belief in the system and in fact to consider more participation in peer review. People of your stature are essential to improving peer review. I also should remind you that in case you remain convinced that your review was flawed due to bias or scientific error,

a formal appeal process is available and can be initiated by contacting Dr. Francesca Bosetti at 301 496-1431 or frances@mail.nih.gov.

I am sorry not to have been more helpful and want to assure you that your points are being taken seriously, are things we think about all the time and about which we are trying to take corrective action. You have reinforced our need to do so. Thank you.

Sincerely,

Richard Nakamura, PHD
Director
Center for Scientific Review, NIH, HHS
Email: rnakamur@csr.nih.gov

# Letters to the Editor

**Letter to The Virginian Pilot – June 2004**

Mr. Dave Addis
The Virginian Pilot
dave.addis@cox.net

Dear Mr. Addis,

re: "Best minds ought to be curing cancer, not cowlicks"

I enjoyed reading your column about our recent work on hair patterning. It was, as Dave Barry might say, brought to my attention by an alert reader.

I can't resist adding my two cents to the discussion, especially the part about whether scientists should be working in scientific areas that seem frivolous - which is a very reasonable point. First, with respect to funding, while it is true that the financial support for this work came from the Howard Hughes Medical Institute, a private medical research organization, it is also true that my earlier training in graduate and medical school was paid for by the National Institutes of Health (NIH). Thus, one could reasonably ask not only about how the Howard Hughes Medical Institute is spending its money, but whether taxpayers' dollars had been wisely invested in the training of a scientist who is now spending part of his effort working on hair patterns.

The answer, in my opinion, is "Yes, this was money well invested" for the following reason. In biology, many apparently unrelated processes turn out to be connected, and these connections allow scientists to figure out biological mechanisms in one place and then apply that knowledge to other, often more complicated, places. Let me offer an analogy. Suppose you wanted to know how an automobile engine works so that you can repair your car - but, like a scientist at the forefront of knowledge, you had to figure everything out on your own. In this analogy, we imagine that there are no blueprints, no repair manuals, and no expert mechanics to offer advice. Of course, you could start by experimenting with your car, but most likely you would simply break it during the learning process. A better way to start might be to take apart the engine in your lawn mower to get a general idea of how an internal combustion engine works.

At this point, I should confess that my older brother and I did exactly that when we were teenagers, and while we learned a few things about internal combustion engines, we never did get that lawn mower to work again. The key point here is that although a car engine and a lawn mower engine don't look much like each other, the essential workings are the same.

Now back to biology. In humans there are ten different Frizzled genes and each one codes for a particular kind of Frizzled protein. These proteins are found in all animals, from worms to flies to chickens to humans. Whatever it is that these Frizzled proteins are doing (and we're still in the process of finding that out), Nature certainly seems to have made use of it in many different animals. More relevant to us, we have already learned enough about the Frizzleds to know that, both in humans and in mice, mutations in one of them, Frizzled4, cause a defect in blood vessels in the eye that can lead to blindness.

In mice, mutations in another one, Frizzled3, cause severe brain defects due to abnormal patterning in the brain. We suspect that there are humans with the same disorder - we just don't know yet which people those are. Perhaps the most intriguing discovery in this field is the finding that the signals inside cells

which are normally triggered by Frizzled proteins are set at abnormally high levels in many human cancers, and that these signals make the cancer cells grow. Most human colon cancers have these signals set on overdrive, and this is now an area of intense research because colon cancer kills more than 50,000 Americans annually.

Over the past few years, my laboratory has been analyzing the function of the Frizzled genes in mice by mutating them one-by-one, and then looking to see what happens. The results are unpredictable, but we are confident that they will ultimately teach us lessons that can be applied to human health. These experiments have shown that Frizzled6 controls hair patterning, and we strongly suspect that Frizzled6 creates or senses patterns in the skin that guide hairs in much the same way that Frizzled3 creates or senses patterns in the brain that guide nerve cells. If that hunch is correct, it may be easier to figure out how this process works by studying the skin (which is simple) than by studying the brain (which is complicated). Is that idea far-fetched? Maybe. But it is no more of a stretch than studying lawn mowers to figure out how a car engine works.

All the best,

Jeremy Nathans
Department of Molecular Biology and Genetics
Johns Hopkins Medical School

**Letter to Johns Hopkins Medical News – January 2006**

Edith Nichols
Editor, Johns Hopkins Medical News

Dear Edith,

Three items.

First, thank you for the nice article and photos about our lab and for including my colleague Yanshu Wang so prominently.

Second, I see that you published my letter about the typo regarding Julie Freischlag signed "faithful faculty reader" – that's perfect.

Third, I have a real letter to the editor that I hope you will publish. The text follows:

The winter 2006 Hopkins Medicine magazine included an essay by a third year medical student in which the author describes witnessing a serious automobile accident. The author's response at the scene consisted of dialing 911 and then driving away. Apparently, she did not get out of her car, attempt to assess the condition of or communicate with the occupants of the vehicle involved in the accident, or remain at the scene until the arrival of the police or emergency medical personnel. Although I commend the author for her candor in describing these events, I find her actions (or, more precisely, inactions) disturbing. Let me suggest a simple and infallible method for determining what to do under circumstances of this sort – and it doesn't involve medical training. Ask yourself: What if there was a member of my family in that car? What actions would I hope to see on the part of a stranger who happened to be at the site of the accident?

All the best,

Jeremy

**Letter to Science: "Written in Our Genes?" – June 2005**

**Science 308: 1742 (2005)**

Written in Our Genes?

In 1983, Langston and colleagues reported that accidental exposure of humans to 1-methyl-4-phenyl-1,2 ,3,6-tetrahydropyridine (MPTP) induces a Parkinsonian state (1, 2). The authors hypothesized that damage to the substantia nigra might reflect a selective toxicity of MPTP for dopaminergic neurons. In the two decades since that initial report, a large body of evidence has accumulated to support this hypothesis. The mechanism of cell death appears to involve the selective uptake by dopaminergic neurons of the toxic MPTP metabolite 1-methy1-4-phenylpyridinium (MPP+). Dopaminergic neurons, such as the ones that populate the substantia nigra, are generally identified by the presence of tyrosine hydroxylase, the enzyme that catalyzes the first and rate-limiting step in the conversion of tyrosine to dopamine. Remarkably, the intimate connection between MPTP and dopaminergic neurons is immediately evident from a cursory perusal of the primary sequences of human, mouse, or rat tyrosine hydroxylase, each of which begins with the N-terminal sequence methionine-proline-threonine-proline ... (MPTP... in the single letter amino acid code) (3). Once again, an answer appears to be written in our genes - in this case, with unusual clarity.

Jeremy Nathans

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References
1. J. W. Langston, P. Ballard, J. W. Tetrud, I. Irwin, Science 219, 979 (1983).
2. J. W. Langston, P. Ballard, N. Eng. J. Med. 309, 310 (1983).
3. S. Ichikawa, T. Sasaoka, T. Nagatsu, Biochem. Biophys. Res. Commun. 176, 1610 (1991).

**Letter to the Baltimore Sun regarding ground rent – December 2006**

To the editor,

I commend the Sun for its investigative reporting on ground rent in Baltimore City. Your series of articles has exposed the ground rent business for what it really is: a medieval system that, at best, parasitizes residential homeowners, and, at worst, robs them of their property. It will also not have escaped the notice of your readers that those citizens who are being most cruelly exploited are the ones who are least able to defend themselves. However, there is reason for optimism. If our state legislators and new governor can put the common good ahead of the narrow financial interests of a few individuals, it will be possible to close this sad chapter in the history of our state and our city.

Let me suggest a few concrete items. (1) Ban the introduction of new residential ground rent contracts. (2) As a first step in phasing out the existing residential ground rents, require that all existing ground rent contracts, including information related to unpaid ground rent, be registered in a transparent and searchable public database. Failure to register within a specified time period would lead to forfeiture of the ground rent contract. (3) Eliminate property seizure in excess of the amount owed as a penalty for

unpaid ground rent. (4) The legislature has already mandated that residential home-owners have the right to buy out ground rent contracts on their property, and this is an important step in the right direction. However, this legislation needs a financial push to be fully effective. I suggest that the state set up a low or no interest loan program to allow residential home-owners to buy out their ground rent contracts. Moreover, as part of the sale of residential property, every bank that offers a residential mortgage should be required to offer a ground-rent buyout loan as part of the mortgage. (5) Finally, a commission should be appointed to determine, in a series of public hearings, whether some compensation can reasonably be made to those individuals who have lost their homes as a result of abuses of the ground rent system. If nothing else, such hearings will serve to fully expose the true nature of the ground rent business.

Sincerely,

Jeremy Nathans

**Letter to Science regarding China's One Child Policy – December 2010**

**Science 330: 1625 (2010)**

China's Plan Flawed But Courageous

In her news focus story "Has China out-grown the one-child policy?" (17 September, p. 1458), M. Hvistendahl explores the consequences of China 's fertility policies. Overall, the story presents the one-child policy in a negative light, buttressed by statistical data, such as the current gender ratio of 119:100 at birth and the projected graying of the Chinese population. These data are accurate but misleadingly incomplete. The single most relevant statistic is the one that drove the original decision to implement the policy: the total population of China as a function of time. Even with the reduced population growth that came with the one-child policy and with China's rapid shift toward an urbanized and export-driven economy, those numbers are sobering. In 1960, China had a population of 646 million; in 1980, it was 981 million; by 2000, it had grown to 1.267 billion ; and in 2010, it is projected to be 1.354 billion (1). In the past 50 years, China's population has increased by an amount equal to or greater than the population of all of Central and North America (500 million). Without defending or criticizing the one-child policy, we can at least recognize that it stands as a brave attempt by the inhabitants of an overcrowded planet to create a more livable future for our children and grandchildren.

Jeremy Nathans

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Reference
1. United Nations, Department of Economic and Social Affai rs, Populat ion Division, Popu lation Estimates and Projections Section, World Population Prospects: The 2008 Revision (http://esa.un.org /unpd/wpp2008/tab-sorting_population.htm).

**Letter to Johns Hopkins Magazine editors regarding Syria – June 2011**

Ms. Catherine Pierre
Editor
JHU Magazine

Dear Ms. Pierre,

This feedback is for you and your staff, not for publication in the JHU Magazine.

I saw the Summer Issue and the travel section with the brief article about Professor Glenn Schwartz and traveling to Syria. Although there is a small nod to the current troubles ("the situation is tense and uncertain"), the tone of the article overall strikes the reader as curiously detached from the reality of a brutal regime that is fighting for survival by killing its own people. Despite the assurances of the article that it is "safe and wonderful to travel as an American in Syria", knowing that the prisons are full and that the interrogators are working overtime just a few miles away might take the fun out of an afternoon stroll in Damascus.

To avoid giving the impression that the JHU community is unaware of the larger issues in the world around us, I think it might be prudent to either delete such articles in the future or to refocus them in a way that more directly acknowledges the “unpleasant” facts.

Sincerely,

Jeremy Nathans
Professor
Molecular Biology and Genetics
Johns Hopkins Medical School

**Letter to The New York Times regarding population and resources - April 2014**

Dear Editors,

Paul Kingsnorth’s concerns are well founded, but the focus of attention has been somewhat off the mark. The 800 pound gorilla in the room is human population, and the challenge of creating a sustainable future won’t be solved until the gorilla is reduced to the size of a mouse. In my view, an ecologically sustainable human population would be somewhere between 0.1% and 1% of its present level, i.e. between 7 and 70 million people. With a steady state population of that size - even with today’s level of per capita consumption - arable land, fresh water, wood, seafood, and many other natural resources would be plentiful. The practical question is: how can we get from here to there? Making the transition would take centuries and require overcoming the most powerful of biological and social drives. If we agree that extreme challenges call for radical solutions, then this is surely the time for us to be thinking radically.

Jeremy Nathans
Baltimore, Maryland

**Letter to The New Yorker regarding Egypt – December 2016**

December 29, 2016

New Yorker

Dear Editors,

Peter Hessler's insightful profile of Egyptian President Abdel Fattah El-Sisi also paints a vivid portrait of a country drifting inexorably toward greater economic, social, and political upheaval. Although recent headlines tend to focus on the ebb and flow of political events, one has the sense that the grinding of history's tectonic plates - demography, geography, and climate – will ultimately determine Egypt's destiny. Consider that Egypt is, to first approximation, a desert with a single river running through it, that Egypt's supply of arable land is declining as a result of salination from rising sea-levels and diversion of water from the Nile, and that the interests of countries upstream of Egypt are very likely to clash with Egyptian interests as the Nile is used more intensively for irrigation and hydroelectric power during the coming decades.

But the biggest elephant in the room is population growth. In 1950, the population of Egypt was 20 million, in 1980 it was 40 million, and in 2010 it was 80 million. It is now over 90 million. In short, the Egyptian population has been doubling every 30 years, a rate of growth that is simply unsustainable. In a less globalized world, local resource limitations would act as the ultimate brake on runaway population growth. But the flow of billions of dollars in foreign aid and loans, and the use of those funds for the purchase of basic commodities such as food and energy has allowed Egypt to delay the day of reckoning. The result is a country driving toward the Malthusian cliff. Without a radical reduction in population growth – essentially an Egyptian version of China's one child policy – it is hard to imagine a viable path to social and political stability or to the sustainable use of Egypt's limited natural resources.

Jeremy Nathans
Professor
Johns Hopkins Medical School

**Letter to Science regarding recessive disease – December 2016**

In the December 9, 2016 Features story describing the challenges and promise of medical genetics research in Saudi Arabia, Jocelyn Kaiser's text and the accompanying photographs movingly convey the human cost of recessive disease in a society with a high degree of consanguinity. It is interesting to consider that for much of the history of our species, consanguinity was the norm rather than the exception, since virtually all of our distant ancestors lived in small and relatively isolated social groups. Today, in a genetically diverse society such as the United States, it is easy to forget that a union between individuals of even modestly different ethnicity represents an historical anomaly. On the assumption that our current pattern of mostly non-consanguineous unions will continue for the foreseeable future, we might ask what effect this will have on the future frequency of recessive disease.

The frequency of deleterious recessive alleles is classically determined by (1) the appearance of new mutations, (2) the frequency of occurrence of affected individuals due to a union of two carriers, and (3) random fluctuation in transmission of alleles at each generation. The first of these mechanisms adds mutant alleles to the gene pool, the second eliminates them, and the third acts in both directions. In a population with high rates of consanguinity, the tragically high frequency of recessive disease also has the effect of reducing the frequency of mutant alleles in the gene pool. In contrast, in a large and genetically diverse population that favors non-consaguineous unions, homozygosity by descent will be relatively less

common, and the frequency of recessive disease will be correspondingly reduced. However, this genetic honeymoon will not last indefinitely. On a time scale of hundreds of generations, the frequency of deleterious recessive alleles would be predicted to increase until equilibrium is eventually established based on the same three mechanisms listed above.

Peering far into the future, we might ask whether the genetic challenges facing Saudi Arabia today presage those that our distant progeny will face. In other words, is our genetically diverse society simply delaying the day of reckoning? At present, the answer is unknowable in part because genetic testing and embryo genotyping have the potential to add a fourth mechanism that would represent the most dramatic historical departure: making decisions about procreation that are not based only on a roll of the genetic dice.

Jeremy Nathans
Johns Hopkins Medical School

# Miscellaneous Letters

**Letter to Roel Nusse – June 1995**

**The collaboration outlined in the letter below led to the discovery that Frizzled proteins are receptors for Wnt ligands [Bhanot P, Brink M, Harryman Samos C, Hsieh J-C, Wang Y, Macke JP, Andrew D, Nathans J, Nusse R. (1996) A new member of the frizzled family from Drosophila functions as a Wingless receptor. Nature 382: 225-230].**

Dr. Roel Nusse
Beckman Center
Room 8271
Stanford University School of Medicine
Palo Alto, California 94305-5428

Dear Roel,

I enjoyed talking with you earlier this week. Thank you for the set of reprints. I am looking forward to working together to test whether the Frizzled proteins are Wnt receptors. Let me summarize our work thus far. We have Identified 7 Frizzled related genes/cDNAs in mice, one of which corresponds to rat Frizzled-2 reported 2 years ago in JBC. We have sequenced a novel Drosophila Frizzled that maps to 76A (we call it Frizzled-2, or Fz-2), and a nematode Frizzled, part of which was in the Waterston EST collection. Complete or nearly complete protein coding sequences have been determined for all of these. Partial coding sequences have also been obtained from PCR products derived from 11 distinct zebrafish Frizzled genes and several chicken and sea urchin genes. All of the deduced protein sequences conform to the same general plan - a signal sequence, an N-terminal cysteine rich domain (in which cysteine number and position is invariant), a highly variable "linker", seven hydrophobic segments, and a variable carboxy-terminal tail. We have generate good rabbit polyclonal antibodies to Drosophila Frizzled-2 and to one of the mammalian Frizzleds. Bacterial fusion proteins from each of the other mammalian Frizzled proteins have been injected into rabbits. RNase protection assays indicate that the mammalian Frizzled proteins each have a distinctive pattern of tissue expression in the adult, and are, in general expressed in multiple tissues. Most are expressed in brain. In situs to the adult brain and during development are in progress. Our initial efforts to express Frizzled proteins in 293 cells look promising - high levels of Drosophila Fz-2 are detected by Western blot, and the protein appears to be predominantly in the plasma membrane. High levels of expression were also observed for the one mammalian Fz that we tested.

As we discussed, there are a number of good experiments to try. Given the multiplicity of Wnts and Frizzleds our work may be multiplied many fold as it may be necessary to systematically test many combinations. I agree with your idea of looking at Fz-2 in clone-8 cells. I think it would also be a good idea to overexpress Fz-2 in these cells to look for a biochemical effect - e.g. supersensitivity to wg or constitutive enhancement of armadillo stability. We have cloned an engineered version of Fz-2 (optimal Kozak site) into Mike Koelle's hygromycin resistant Drosophila metallothienin vector which would be suitable for this experiment. We are working to produce soluble extracellular Frizzled domains to look for binding to Wnt expressing cell lines. How many Wnts are currently set up for expression? Should we plan to transfer them into vectors for expression in 293 cells (our favored line for high level expression)?

Let me close by observing that a collaboration such as this - where a lot of hopes and hard work are in the balance - requires the right personal 'chemistry'. We need to think carefully about who should do which experiment and we should keep the lines of communication open so that there are no bruised egos at the

end of the day. My sense is that this will not be a problem, but I raise the issue now because it seems likely that a lot is going to happen quickly. Let's talk by phone to go over specifics.

With warm regards,

Jeremy

**Semir Zeki – May 1996**

**Semir Zeki, a Professor at University College London, is one of the leading explorers of the primate visual cortex. Beginning in the 1990s, he turned his attention to the relationship between visual cortical physiology and art.**

Dr. Semir Zeki
Department of Anatomy and Developmental Biology
University College London
Gower Street London WC1 E 6BT
United Kingdom

Dear Semir,

I cannot resist writing to you after hearing your superb talk on art and vision. That was a truly inspiring lecture - erudite, original, passionate, and beautifully delivered. By contrast, I am afraid that the fellow who followed you did not bring any great honor to our institution - I walked out at that point. Incidentally, it occurred to me in listening to and thinking about your lecture, that the lecture itself embodies some of the cardinal principles that you attributed to art - that is, the observer absorbs the central points both at an objective level that more or less matches the level at which other observers absorb them and also at a more individual level, colored by the observer's unique experiences and tastes. Most likely, each person in that audience saw parts of the lecture in a light that was different from that of the next person.

Over the past few years, I have also been ruminating about art and visual processing, and I have a few thoughts that you might find interesting. Our still primitive understanding of higher order processing in vision makes it most fruitful to ask, as you did, whether insights at the simpler levels of visual processing can inform our appreciation of art. I think that one way in which modern visual art challenges and pleases us is by delivering an image to the visual system at a level or through a route or subset of routes that is out of the ordinary. Black and white photography is the best example of this. The power of black and white photography lies in the supremacy of form and lighting, which are delivered with much greater impact in the absence of color. Compare color vs. black and white photographic portraits of just about anyone and the black and white is invariably the more striking of the two. Another example is the use of color contrast - often with highly unusual colors - to deliver form information, as in the famous multi-colored self portrait of van Gogh. Similarly Seurat's pointillism challenges us by confounding chromatic and form information. I wonder whether one aspect of the beauty of impressionist art is that the painting directly accesses a higher center's level of analysis by delivering an image that cannot be dissected by V1 in the ordinary way. For example, the picture may contain a degree of spatial resolution that is too low to be integrated in the usual manner by the form pathway, and it therefore sets up a tension between the expected dissection of real world scenes and the incomplete or unexpected information delivered by the painting. Monet's lilies are like this.

You mentioned the many possibilities - often contradictory - that Vermeer's paintings create. This is a great insight, and I think it applies at lower levels in the system. A visual image that matches exactly the real world appearance of the objects it portrays is almost never beautiful or striking because it leaves

nothing to the imagination. If, however, we observe an image that is a distillation or a distortion - that looks in fact like a memory trace - we are struck by something essential in the picture. Simple line drawings, especially portraits, are wonderful examples of this.

Finally, I am struck by the similarity between these artistic devices and the telling of good jokes. Arthur Koestler emphasizes this in 'The Act of Creation'. If a joke leaves nothing to the imagination, it is no joke at all - it simply falls flat. There must be a spark, a connection that is unexpected, one that challenges the listener and then takes the listener by surprise. Only by holding two wires at some distance do we get a spark. This is the essence of all good jokes and perhaps of all good art.

With warm regards,

Jeremy

P.S. I enclose two reviews of our recent work that you may find interesting.

Dear Jeremy,

Thank you very much for your warm and generous letter, which I was very pleased to receive. Had I known of your interest in art, I would have very much liked to have had the occasion of discussing the general problem of art and the visual brain in greater detail with you. I do hope that the future will provide an occasion to do so.

I am pleased that you raised the question about black and white photography. It has been much on my mind and I agree with your comments. The superior aesthetic quality of black and white photographs is perhaps the best example (though there are others) of the inadequacy of the gesamtkunstwerke approach in visual art and the difficulty of equating greater aesthetic experience with more widespread neural activation. But I still do not understand why, in neural terms, the absence of colour should enhance form so much, why this is especially true of portraits and what led painters like Cezanne, supremely interested in form, to use colour instead of black and white to highlight form. If you have any insights on these matters, please let me know.

I also agree with you about the tension set up by a painting because of a departure from the expected, though I am not certain about how much Vl itself would be involved in a specific sense. You are indeed right in supposing (implicitly) that any work of art that is incapable of setting up such tension is unlikely to be great art, for the brain, as Gleizes and Metzinger said, must be the concrete birth-place of certain forms, which are only implicit in the painting.

I would like very much to continue our dialogue as the occasion arises. I am sure that I shall have much to learn from your insights. Please also send me reprints of your papers; I appreciated receiving the last two. Finally, let me know when you next are coming to London so that we can meet up.

In the meantime, please accept my warm regards and best wishes.

Sincerely yours,

Semir

**Letter to Elizabeth (Betty) Turner – February 1998**

**Tench Tilghman Elementary School is a Baltimore City school located five blocks east of the Johns Hopkins Medical School campus. Most of its students come from poor households.**

Ms. Elizabeth Turner
Principal
Tench Tilghman Elementary School #13
600 North Patterson Park Avenue
Baltimore, MD 21205

Dear Betty,

Thank you for your letter of February 8. I hope you will share this response with your teachers and staff.

I was as surprised as you were to see Tench Tilghman on the list of "failing" schools. That is a hard pill to swallow. Tench Tilghman's staff and students have made great progress in the face of extraordinary challenges. Perhaps the most frustrating aspect of the latest news is that it does not acknowledge how hard the teachers and staff work, and how much the Tench Tilghman family has accomplished. I have certainly seen those accomplishments in your classrooms, in the reading program at Johns Hopkins, and in observing how the children carry themselves in public. The students, staff, and teachers of Tench Tilghman should be proud of their many accomplishments.

It is heartening to see your vigorous response. I want you to know that I am with you one hundred percent. There is a lot of work ahead and we all need to roll up our sleeves and do it together. The work of the Tench Tilghman teachers and staff is absolutely critical to our future as a society - your success will directly impact the students, their families, and our entire community. If Tench Tilghman succeeds in teaching and motivating its students, then those students will be able to continue to do well in middle and high school and avoid the tragic paths that so many of our teenagers are taking. The elementary school experience is a critical first step for heading these children in the right direction.

I look forward to seeing you on Tuesday February 17 for the school improvement meeting.

Yours sincerely,

Jeremy Nathans

**Letter to Sandra Wighton, Baltimore City Schools Assistant Superintendent – June 1998**

Sandra L. Wighton
Area Assistant Superintendent/Southeast Area Schools
Lake Clifton-Eastern Senior High School
2801 St. Lo Drive
Baltimore, MD 21212

Dear Ms. Wighton,

I am writing to you in reference to Ms. Elizabeth Turner, the principal of Tench Tilghman Elementary School #13. By way of introduction, I am a professor in the Department of Molecular Biology and Genetics at the Johns Hopkins Medical School. Tench Tilghman is located several blocks from Johns Hopkins and that proximity led me to contact Ms. Turner six years ago and join the school improvement team. From that first contact to the present, I have been most impressed with Ms. Turner's leadership,

with the challenge that she and her staff face each day at Tench Tilghman, and with the creative ways in which she and her staff have worked to give their students the best possible education. My participation has principally involved raising money to purchase books and other school supplies and to support the school's "Inside-Out" program, a weekend trip to a nature camp for approximately 50 students. As perhaps the most concrete measure of my confidence in Ms. Turner's leadership, I have donated during this time over $25,000 of my own money to support her programs at Tench Tilghman.

I am writing now because I understand that Ms. Turner is being considered for reassignment as a result of the recent disappointing student test scores at Tench Tillman. I do not want to minimize the importance of student performance on these tests or to criticize the current system of accountability, which places the ultimate responsibility for academic performance with the principal. However, I want to share with you my view that it will be virtually impossible to find a more effective principal for Tench Tilghman than Ms. Turner. She has done an extraordinary job of bringing enriching educational experiences to her school, holding together and motivating her staff, and increasing parental participation. Moreover, she has done these things in the context of difficult budgetary constraints. Let me cite one example. Several summers ago she orchestrated the painting of the school interior by local volunteers - the only way to do it within her budget was with free labor. When the doors opened in September the inside of the school looked beautiful.

Tench Tilghman and many other schools like it are in for a long and difficult struggle to bring student performance up to a satisfactory level. You know as well as I the various factors that make this a difficult goal to achieve. The pragmatic question is how to arrange the staff within the system to make the most efficient progress toward that goal. I think that transferring Ms. Turner at the present time would be a step backwards for Tench Tilghman. Ms. Turner would very much like to continue at Tench Tilghman and be able to leave it stronger than it now is. I think we owe her that opportunity. Please feel free to contact me if I can be of further assistance.

Yours sincerely,

Jeremy Nathans
Johns Hopkins Medical School

**Letter to Leon Kass - March 2005**

**Dr. Leon Kass was the director of the President's Council on Bioethics under President George W. Bush. In March 2005 he addressed a meeting of scientists and staff at the Howard Hughes Medical Institute headquarters in Chevy Chase, Maryland. His vigorous defense of Bush administration policies elicited a strong reaction.**

Dear Leon,

I have been thinking more about your recent visit to HHMI headquarters, and I think I owe you a written apology for grilling you so aggressively in public about the Bush administration. It was ungentlemanly of me, and not the appropriate approach to a guest who had generously taken the time to visit. I suspect that my remarks also contributed to the somewhat confrontational tone of the evening, a tone that was both unnecessary and unfortunate.

Having grown a bit wiser from the experience, I hope that when we next meet I can offer you a cordiality that makes up for the recent evening.

With warm regards,

Jeremy

Dear Jeremy,

My deep thanks for this lovely note. Meeting and chatting with you, even across the public space, was one of the best rewards of the evening. I look forward to our next meeting, which I hope will be soon.

As it happens I am lecturing at Loyola in Baltimore next Tuesday evening on a biblical topic: "The Love of Woman and the Love of God: The Case of Jacob". Biblical exegesis is much more engrossing than the ethics of stem cell research. If you have any interest, come along.

All best wishes,

Leon

**Letter to Ralph Cicerone (President of the National Academy of Sciences) regarding a manned mission to Mars – September 2005**

Dr. Ralph Cicerone
President
National Academy of Sciences

Dear Dr. Cicerone,

As a member of the National Academy of Sciences, I am writing to you about NASA's plans for a manned mission to Mars and the effect that pursuing this plan is likely to have on space science over the next 2-3 decades. I hope that this letter might help promote a public discussion of the risks, benefits, and likely costs of such a venture, and that the National Academies of Science and Engineering would play a leading role in such a discussion.

First, let me note that I am not an expert in this area. I am a biomedical researcher. However, as an M.D., I have some general sense of the challenges that are involved in manned space flight over an extended period. In reading about NASA's plans, my impression is that the venture is largely being driven by nonscientific considerations, and that the costs involved in launching and maintaining humans for the ~1 year required to complete a mission are going to be extremely high. With respect to scientific motivation, it appears increasingly likely that any manipulations (e.g. soil analyses) that a human might do on Mars could be done at a small fraction of the cost - and at no risk to human life - by robotic means. The next ten years will see further advances in the robotics field, so we can reasonably expect the costs to drop and the sophistication of robotic systems to increase. By contrast, the weight and bulk of a manned payload and the challenges of providing a year's worth of oxygen, food, and water, processing a year's worth of human waste, and preparing for unexpected medical or system emergencies related to carrying a human payload are essentially fixed.

In a nutshell, I am skeptical of the entire program. Not that it can't be done. It can be done, but only at enormous cost. Furthermore, once a manned program like this is set into motion, it may be very difficult to cut or substantially modify. For public relations reasons, it is likely to take on a life of its own.

It seems certain that within NASA's budget, the manned Mars mission will be competing for limited resources with valuable science-driven projects. The result is likely to be less support than would otherwise be forthcoming for new earth- and space-based observatories and for new unmanned missions. Given that these decisions are being made at the highest levels in government and that nonscientific

considerations are part of the decision process, it is critical that there be an open discussion of the most thorough and unflinching sort. The NAS and NAE can bring an expert and dispassionate eye to this discussion.

Finally, I wonder whether the NAS might venture to scientifically weigh the public relations effects of manned vs. unmanned missions, since this seems to be a major part of the nonscientific motivation for a manned Mars mission. I am not convinced that manned missions have the unique cachet that is so often ascribed to them. Unmanned missions have had a huge positive public relations impact, as evidenced, for example, by the public interest in the Hubble's images and the recent comet collision experiment.

Thank you for your time and effort in this area.

Sincerely,

Jeremy Nathans

**Letter to Lisa Thomas – September 2005**

**Lisa Thomas, a member of the Animal Services staff, was instrumental in helping JN transfer his lab's mouse colony to a clean facility at Johns Hopkins.**

Lisa,

I've been meaning to e-mail you for a while, and seeing you this morning reminded me to do it. My only excuse for not doing it earlier is that until yesterday's final exam I was inundated with teaching medical students – now all I need to do is grade the exam.

First, I want to thank you for all of your help over the past year - it really kept our mouse research program going, and it was a lot of fun working together. Second, now that everyone in my lab is tending their own cages, they are taking care of much of the husbandry, ear clipping and tail cutting. The result is that there is not a great need for the two of us to do this. However, I hope that I can still call on you every now and again if we hit a crisis (like someone in the lab getting sick) and that you and I can then step in and keep the mice going.

Given that business from my lab is minimal, are you interested in working with other investigators? Assuming that the answer is "yes", I would be happy to serve as a reference for any potentially interested investigators.

Let's keep in touch. I'd like to know how you are doing. And besides, if we don't, my cultural education is going to go badly downhill.

All the best,

Jeremy

**Letter to Ben Barres – October 2005**

**At the time of this letter, Ben Barres was a Professor of Neurobiology at Stanford Medical School and a leading researcher in the area of glial cells and their role brain plasticity and disease. He was born Barbara Barres and underwent a sex change procedure in his 40s. As one of the most prominent transgender individuals, he has spoken and written widely about his experiences.**

Dear Ben,

Deborah Rudacille, who works at Johns Hopkins, just gave me a copy of her new book "The Riddle of Gender", and I read in it the interview she did with you. Your candor, insight, and common sense are really refreshing. I can only imagine the personal discomfort before the switch, and I am delighted to read that things are much better afterwards.

Unrelated to the above, I've been following your recent work on thrombspondin's role in synaptic remodeling. Very interesting.

With warm regards,

Jeremy

Hi Jeremy,

Thanks very much for the nice note! I was glad to see the book favorably reviewed by the NEJM this month. I thought Deborah did a great job with the book, and I keep meaning to read her previous book (scalpel and the butterfly) about animal research and animal rights activism. As you probably know, Hopkins has historically been a focus of much work on gender identity, from John Money (who insisted gender identity was all socially determined) to Paul McHugh (who thinks transgendered people are all mentally ill) to William Reiner (who's actually doing some real science on the subject and finds evidence for a substantial inborn component). As for McHugh's view, my impression is that the incidence of mental illness is far higher in psychiatrists than in transgendered folks! Anyway, I really don't even think about these things any more as I have felt so much better since changing sex and fortunately everyone has been so great to me about it.

Take care,

Ben

P.S. We are slowly learning some more about thrombospondin since our paper. We have found that all 5 isoforms are strongly synaptogenic. We've mapped all of the synaptogenic activity to a small domain of TSP, shared by all of them, which is the one domain that doesn't have known receptors. And we are using that domain, tagged, to screen a cDNA library for the receptor now. By the way, I've got an unusually talented postdoc in my lab now, Andy Huberman, who is interested in how RGCs form specific synapses and already has some interesting data. Someday I hope he gets a chance to meet you. Andy also is involved in a collaboration with Mike Stryker's lab to see if delivering TSP into the adult primary visual cortex might help restore ocular dominance plasticity (admittedly a long shot!)

**Letter to Dean Bok – July 2006**

**Dean Bok is a Professor of Ophthalmology at the Jules Stein Eye Institute at the University of California at Los Angeles. He and JN served together on the Scientific Advisory Board for Ophthalmology at Novartis in the mid-2000s.**

Dear Dean,

It was very nice to see you last week in Cambridge. I am sending this note because I was really at a loss for words when you described your oldest son's tragic death. Even years later talking about it must be difficult. Were it one of my children, I do not think I could have recounted such an event with the composure that you showed. My thought now, which I should have said then, is that after a loss like that, I hope that fate will give you and your family a future free of tragedy.

With warm regards,

Jeremy

Dear Jeremy:

Thank you so much for your kind words. As you are clearly aware from your remarks, this is probably the worst thing that can happen to a parent. The word "closure" is often used in the context of such a tragic event, but this really does not happen. Time attenuates the emotions a bit, but the pain never goes away. I also hope that our future holds nothing but happiness. We have two other sons, their wives and two little grandchildren plus one on the way. It was a pleasure working with you as always.

All the best to you and your family.

Warmest regards,

Dean

**Letter to the Foundation Fighting Blindness regarding donors and research subjects – April 2010**

**JN has been a member of the Scientific Advisory Board of the Foundation Fighting Blindness (FFB) since 1995. The correspondence below was in response to a query regarding Foundation policy related to major financial supporters who want to participate in research studies supported by FFB grants.**

Dear all,

I think this is potentially a slippery slope. FFB is collecting money from thousands of donors, most of whom are not in the VIP category. We will be asking for trouble if we say that we are using FFB funds to try out the technology using DNA samples from a subgroup of patients who are participating based on their level of financial support rather than on a purely scientific or clinical basis. If the VIP donors would like to make a contribution directly to X so that she can try this method, that would be fine; but I think we should make it clear to donors that we have to draw a clear distinction between personalized medicine and FFB sponsored research.

All the best,

Jeremy

Jeremy Nathans
Molecular Biology and Genetics
805 PCTB
725 North Wolfe Street
Johns Hopkins Medical School
Baltimore, MD 21205

**Letter to Wenlan Wang – April 2011**

**Reply to a letter from Wenlan Wang, who had been a postdoctoral fellow in the laboratory of Daniel Nathans, JN's father, in the 1990s. She had advanced metastatic cancer at the time of this letter.**

Dear Wenlan,

I had been hoping that this moment would be delayed for as long as possible. Your grace, courage, and good humor are inspiring, and I hope that each day brings you beauty and love.

I am sure that you know how proud Dan was of you and how he would have been even more proud if he had lived to see the way that you have made your career, raised your children, and lived your life. Joanne feels the same way.

Don't worry about the R01. Give your children and your husband a hug - that is more important. I will convey your letter to Joanne.

With warm regards,

Jeremy

**Letter from a Korean engineer regarding curly hair – May 2011**

Hello, Mr. Nathans.

This is not spam mail. I have a question to you about Frizzled 6. My name is X. I live in Korea. I work in Samsung Electronics, engineer. I have a worry about my hair pattern. My hair pattern is curls. So, I have a lot of complex about my hair. I undergo stress very much. When I searched solution about my hair, I knew your paper about Frizzled 6. So, I try to find your e-mail address. I have heard that if we use the Frizzled 6 then we can change a hair pattern, from curls to straight hair.

I know that this paper is published long time ago. I want to know that the current level of technology and is this procedure possible? In Korea, I can't search this procedure. Can I undergo the procedure in your country? If the procedure is possible, do you use drugs or surgery?

Please help me. I just want to know the solution. I want your help. Thank you for your reading.

X

Dear X,

Curled hair reflects the curling of the hair follicle within the skin. I don't know of any permanent way to change that, although the hair shafts that have already emerged from the skin can be straightened (see the enclosed wiki article: http://en.wikipedia.org/wiki/Hair straightening).

My advice: don't worry about this. The narrow views of our rigid society are the real problem, not your hair. Every person is unique, and that is the greatest gift we could have. Also, what is going on under the skull is much more important that what sits on top of it!

All the best,

Jeremy

Jeremy Nathans
Molecular Biology and Genetics
Johns Hopkins Medical School

**Letter to Henry Bourne – November 2013**

**Henry Bourne is a Professor of Molecular and Cellular Pharmacology at the University of California at San Francisco.**

Dear Henry,

Thank you for forwarding your three eLife essays on the biomedical research situation. I enjoyed reading them - they are provocative, well reasoned, and timely. I hope that you will continue to write on this and other topics.

Below are a few thoughts, stimulated by your essays.

I completely agree that we have built a system that is unsustainable. The entire biomedical research and training enterprise is built on the (delusional) premise that funding will increase exponentially. At its core, the problem is one that every population biologist would recognize: PIs are training more students and postdocs than are required to maintain the PI population at a constant level. Since many of those trainees aspire to become PIs, there is a mismatch between reality and expectations. A collision is inevitable, and reality is going to prevail over expectations.

I largely agree with your prescription that we need to downsize individual labs and force universities and research institutes to put some financial skin in the game. On the issue of how to downsize the trainee population, the devil is in the details. I think market forces are already at work to decrease the postdoc population. But the process is very stressful for many postdocs - it is not the soft landing that one would like. The market forces can be seen at the level of postdoc hiring decisions. As a PI, I view the hiring of a postdoc as an increasingly expensive and risky commitment, since it is hard to know how long the person will need to stay in the lab (and on the payroll) before they can land a job. For this reason, I suspect that many of my colleagues are, like me, focusing more on graduate students. If this is, in fact, a trend, then the graduate student-to-postdoc transition point may be a time when large numbers of trainees will exit the research track for other careers. That would mean that fewer graduate students would go on to become postdocs, and the ones who do go on would comprise only the most promising subset.

The preceding paragraph basically argues that market forces are (partially) solving our problems. It would be reasonable to point out that this argument is just the biomedical research version of the usual free-market clap-trap, which also assures us that deregulating the financial industry is a good idea. Part of the problem with the biomedical research version of the free market approach is that there is a very long time horizon to training scientists, constructing research buildings, etc. With time scales of ten or more years, the system doesn't respond quickly enough to changes in macroscopic trends, like decreases in funding.

Despite our obvious failure to react in a timely way to market forces, I am wary of capping the number of graduate students entering biomedical research, for a variety of reasons. First, very few students know at age 21 where their real interests and talents lie. No one can accurately judge their potential, and we don't want to rely on grades or standardized tests to make an early cut. So why not make the opportunity available for the many talented undergraduates who want to try research? Of course our responsibilities should include giving them a realistic view of the challenges ahead if they choose this career path, and doing this at the beginning (i.e. before they apply to graduate school). Everyone who is in graduate school should be there with their eyes wide open regarding the market forces.

A second reason for my more relaxed attitude about graduate students is that I think PhD training in biomedical science is a great start for many careers, especially high school and college science teaching. One reason that central European secondary school education (the gymnasium system, equivalent to our high schools) has been so good for the past century is that they routinely select PhDs to teach in their schools. One reason that the US public doesn't understand science and doesn't think scientifically is because they have gotten their science education from people who were educated in teacher's colleges and don't know what science is. If a student goes off to a non-research career after a PhD, they should be proud of having devoted a few years of their life to an honorable and stimulating endeavor - a bit like being in the Peace Corps for a few years. If a PhD student spends the next 40 years in business, the business world won't be any worse off for having had that person for 40 instead of 45 years. I note that the preceding argument is a lot easier to make if it refers to students making a career switch at ~26 years of age (i.e. before postdoctoral training), rather than at 33 or 35 when the trainee has been a postdoc for many years, might already have or want to have children, etc.

A third reason for my more relaxed attitude is that we should be wary of encouraging government regulations - for example, regulations that forbid supporting trainees from research grants. Government regulations are occasionally inspired, but far more often they are mediocre one-size-fits-all affairs that become entrenched and increasingly onerous. One should never under-estimate the ability of the government to screw things up.

In looking at the graduate student and postdoc population from a "labor market" point of view, one huge change in the past couple of decades is the internationalization of that market. Just flip through a few issues of Cell and count the number of Chinese first authors on papers from US labs. This is the labor market equivalent of the cargo-container revolution that leveled the playing field for shipping manufactured goods anywhere in the world. One result is that what we in the US see as a "tough" lifestyle, doesn't look so bad to a poor kid from China or India. When I started in grad school there were far fewer foreign-born scientists here in the US, and the result was that the average quality of the students was lower than it is now (and I'm talking here about the Stanford Biochemistry Department - not exactly a "B" team). As a PI, my highest priority is attracting the most talented students and then giving them what they need to succeed, and I am happy to scour the planet looking for that talent. In the end, if some of them stay here in the US (and many do), it is hard to argue that our country has suffered for that.

Re: Cold Spring Harbor. I asked some of my colleagues about the Watson School at CSH, and the feedback I got was that many CSH graduate students stay on at CSH after they receive their degrees so that they can finish their thesis work and the papers from it. If true, then the CSH "miracle" is a mirage. It would be interesting to ask CSH administrators for the data on the total length of time that CSH grad

students stay at CSH, summing up before and after receipt of the PhD. In any case, it isn't just happening at CSH. The post-graduate mini-postdoctoral stay in the thesis lab seems to be increasingly common. If it extends beyond a few months, it doesn't do the student any favors since a whole series of clocks start to tick once the PhD is awarded, including clocks related to eligibility for postdoctoral fellowships.

With warm regards,

Jeremy

**Letter to Jerry Crabtree – August 2014**

**Gerald (Jerry) Crabtree is a molecular geneticist and biochemist at Stanford Medical School. In 2013 he published a widely discussed essay suggesting that modern humans are evolving toward lower average intelligence.**

Dear Jerry,

I enjoyed reading your 2013 essays on "Our Fragile Intellect" and the follow-up correspondence. I thought I would share a few thoughts that might interest you.

I find the general idea of relaxed selection for mental ability an intriguing one. My understanding is that this question was already being vigorously debated in Victorian England. The debate seems to have lost none of its vigor over the ensuing 150 years. I wonder whether there might now be quantitative data that could shed some light on whether the effect you describe - which seems plausible - is actually operating in present day societies. In particular, there may be large longitudinal studies that could clarify the relationship between "intelligence" (narrowly defined for practical purposes as the score on a standard IQ test) and number of offspring. My impression is that those with the highest and the lowest IQ test scores are having fewer children than the ones in the middle of the distribution.

Two extremely recent trends in our species' history that might accelerate the accumulation of deleterious IQ alleles – and ones that you wisely avoided mentioning since they are real lightning rods - are the appearance of the welfare state and the legal and professional emancipation of women. My impression is that the second of these phenomena has led to a relative decline in the mean number of offspring for the most highly educated women in first world societies, a segment of the population that is also enriched for high IQ. This effect is further exacerbated by non-random mating for IQ - indeed IQ is one of the attributes with the highest correlation between spouses, i.e. smart women almost invariably marry smart men - so lower female fecundity lowers the frequency of high IQ alleles coming from both parents.

The professional emancipation of women has also increased the average age at which high IQ women (and their high IQ husbands) bear children. This, in turn, produces a higher mutation frequency (from the older fathers) and a lower rate of population growth (if there is any growth at all) compared to couples who have their children at a younger age. This is not a trivial effect. Here in Baltimore, it is a good guess that a highly educated woman in her 40's who is pushing a stroller is out for a walk with her child, and that a poorly educated woman of the same age who is pushing a stroller is out for a walk with her grandchild. But we should also note that other recent social trends in the US, such as mass incarceration of relatively low IQ individuals during their peak child-bearing years, are working in the opposite direction.

A third trend, which you mentioned very generally, is the increase in the effective size of the inter-breeding population. This "relatively" recent (~500 years) trend relates to very large scale mixing of the gene pools of groups that previously existed in geographic isolation. For most of human history, matings were between closely related members of relatively small social groups, as seen among highland

tribesman in New Guinea, Amazon Indians, and subsistence farmers all over the world. That started to change on a large scale with the movement of Europeans, their slaves, and their colonial subjects. Today, Brazil, Mexico, the United States, and South Africa are a testament to the allelic mixing that occurs when large numbers of people move long distances. One effect is positive: the well-known benefits of hybrid vigor. But there is no free lunch. The flip side is that these very large and genetically diverse interbreeding populations have relaxed the painfully efficient manner in which deleterious recessive alleles are culled from the gene pool in small interbreeding populations, i.e. by eliminating two alleles each time a homozygote or compound heterozygote dies or is unable to reproduce. The prediction is that hundreds or thousands of generations from now, the gene pools of large and genetically heterogeneous societies, such as the United States, will have a larger burden of deleterious recessive alleles than they have today.

I can't resist adding one more, somewhat tangential, thought that was stimulated by your essays. There is an analogy between social support systems that maintain deleterious alleles in the gene pool and economic and technological support systems that maintain ecologically unsustainable communities (like Las Vegas). In the latter case, the regionalization – or in many cases, globalization – of resource markets makes it possible for humans to survive in environments that cannot in isolation support such a large population. Without a modern support network, the desert of southern Nevada would probably permit no more than one human per square mile, but with large scale movement of water, food, clothes, electricity, etc. we can sustain an ecologically irrational number and distribution of people.

I hope that you will continue to write on this topic. It is fascinating and important.

All the best,

Jeremy

**Letter to Wayne Hendrickson – October 2014**

**Wayne Hendrickson, is a structural biologist and Professor of Biochemistry and Molecular Biophysics at the Columbia University College of Physicians and Surgeons.**

Dear Wayne,

I just saw your beautiful paper on the bestrophin crystal structure. [Unfortunately, I was unable to attend your recent lecture here.]

That structure is very gratifying.

We got quite a lot of pushback when we tried to publish our work showing that bestrophins were anion channels (Sun et al., 2002). Your structure seals it.

My congratulations to you and your colleagues on a lovely piece of work.

All the best,

Jeremy

**Letter to Richard Mains – October 2015**

**Richard (Dick) Mains and Betty Eipper were Professors of Neuroscience at Johns Hopkins Medical School. Jodi, their daughter, was a medical student at the time that this letter was written. She subsequently trained in psychiatry.**

Dear Dick,

I hope that this e-mail finds you and Betty doing well.

I am writing with a very belated follow-up to a conversation that you, Jodi, and I had about two years ago in the Kennedy-Krieger Institute cafeteria.

At one point in that conversation, I said something about practicing medicine that was both factually incorrect and potentially discouraging to Jodi. I hope that you and she did not pay too much attention to it. But whether you and she did or did not make note of it, I want to correct it. If I recall correctly, the gist of what I said was that as a physician, one can have a greater impact by working with children and adolescents than with adults, because in adult medicine one faces intractable pre-existing problems such as the effects of smoking and drinking. In retrospect, I can't believe that I voiced such a shallow opinion. In truth, physicians have much to offer patients at every stage of life, from the first day to the last, and a large part of what they offer includes empathy and sound advice.

Although I cannot now recall what other things we talked about on that day, I hope that the discussion conveyed the idea that the medical profession is the most honorable of callings, and that whatever path Jodi chooses, she will be a force for good in the lives of those around her.

With warm regards,

Jeremy

**Vanitha Ramakrishnan – November 2016**

**Dr. Vanitha Ramakrishnan is a molecular biologist and has spent her career in the biotechnology industry. She and JN were postdoctoral fellows together at Genentech in the late 1980s.**

Nov 27, 2016

Dear Vanitha,

Thank you for the update on multiple fronts. Thanh and I are leading quiet lives by comparison. Our daughter Rosalie is in your neighborhood now. She and her boyfriend moved to SF a month ago and she works at Linked-In. Riva is married and living in Prague. She started working at Barclays in their software division a couple of months ago.

You have been strangely quiet about the disastrous election results. I am still incredulous that our fellow citizens could elect a carnival barker as president. The Republican mainstream, the Fox News mafia, and their fellow travelers have been preparing this toxic soil for a long time. Now we will have to live with the fruits of their harvest. The most astute analysis of the election that I have seen is in a letter from Michael Moore - and it is more impressive because it is in the form of a prediction well before the election. I enclose the pdf.

It will be an interesting 4 years. The sane part of this country needs to find its Winston Churchill. In the

meantime, we need to heed Churchill's immortal advice: "in defeat, defiance".

All the best,

Jeremy

Yes.
Quiet is strange for me.
More than 30 years ago I left a corrupt country because I wanted to work in a place where people were judged by their work and not by their birth. I remember that I felt that I had come to that Shining city, when, during my first exam here, the professor gave us the questions and left the room: AND NO ONE cheated!! I was so very happy I wrote home in tears about how great it was. After years of feeling like I was the only honest student, and my Dad and family were the only ones who paid taxes and did not take bribes, I felt I was really home. It is not that country now, there is graft on a scale that dwarfs the rest of the world combined and can and has brought the world economy to its knees.

I have always felt that there were many many parallels between Ancient Rome and the US. Not surprising as Jefferson did draw heavily from that Republic. In the Roman republic, the engine was war, and the US has its military industrial complex. Once they became the only superpower in the West, stuff started to unravel. Generals with big armies....I can go on and on but you know this: it was a bloody beginning and a bloody end.

I must say that Trump ran a brilliant campaign and saw what everyone had missed, and tapped into the anger of a group that felt forgotten. I have to say that this group feels the pinch of this path of globalisation more than others, and its a reaction to that. Some are racist and bigoted, but most are just worried for their families and their livelihoods. I went to Grad school in the Midwest, and those farmers were wonderful people, caring, friendly and down to earth: and incredibly hard working. They were not sophisticated but were practical.

Obama ran a similar campaign with a similar strategy but for a different group, the forgotten inner cities. I guess that is how democracy works.

I knew when Florida was all red that the democrats had lost. I must say I am neither a democrat nor a republican, and that I am heartily sick of Washington. This election was about the failure of both parties and the failure of the TV media bar none. Only Alan Lichtman got it right, I read and shared his article with Bob but he did not believe me.

He is indeed a carnival act, loud, boorish, petty. I could not ever vote for him. I could not vote for Hillary either: she spent 2 Billion on her campaign and I find that obscene. That could be in our schools, our roads..... She had a dinner here in SF and the per plate cost was 350000. To me that is just appalling.

I would have cast my vote for her though, if California was ever at risk; but it never was and so I voted for the Libertarian: not the best libertarian but a reactionary vote. I like small Government and being socially liberal.

But I feel, sadly, that this Information Age has created an army of drones, easily manipulated. The Diamond Age indeed. There is so much misinformation, just read the news. It's biased and shallow.

But we are outnumbered in our various ivory towers: this is the country that allowed an ignorant and slutty (pardon me) family of fools to make more than 70 million last year. I speak of course of the Kardashians: apparently many in the country want to keep up with them even though I do not!

Can you believe Yahoo news ran a story on what celebrities wore to the voting booth following this disastrous election?  I rest my case.

Sadly we may be the first generation that leaves the world for our children worse than we found it.  "O Brave New World that has such people in't"

I hope for the best or it's Mars for me.

Love,

Vanitha

# Politics and Society

**Letter to the Federal Bureau of Investigation – September 2001**

Mr. Robert Mueller
Director
F.B.I.
J. Edgar Hoover Building
935 Pennsylvania Avenue, N.W. Washington, D .C. 20535-0001

Dear Mr. Mueller,

I am a biomedical researcher at the Johns Hopkins Medical School. I have no special expertise in security issues, but in the wake of the events of September 11, I have been thinking about these issues and want to bring one of these thoughts to your attention.

Consider the following question. Is there a widely accessible, inexpensive, and difficult to monitor system for importing a large, heavy (e.g. several ton) object into the U .S. without surveillance? In particular, is there an existing system that might permit the importation of an object of the weight of a nuclear device, or several tons of high explosive, or chemical or biological agents? This question addresses what I think will be the main technical challenge for hostile nations or terrorist groups that may have the capability of obtaining or producing these materials: delivery to the United States and accurate detonation/release.

The most obvious answer is the modern and ubiquitous universal cargo container into which virtually all goods are packaged for international transport on cargo ships, trucks, and flatbed freight cars. These sealed metal cargo containers come and go in U.S. ports by the thousands each day. For example, it might be possible to ship a nuclear device or biological agents from the country of origin via a sham company in a neutral third world country and from there to the U.S., so that the U.S. would have difficulty tracking the origin of the shipment. Repackaging of the materials, changing cargo carriers, delaying the second shipment for months or years, etc., would all interfere with our ability to trace the origin of the material.

How to detonate explosives or release chemical or biological agents on schedule? A simple timer would potentially lead to early or late detonation/release. Alternately, as an indication of arrival at the U.S. port, if two cargo containers were placed on the same ship - one sending an intermittent radio signal and the other receiving it - then an increase in distance as measured by a decrease in signal strength could be used as a signal for timed detonation/release. Release triggered by the sensor could be insidious in the case of biological agents. For example, the trigger might cause a small door to open allowing a biological agent to leak continuously during a truck journey of hundreds of miles from the seaport to a point inland. Another strategy might be for a radio transmitter to send a signal from the point of destination, for example, from a sham company in the middle of a large city. When the cargo container is within a prescribed distance from the origin of the signal, as measured by its strength, that would trigger detonation/release.

What mechanisms could be instituted that would allow monitoring and/or inspection of the contents of cargo containers? Since the economic utility of the cargo container technology derives precisely from the fact that the contents are not disturbed en route, and the volume of cargo container shipping is now vast, some sort of noninvasive monitoring of the contents of these containers would seem to be the goal.

Secondarily, we might ask whether the existing commercial systems for electronic tracking of the world's cargo container traffic could be put to use for security purposes.

I hope these thoughts are of some use to you and your colleagues. If further discussion of these or other issues would be helpful, or if I can be of assistance in any other way, please feel free to contact me.

Yours sincerely,

Jeremy Nathans
Professor
Molecular Biology and Genetics
Johns Hopkins Medical School

**Islamic Terrorism and the West – October 2001**

**An unpublished essay in response to the events of September 11, 2001.**

The events of September 11 have served as shot across, if not into, the bow of our ship of state. Taken as an act of aggression, of war, or of criminality, they were extraordinarily destructive. They were also extraordinary in their global and historical overtones, and they pose a challenge which can only be met by an equally global response. As the U.S. and its allies lay the groundwork for that response it is appropriate that we critically examine the historical, social, religious, and psychological roots of Islamic terrorism.

For the past 500 years, the paths of Western and Islamic societies could hardly have been more different. Between 700 and 1400 A.D., Islam expanded from the desert of what is now Saudi Arabia to conquer an empire that stretched from Spain to India. During this period, the Muslim world saw a flourishing of the sciences, mathematics, literature, and poetry that stood in marked contrast with the backwardness of medieval Europe. Following this period of expansion and well into the twentieth century, much of Islamic society continued to function as it had for the previous millennium. In general, that society was characterized by social and economic stability, but not by technological or political innovation. By contrast, in sixteenth century Europe a potent combination of economic competition and relatively free intellectual activity ignited a period of growth that remains unparalleled in human history. In Western Europe and North America, these activities led to religious schisms, to the industrial revolution, and to the spread of representative government. Given the smallness of the globe and the predictable drive of powerful societies to expand their reach, encounters between Islam and the West were inevitable, and - like the first encounters between imperial China and industrial Europe - the meetings were on very unequal terms. Beginning in the 18th century, European military and economic superiority led to the subjugation of much of the Muslim World, culminating in the destruction of the Ottoman Empire after the First World War.

For much of Islam, the period of direct control by European powers came to an end by the middle of the twentieth century. But the citizens of these newly minted Muslim countries have discovered that political autonomy at the national level has not been accompanied by political autonomy at the individual level. This should come as no surprise. It took centuries for the hereditary monarchies of Europe to give way to representative government and relative freedom of expression, and the history of twentieth century Europe bears witness to the fragility of that historic transition to democracy. The result today is an Islamic world in which most governments are somewhere between authoritarian and brutally repressive. In some cases, these governments have been, either directly or indirectly, supported by Western interests.

The citizens of the Muslim world have also discovered that traditional society and authoritarian government come with a steep price in the realms of technological and social innovation. It is a

remarkable fact that Muslim society has made few if any original contributions to the technologies that distinguish the modern from the medieval world. Despite this lack of original contributions, Muslim society has readily assimilated the full range of Western technological innovations - medicines, cars, airplanes, computers, light bulbs, television, military equipment, etc.

Social innovation is a different story. For those whose authority derives from the continuity of tradition, social innovation represents a far greater threat than technological innovation. At the top of the list are the two greatest social advances of human history - democracy and the liberation of women - both of which have come from the West. At its core, democracy carries with it an extremely radical idea: that each person should be free to decide which beliefs to follow, and, as a corollary, that no single set of beliefs holds a special place above others. This idea is the essence of the freedom of religion, freedom of speech, and freedom of the press that forms the backbone of an open society, and it is a direct affront to those who preach that only believers possess the truth. Today, the U.S. is the most visible representative of those ideas, and the social, economic, and military strength of our and other open societies is therefore a direct challenge to the authority of traditional Islam.

An added challenge, and one that the Muslim world shares with many other third world countries, is demographic. High birthrates in Islamic countries during the past half-century have led to a doubling of the population approximately every 30 years, with no signs of slowing. One hundred years ago, Egypt had a population of 10 million. Today the population stands at 68 million, and in 25 years - within the lifetimes of most of the readers of this essay - it will be roughly 97 million. Today Algeria has a population of 31 million, and in 25 years it will be roughly 48 million. No economy, let alone a developing one, can create jobs at a rate of 2-3% per year continuously for 50 years. The results, fully predictable, are high unemployment or marginal employment, widespread poverty, and a society in which over half the population is under 25 years of age. Moreover, the limited carrying capacity of the Middle East environment, where much of the land is not arable and rainfall is often minimal, is a looming unknown in countries with ever more mouths to feed.

The social and economic stresses that accompany such rapid population growth would tax even the wealthiest nations. In the context of a traditional society, the most likely result is either anarchy or ever-tighter governmental control, the paths down which Algeria and Egypt are proceeding, respectively. What makes the present situation especially ominous is the unprecedented scale of recent population growth, and the potential of Islam to channel the resulting desperation into a collective scapegoating of the West. Why the West? First, because channeling anger outward is the oldest trick in the book for leaders looking to escape the wrath of their own populace. But there is something deeper than that at work here. Modern telecommunications, most especially television, has brought the image of Western wealth, freedom, and power to every village and hut around the globe. Whether the image reflects reality or simply Hollywood's version of reality is largely irrelevant. For a poor teenager with little hope for a materially secure future, it must be painful indeed to see this vision of Western existence dangling so close, yet out of reach.

It should be clear to U.S. policymakers that it is but a few short steps from desire to envy to hatred, and that the current social and economic situation makes much of the Muslim world ripe for this psychological transition. It should also be clear that even the most effective military and diplomatic responses will not bring stability to the Muslim world unless this demographic time-bomb is met head on. One of our roles should therefore be to provide stable, long-term family planning assistance so that the Muslim world can make the transition to an economically and ecologically sustainable population level, a prerequisite for the widespread enjoyment of a basic level of material prosperity.

Many of these demographic, social, and economic stresses are shared by countries in Latin America, sub-Saharan Africa, and Southeast Asia. Why, in Islamic countries, have they found expression in a terrorist war against the West? The answer likely lies in the power of Islam to mold the behavior of its devotees. To the many secularized citizens of the West, religion is just one of many activities competing for

attention, generally looming no larger in daily life than work, family, and hobbies. In the traditional Muslim world, religion looms much larger. The Koran addresses social and personal actions of all kinds, and serves as a comprehensive guide for society. Like all great religions, Islam gives meaning and grandeur to life, and it serves as an island of psychological stability in an uncertain world. It also makes a clear distinction between the relative worth of believers and nonbelievers.

It is fair to say that 500 years ago Christianity and Islam were equally militant in advancing their respective causes and equally prepared to condone brutal methods as necessary means to an end. Since that time, advances in science and technology, the material progress of the population, and the increasingly free exchange of ideas have all chipped away at the authority of Christianity in Western society. These changes did not occur without resistance. But spread as they were over half a millennium and coming as they did from within Western society, their effect has been a gradual transfer of authority from the ecclesiastic to the secular. For Islam, this challenge has been compressed into a tenth that time and it is coming largely from the outside. Faced with such a challenge, traditional Islam's reaction has been to fight rather than give ground. Should we expect Islam to follow the path of Christianity and allow its influence to become more circumscribed in the years ahead? This is a great unknown.

There are, of course, many reasonable Muslims who are sympathetic to the anti-Western backlash but are not themselves overt supporters of terrorist violence. It is with them that this war will be won or lost. If the center of gravity of Muslim public opinion remains openly hostile to the West, then those who subscribe to the anti-Western extreme of that opinion will remain sufficiently numerous to disrupt any attempt at peaceful coexistence. To those anti-Western Muslims who say that their nonparticipation absolves them of responsibility for any terrorist acts, we should make it clear that this is disingenuous. The vilification of the West (and, one might add, of Israel) in the Islamic press and in other public discourse has created fertile ground for the emergence of terrorism. As we did with Eastern Europe during the Cold War, we must make the delivery of objective, unbiased news to the Muslim world a top priority. In this war, one of the most powerful weapons in our arsenal is the truth. We should not hesitate to use it.

**Letter to the Federal Bureau of Investigation – October 2004**

Mr. Robert Mueller
Director
F.B.I.
J. Edgar Hoover Building
935 Pennsylvania Avenue, N.W. Washington, D .C. 20535-0001

Dear Mr. Mueller,

I am a U.S. Citizen and I am writing this letter to summarize a few thoughts that you or your colleagues may find useful regarding potential terrorist targets. By way of introduction, I am a biochemist but I have no special expertise in security issues.

Consider the following question from the point of view of a terrorist: Where can one find large numbers of Americans (and other Westerners) concentrated in a small space, outside of the borders of the U.S., and essentially undefended? One obvious answer is on luxury cruise ships. These ships typically carry several thousand passengers, sail in international waters, and publish their arrival and departure schedules well in advance. Moreover these ships can easily be recognized from a great distance with a simple telescope. They have distinctive silhouettes and, at night, they have a large number of lighted windows. A terrorist attack along the lines of the attack on the U.S.S. Cole, in which a small boat laden with explosives detonates adjacent to the target vessel, would not be difficult to carry out, especially in international waters.

The logistical challenge for the terrorists would be to get the attack boat and explosives to a distant port. I do not think this would be an insurmountable challenge, especially working through countries with relatively weak security. For example, a dummy company set up in a Caribbean country could import explosives, arrange for the rental or purchase of a seaworthy vessel, and carry out the attack with little more than a skeleton crew.

I suspect that the F.B.I. and/or the U.S. Coast Guard has already considered this problem, but let me suggest a couple of ideas that might be worth considering. First, since many cruise ships are not registered in the U.S., we have limited leverage in any effort to have them beef up their security. However, the cruise ship companies and the companies that insure the cruise ships should have a strong financial interest in avoiding the sort of lawsuits that would inevitably follow any attack. From a business point of view, having a dozen security personnel and defensive equipment on board would be a modest expense relative to the potential financial risk. The specific equipment I have in mind would be a sophisticated radar and surface-to-surface missile system that could detect and destroy an approaching vessel, including very small ones. All of this thinking also applies to oil tankers, which are similarly vulnerable.

Thinking beyond the low technology attack of the kind suffered by the U.S.S. Cole, the situation gets more difficult. Recall that during the Falkland Islands War (1982) the British Navy suffered one major setback: the loss of a light cruiser to a direct hit by a single Exocet missile fired from an Argentine plane that was 20 miles away. This missile technology - exemplified by the Exocet (French) and Silkworm (Chinese) missiles - is now widely disseminated. It is not inconceivable that one or more of these missiles could find its way into the wrong hands. Their relatively small size would allow the missiles to be shipped in standard sealed cargo containers, and the scenario outlined in the preceding paragraph might play out with the dangerous difference that the attacking vessel could launch the missile from a distance of many miles, well beyond the distance where it would raise any suspicion.

I hope these thoughts are of some use. Please feel free to contact me if I can be of assistance.

Yours sincerely,

Jeremy Nathans
Johns Hopkins Medical School

**Letter to the Obama campaign - August 2008**

Dear Obama campaign staff members,

I am a strong supporter of your campaign and a long-time observer of the political scene. I am writing to offer a strategic comment related to the way in which the Obama campaign is framing the issues and the differences between candidates Obama and McCain.

Thus far, the Obama campaign has failed to aggressively claim the most important high ground: competence. Many voters are not persuaded by or do not understand policy issues at a level that permits the Democratic Party's policies to emerge as superior. For example, the disastrous Republican tax policies and their resulting effect on income disparity and national debt - an issue that should be a no-brainer for every American earning less than $200,000 per year - have largely failed to register in the public consciousness. These and other Republican Party policies or actions – such as failing to get someone off of the roof of their flooded New Orleans home in less than three days - need to be framed in terms of Democratic competence vs. Republican incompetence.

Importantly, the use of competence vs. incompetence frames the issues in non-ideological terms. This will resonate more widely with the critical swing voters. It will also leave McCain less wiggle room to dissociate himself from policies that he would prefer to label as strictly Bush's rather than representative of the Republican Party. Without mentioning former President Clinton explicitly, Mr. Obama might note that from 1992-2000 with a Democrat in the White House, we had a budget surplus, we performed flawlessly in our intervention in the former Yugoslavia, etc. All political campaigns are in part a battle for control of the English language. The Republicans realized this years ago when they appropriated the word "morality", and turned "liberal" into a dirty word. The Democrats need to play this game, and a good way to start would be to lay claim to the word "competence".

In summary, Mr. Obama's campaign and the Democratic Party need to get across the message that the last 8 years show that the Republicans are incompetent - they cannot balance the budget, they cannot effectively address the country's energy needs, they cannot manage the economy, etc. The positive message is, of course, Mr. Obama's own competence and the historical competence of the Democratic Party. McCain's campaign will do its best to avoid being tarred with any brush that is tarring the Bush administration, and for this reason the Obama campaign needs to clearly link Republican policies in the Senate, House, and White House in the minds of the voters, so that people realize that electing a Republican means that the country gets the complete Republican package.

Sincerely,

Jeremy Nathans

**JN's philosophy on investing in the wake of the 2008 financial meltdown – January 2009**

I favor a strategy that is risk averse. I would be happy to preserve value with only modest returns above inflation.

Potential risks (in order of increasing severity): market volatility (most relevant for stocks and real estate); inflation (most relevant for fixed income investments); devaluation of the dollar; financial collapse of major investment vehicles (TIAA/CREF or Vanguard); other drastic (but hopefully unlikely) possibilities.

Potential major unknown future expenditures: health/disability-related for ourselves or our close relatives.

Investments in the stock market (including index funds) should be periodically evaluated to reassess overall assumptions and strategy. Benchmarks are nearly zero risk investments such as 1-2 year CDs, Treasury notes, and money market. If the stock market can beat these low-risk investments when averaged over some longer time scale (as it has historically) then that is the only objective reason to invest in the stock market. Therefore, the expectation is that stock market investing may exhibit short-term fluctuations but when averaged over the longer term it will beat the safe investments. This assumption needs to be evaluated with real data, and "long term" needs to be precisely defined. I would suggest that ten years constitutes "long term", and a failure to beat the benchmark on a ten-year time scale means that we should rethink the initial assumption of what constitutes an acceptable level of risk. At present the stock market has fallen short of those benchmarks on a ten-year time scale.

The 2008 financial meltdown with bankruptcies (or near bankruptcies – saved only by Federal intervention) of AIG, Lehman Brothers, Bears-Stearns, Wachovia, etc; the current near bankruptcy of all three US automakers; the high and unsustainable level of American consumer debt; and the unsustainable Federal deficit all suggest a potential for long-term (e.g. >ten-year) financial turmoil. Japan experienced this in the 1990s, and the US did in the 1970s. We should recalibrate our assessment of investment risk based on this new situation.

The most positive scenario is that massive Federal borrowing and spending will lead to another bull market. But even if that happens, the economic foundation within the US will remain weak unless manufacturing and exports increase, and US wages and living standard decline to make our goods more competitive.

**Letter to Bill Foster after his congressional defeat – November 2010**

**Bill Foster, a physicist-turned-congressman from Illinois, won election in 2008, lost in 2010, and was then re-elected in 2012, 2014, and 2016.**

Dear Bill,

The unwisdom of our fellow citizens is a sad fact of life, and in a democracy its consequences are inescapable. You have set an extraordinary standard of intelligence, sound judgment, command of the facts, and willingness to put the greater good of our country (and planet) first. I am honored to have been able to help in a small way. In the years ahead, I hope that you will be able to continue in some other capacity in shaping national policy - the country needs you more than ever.

One very specific thought: is there an opportunity to shape policy at the DOE? Energy challenges are at the core of our economic, environmental, and foreign policies. I imagine that Steve Chu would be delighted to have you on his team.

With warm regards,

Jeremy

Jeremy Nathans
Molecular Biology and Genetics
Johns Hopkins Medical School

**Letter to President Obama regarding gay marriage – May 2012**

Dear President Obama,

I am a life-long Democrat and a strong supporter of your presidency and re-election bid. I am writing with some practical strategic advice regarding the same-sex marriage issue. I hope that you and your team will consider this advice seriously, as I believe you have just stepped incautiously on one of the third rails of American politics. Hopefully it will be possible to strategically adjust your position before the Republicans and their PACs turn up the voltage. Obviously, there is nothing that would please the Republicans more than to see this become a get-out-the-conservative-voter issue in states like Ohio.

First, I think you should make it clear that it is not the place of the federal government to redefine the meaning of words in the English language. The word "marriage" has had a clear meaning for centuries – it is a union between a man and a woman. See, for example, the Oxford English dictionary. One problem with redefining any word is that one is sliding down the slippery slope of "1984-speak" in which a word can be made to mean whatever the government wants it to mean. Although this has not been a central issue in the current discussion, I would not underestimate the extent to which it is irking the traditionalists. To shed this particular piece of baggage, you should make clear that the word "marriage" should remain exactly what the dictionary says it is.

Second, the issue is really about the legal status of individuals, or, in this case, pairs of individuals. Whatever word is used to describe the pairing should not be permitted to distract us from this central issue. The question is whether some pairs of individuals are permitted a particular legal status that is denied to other pairs of individuals. The point of principle should be that every adult should be permitted to choose one other adult with whom to have this special legal relationship. For those couples who are married (in the traditional sense of that word), the spouse would generally be chosen as the person who carries the special legal status. The special legal status refers to finances, taxation, power of attorney issues, medical issues, etc – and it should therefore not be dictated by or ancillary to religious or social traditions. Mathew 22:21 summarizes it perfectly: "Render unto Caesar those things that are Caesar's, and unto God those things that are God's".

Returning to language, it would be appropriate to consider which word or combination of words, should refer to the relationship between those pairs of individuals – whether married or not – who have that special legal status. "Civil union" is pretty close to the right phrase. It is important to emphasize that this phrase could refer to either same sex or opposite sex couples. That is, the entire argument should be framed in a way that is agnostic with respect to whether the couple consists of two individuals who are of the same or opposite sex. Although some of this may sound like an excessive parsing of words, the words determine the ground rules of the debate.

In summary, it is important to keep the conversation focused on the legal and not the social or linguistic aspects of the debate. That is, the issue needs to be couched strictly in terms of equal rights before the law for all U.S. citizens, and not as an experiment in social engineering or linguistic sleight of hand. By narrowing the debate, the issue of fairness becomes clearer and the nebulous idea that same sex unions are somehow a threat to "family values" becomes less tenable.

I hope this is of some help.

Sincerely,

Jeremy Nathans

**Letter to Jimmy Carter about how Jews are treated in Arab countries – December 2012**

President Jimmy Carter
The Carter Center
One Copenhill
453 Freedom Parkway
Atlanta, GA 30307

Dear President Carter,

I have long admired your work, your forthrightness, and your moral clarity. By way of introduction, I am a biomedical researcher and a Professor at the Johns Hopkins Medical School.

I recently heard an interview that you gave on CNN, and I wanted to give you some feedback on a point that you made regarding the Middle East. It is often stated, without offering much in the way of supporting evidence, that over the past many centuries Jews lived relatively peacefully under Moslem rule. The logic goes that Jews, and also to some extent Christians, were considered "people of the book" and therefore had a legal status under Islamic law that protected them. Certainly, there were, until recently, large Jewish communities in Iran, Iraq, Egypt, Algeria, and elsewhere in the Moslem world.

However, historical research reveals that these communities existed under conditions of substantial duress, and it is therefore no surprise that when given the opportunity to leave their homelands most of these Sephardic Jews chose to emigrate to Israel. As an example, I have enclosed for your interest a brief summary written in the 1850s that describes the social conditions for Jews in Iran; this was published in Bernard Lewis' recent book "A Middle East Mosaic".

I think we can find a close analogy with the plight of African-Americans in the post-Civil War South. If one had asked only members of the white power structure about the quality of life for African-Americans, one would have been reassured that they were happy and carefree, and that one should not upset the relatively peaceful state of affairs by "agitation". Of course, a bit of research would reveal that the "peace" was being maintained by the terror of the Klan and the tyranny of Jim Crow. In the case of Middle Eastern history, let me suggest viewing the scene with a similarly critical eye. Historical research and interviews with living non-Moslem emigrants shows that from the point of view of many Moslems in a predominantly Moslem society, it was deemed appropriate that members of minority religions – whether they be Jews, Christians, Zoroastrians, Hindus, or others – be relegated to the status of second or third class citizens. In sum, as I am sure you know, one needs to listen to the folks on the bottom, not just the ones who are sitting on top.

I hope that you will continue to speak and write on these and many other important issues.

With warm regards,

Jeremy Nathans

**The Physics of Extremism – December 2015**

**An unpublished essay on the origin of extremist views.**

For those who follow national and international news, it is impossible to ignore the pervasive role that extremes of human behavior play in the world's affairs. I am not referring here to those extremes of athletic, musical, artistic, or scientific accomplishment that evoke our admiration. Today's headlines are dominated instead by extreme behavior of a sinister sort, animated by ideas that most of us consider pathological. Whether the events are in Paris, California, Colorado, or South Carolina, the focus of the news media, policy-makers, and the law enforcement community is largely on combating extremism per se, without connecting it to more widely accepted ideologies. I argue here that this focus misses the mark: extreme behaviors and the extreme ideas that animate them invariably have their roots in the soil of more conventional beliefs.

This general thesis has an interesting analogy in the physics of gas molecules. One hundred and fifty years ago, the great Scottish physicist James Clerk Maxwell derived the equation that describes the distribution of velocities for molecules at thermal equilibrium in a closed container. Maxwell's equation and subsequent confirmatory experiments show a bell-shaped distribution of velocities, with most molecules moving at velocities close to the average. Interestingly, both theory and experiment show that a small fraction of the molecules have very high velocities. Moreover, it is a fundamental fact of statistical physics that if those molecules with the highest velocities - for example, the most rapidly moving 0.1% - could be instantly eliminated from the container, then the distribution of velocities would rapidly re-establish itself in almost exactly the original form, the only difference being a small shift in the overall distribution toward smaller values. How do we explain this striking result? The explanation is that gas molecules are constantly exchanging energy via random collisions, and those molecules with lower velocities serve as an energy reservoir that can rapidly replenish the high velocity end of the distribution.

Let's consider now a distribution not of velocities but of some ideological trait, such as nationalism. At the benign end of the distribution, we find pride in regional music, language, art, etc. More centrally within the distribution, we find a desire to stay economically and militarily competitive with rival nations. Higher still on the distribution, we find chauvinistic support for wars of conquest, and, at the very highest end of the distribution, a supremacist ideology that condones barbaric behavior. Sound familiar? This continuum of ideas is an especially good description of the apparently universal human instinct for tribal thinking and the myriad ways in which it is manifest. Whether we are looking at the expansionist drive of imperial Rome two thousand years ago, the white supremacist foundations of the Confederacy one hundred and fifty years ago, or the relationship between conservative Islamic teachings and Islamic extremism today, in each case the roots of the behavioral excesses can be traced back to their ideological core. It is no accident that the Romans - supremely confident of their cultural, technological, and military superiority - imposed barbaric punishments, such as crucifixion, on those they deemed enemies of their empire.

Viewing each ideology as a continuous and interconnected distribution of beliefs imposes a moral responsibility on those who inhabit the center of the distribution. The German nationalists of the 1920s, whose cultural chauvinism stopped short of the genocidal ideology of National Socialism, might deny any responsibility for the excesses that followed, but that claim ignores the exchange of energy among molecules in the ideological gas. Similarly, the Soviet Union's terror in the 1930s, the Chinese cultural revolution in the 1960s, and the genocidal policies of the Khmer Rouge in Cambodia in the 1970s can all be seen as unsurprising extremes within the underlying ideological distribution curve for communism. In other words, it was more or less inevitable that a totalitarian ideology that claimed to govern in the name of "the people" would also brand various categories of citizens as "enemies of the people" and deal with them accordingly. For those idealistic believers in the Marxist vision of a government for the workers, this may be a bitter pill to swallow.

Today, there are a wide variety of pathologically extremist behaviors, some with secular and others with religious roots. Like the resilient distribution of molecular velocities described above, if we merely focus on eliminating the extremes of these ideological distributions without critically examining the core beliefs from which they arose, we should not be surprised to see their rapid return.

Is this view of human behavior all gloom and doom? Not at all. On the flip side of the same coin are those cultural traits that most of us hold in high esteem, such as a love of learning, appreciation for the arts, and altruism. The cultivation of these traits can also be described by distribution curves, with their overall value being determined by the thoughts and actions of the millions of individuals who make up each society. Here we can celebrate the individuals who inhabit the extremes, and we can hope that the next Einstein, Mozart, or Mandela will be nurtured by the fertile soil that we have prepared.

# Climate Change

**Letter to Graeme Davis (University of California at San Francisco) - April 2010**

Dear Graeme,

Thank you for your kind e-mail. I am honored to be an invitee and I haven't forgotten last year's discussion.

I have a possibly radical proposal that I'd like to discuss with you: perhaps I could present the lecture and talk with the students by video hook-up. This is motivated by my observation that despite the view among scientists like ourselves that global warming/carbon emissions/environmental degradation represents one of the most important challenge to our species, we are collectively doing very little to actually solve the problem.

It seems to me that the part of our business that is most ripe for change to decrease carbon emissions is long-distance travel. Conveniently, video technology now provides a low cost, environmentally friendly, and inexpensive alternative. I recently delivered a lecture to an audience in India by video link and it worked quite well, including a real-time Q and A at the end of the lecture We have a studio here at Hopkins that has the latest equipment, and except for about a 1 second delay, it is a lot like being there in person.

Addendum on air travel and jet fuel:

According to Boeing's website (http://www.boeing.com/commercial/747...technical.html), the Boeing 747-400ER in a typical 2-class seating configuration can carry 524 passengers and 63,705 gallons of fuel, and has a maximum range of 7,670 nautical miles. Each passenger, therefore, can travel up to 7,670 nautical miles using 122 (63,705/524) gallons of fuel; thus, each person would get 63.1 (7,670/122) mpg.

Let me know what you think of this.

All the best,

Jeremy

**E-mail with Menqing Xiang (Rutgers University) – September 2015**

**Menqing Xiang was a postdoctoral fellow in JN's lab from 1990 to 1995.**

Dear Meng,

I am totally serious about the carbon footprint. One hundred years from now, climate change will dominate human society. It will be the main issue that our great grandchildren will think about when they think of the legacy of our generation. As you know, China is wrestling with a serious environmental pollution challenge - so this is not just a theoretical issue.

Here's the data: burning one 1 gallon of jet or car fuel produces 25 pounds of carbon dioxide (the direct product of burning is 20 pounds, and it takes another 5 pounds to drill, transport, and refine a gallon).

According to Boeing's website (http://www.boeing.com/commercial/747family/pf/pf_400er_prod.html), the Boeing 747-400ER in a typical 2-class seating configuration can carry 524 passengers and 63,705 gallons of fuel, and has a maximum range of 7,670 nautical miles. Each passenger, therefore, can travel up to 7,670 nautical miles using 122 (63,705/524) gallons of fuel; thus, each person would get 63.1 (7,670/122) mpg.

A round-trip flight from the east coast US to China consumes about 300 gallons, which results in 7,500 pounds of carbon dioxide. That is more carbon dioxide than my car generates per year.

All the best,

Jeremy

**Letter to Martin Stratmann (President, Max Planck Society) – November 2015**

Dr. Martin Stratmann
President, Max Plank Gesellschaft
Munich, Germany

Dear Dr. Stratmann,

Thank you for your letter of November 10, 2015. I am very honored to be on your list of invitees for the Scientific Advisory Board of the Molecular Neurogenetics Research Unit at the Max Planck Institute of Biophysics in Frankfurt. I have followed and admired the work of Dr. Mombaerts for many years, so I would anticipate that service on this SAB would be intellectually stimulating.

After carefully thinking this over, I feel that I should decline for what may seem to be an odd reason: concerns about human-induced climate change. For the past 20 years I have been trying to limit my carbon footprint, and curtailing long-distance travel is a large part of that effort. The data on carbon emission related to plane travel is as follows (from the Boeing web site): the jet fuel burned per passenger is 1 gallon per 65 miles, equivalent to 1 liter per 28 kilometers. A gallon of hydrocarbon fuel produces 25 pounds of carbon dioxide (20 pounds directly and 5 pounds for drilling, refining, and transport); in metric units this translates to 3 kilograms of carbon dioxide per liter of hydrocarbon fuel. The 13,000-kilometer round-trip distance from Baltimore to Frankfurt therefore produces 1,400 kilograms of carbon dioxide per passenger. In my view, the intertwined phenomena of human population growth and climate change represent the central challenges for our species and our planet, and I would like to do my part to nudge our current trajectory in the right direction.

Let me suggest an environmentally conscious solution: identify an outstanding European neuroscientist who could serve on the SAB. For example, you might consider the following two highly accomplished mouse developmental neuro-geneticists: Dr. Andre Goffinet (University of Louvain, Brussels, Belgium) and Dr. Silvia Arber (Biozentrum, Basel, Switzerland).

I apologize for not accepting your very kind offer, and I hope that I am not creating an inconvenience for you by declining.

Sincerely,

Jeremy Nathans
Samuel Theobald Professor of Ophthalmology
Professor of Molecular Biology and Genetics
Professor of Neuroscience

**In late 2015, Peter Sterling, a neuroscientist at the University of Pennsylvania, and JN worked together to try to galvanize support within the scientific community for changes in long-distance travel that would systematically lower the community's carbon footprint. One effort involved lobbying the Society for Neuroscience leadership to reduce the frequency of its major international meeting (one of several letters to the Society's leadership is reproduced here), and a second effort culminated in an essay published in eLife (reproduced below). Nature and Science rejected earlier versions of the essay, and the initial submission to eLife was also rejected. An in-person appeal by JN to eLife editor-in-chief Randy Schekman, followed by multiple e-mails and a substantial rewriting of the essay, eventually led to the publication of an expanded and improved version in early 2016. Also reproduced below are two letters to Science that failed to convince the editors to publish an earlier version of the essay as a guest editorial or a commentary.**

**Letter to the senior leadership of the Society for Neuroscience – January 2016**

Dr. Hollis Cline
President
Dr. Marty Saggese
Executive Director
Society for Neuroscience

Dear Drs. Cline and Saggese,

We are writing with a proposal that we hope you and the extended leadership at the Society for Neuroscience will formally consider. By way of introduction, we are both neuroscientists. One of us (Jeremy Nathans) is at Johns Hopkins, and the other (Peter Sterling) is at the University of Pennsylvania.

Anthropogenic climate change is the single greatest challenge now facing our planet and our species. What was once "an inconvenient truth" has become an imminent global emergency. Beyond the certainty of rising seas and mass extinctions, there is the strong likelihood of widespread and severe social disruption.

Thus far, government actions have had only modest effects on reducing greenhouse gas emissions. It is clear that individuals and communities need to take independent action. We propose here a relatively simple step that could be implemented rapidly by the world's neuroscientists. It would not solve the problem, but it would lead by example and perhaps stimulate other communities to follow suit. The idea is to reduce greenhouse gas emission by reducing long-distance air travel.

For most of us, air travel represents the largest source of carbon dioxide emission that we could easily reduce. Consider the carbon footprint of our annual SfN meeting, with ~30,000 attendees from across the globe. On a typical commercial carrier, a round-trip plane flight of 3,000 miles leads to the emission of 1,200 pounds carbon dioxide per passenger. If we take 3,000 miles as the mean distance traveled per attendee and sum over all attendees, then the total carbon dioxide emission for travel to and from the annual SfN meeting is ~36 million pounds.

Our proposal is that the SfN cut its contribution to greenhouse gases in half by meeting, not annually, but every other year. If the SfN can take this clear and thoughtful leadership position, other large scientific societies might follow suit. If ASCB, ARVO, OSA, AMA, ACS, etc. also halve their meeting frequency, the effect on carbon dioxide emission will be substantial. And, if the consciousness of the scientific community is raised, the general population might also take note. This pro-active approach is a critical first step in changing global attitudes.

We expect that your initial reaction will be that the value of the SfN meeting outweighs considerations of its impact on climate change. We agree that meetings play a critical role in the life of a scientific field, and that there is great value in the face-to-face discussions and chance encounters that one has at meetings. However, the cost-benefit balance has shifted: climate-change costs are long-term and they are going to be staggeringly disruptive. This new reality calls for greater flexibility and greater creativity in how we conduct our business. Conveniently, we can be more connected now than ever before thanks to electronic communication technology - so we may be able to reduce some things (in-person meetings) while increasing others (electronic communication). In sum, we are arguing for a rebalancing that reflects the new reality of climate change, and we believe that SfN is uniquely positioned to lead by example.

Thank you for considering this proposal. We look forward to hearing from you.

Sincerely yours,

Jeremy Nathans
Johns Hopkins Medical School

Peter Sterling
University of Pennsylvania School of Medicine

**Editorial correspondence with Science magazine – November and December 2015**

Dr. Marcia McNutt
Editor-in-Chief
Science
AAAS

Dear Dr. McNutt,

Enclosed please find a submission for a guest editorial, authored by Jeremy Nathans and Peter Sterling. The editorial proposes practical actions by the scientific community to address climate change. Science has published many outstanding research articles, news reports, and editorials on the topic of climate change, but none have clearly laid out the case for individual and collective action by the scientific community. Our editorial presents the data on carbon dioxide production and long-distance air travel and makes a cogent case for reducing long-distance travel as a practical approach to addressing climate change.

By way of introduction, Dr. Sterling is a Professor Emeritus of Neuroscience at the University of Pennsylvania School of Medicine, and I am a Professor of Molecular Biology and Genetics at the Johns Hopkins University School of Medicine and an Investigator of the Howard Hughes Medical Institute.

We look forward to hearing from you.

Sincerely,

Jeremy Nathans, M.D., Ph.D.
Samuel Theobald Professor of Ophthalmology
Professor of Molecular Biology and Genetics
Professor of Neuroscience
Investigator, Howard Hughes Medical Institute
Johns Hopkins Medical School

Dr. Lisa Chong
Senior Editor
Science

Dear Dr. Chong,

Thank you for your detailed comments. Before addressing them, we would like to make three general points. First, our message is data-driven, timely, focused, and directly relevant to the day-to-day activities of the scientific community. Second, as determined by one of us (J.N.), the vast majority of scientists are unaware of the basic facts regarding fuel consumption per mile for air travel and the resulting carbon dioxide output per passenger per mile. And third, although our proposal is logical and reasonable, it appears to be off the radar screen for most scientists, who rarely, if ever, consider their carbon footprint when planning business travel. We hope to change that.

Your comments and our responses:

*1. At what cost are meetings cancelled? US federal agencies have fought hard against congressional attempts to limit federal scientist travel to meetings (for budget reasons) and have argued that it is necessary for scientific advancement. This editorial could undo all that good messaging.*

Point 1. We are not anti-meetings. We agree that meetings play a useful role and that there is great value in the face-to-face discussions and chance encounters that one has at meetings. However, this is a question of balancing costs and benefits. The costs are long-term and they are going to be staggeringly disruptive. This calls for greater flexibility in how we conduct our business.

There is also a credibility issue here. If the scientific community has done nothing significant to cut its own carbon footprint, how can we expect other people to listen to us when we say this is an important issue? If we are going to talk the talk then we need to also walk the walk.

Conveniently, we are more connected now than ever before thanks to electronic communication technology. We need to decrease some things (in-person meetings) while increasing others (electronic communication). In sum, we are arguing for a rebalancing that reflects the new reality of climate change.

2. *Are there other ways to offset meeting travel? E.g. Carbon credits?*

Point 2. That is possible, but the carbon credit system is complex and also a bit of a cop-out. There is simply no getting around the fact that each of us needs to burn less fossil fuel.

*3. Can meetings still be held, but fewer people travel? Use new technologies?*

Point 3. We think that the only way to make a real dent in long-distance travel is with more widely spaced meetings, because scientific societies are unlikely to impose an attendance cap. Note: our second recommendation – equally important – is to take travel distance into account when planning seminars, grant reviews, etc.

Yes, new technology has enormous potential. First, we might note that at large meetings with thousands of people in a lecture hall for a plenary session, one is watching the lecture on a large screen, and the experience for the audience members would be nearly the same if the speaker was 3,000 miles away and the lecture was being delivered remotely. One of us (JN) had an excellent experience with remote technology recently when he gave a lecture to an audience at the Eye Hospital in Hyderabad, India. There were three screens in the lecture hall and in the video-conferencing studio showing, respectively, the audience, the speaker, and the PowerPoint presentation. Except for a small delay in transmission time,

which was barely apparent during the question and answer session after the lecture, it was just like being there in person.

*4. Scientific meetings have been touted as essential for science training and career development*

Point 4. A valid point. We need to develop local events that help to fill this niche. We note that a graduate student or postdoctoral fellow does not require a national or international meeting to road-test his or her public speaking skills - a local audience is perfectly fine. Many cities have developed scientific networks that bring people together from different local institutions. Even within a single institution, there are many opportunities for career development that mimic opportunities at meetings, and more of these local opportunities can be created.

*Also, what is the evidence that travel represents the largest carbon footprint for a scientist?*

The statement was "For many scientists, long distance travel represents the largest source of carbon dioxide emission that they could easily reduce." The key word here is "easily". The details are in our reference 3, a practical guide to low-carbon living authored by The Union of Concerned Scientists. The major sources of fuel consumption that we can control are: (1) home heating and cooling and hot water consumption, (2) car travel, and (3) plane travel. Items (1) and (2) have limited flexibility. We would challenge anyone to try saving 200 gallons of home heating oil or gasoline per year. The first would require a dramatic reduction in home temperature in the winter for those locations with a real winter (e.g. a reduction of 10 degrees), and the second would require a lot less driving (e.g. a reduction of >5,000 miles). But each of us can save 200 gallons of fuel by simply forgoing one round-trip flight from the west coast of the U.S. to Europe or Asia.

*Additionally, in the Society for Neuroscience example, not all 30,000 attendees require long-distance travel.*

The Society for Neuroscience (SfN) meetings are always held in the United States and they attract neuroscientists from all over the United States and Canada (round trip distance traveled: 0 to 6,000 miles), as well as many European and Asian scientists (round trip distance traveled 10,000-15,000 miles). Based on our experience as members of the neuroscience community, we have made a conservative estimate that for SfN meetings the mean round trip distance traveled is 3,000 miles.

*It may be possible to consider this piece as a Letter, but it would have to be shortened. Let me know if that is of interest.*

We appreciate that the guest editorial venue likely implies a tacit endorsement of the contents by you and your colleagues on the Science staff, and that may not be the case here. Given the content and length of our piece, perhaps the Policy Forum venue would be a better fit. We would also be willing to consider this piece as a letter. In this case, we would be willing to have the text modestly shortened, but we do not want the piece to lose its logical flow or its power of persuasion. The 300 word limit for letters (as per the Science Information for Authors section) is definitely too short; we need at least 600-700 words.

Climate change is the single most important challenge facing our planet, and this piece is distinctive in making the case for direct action by individual scientists and by the scientific community.

Thank you for your attention to this submission.

Sincerely,

Jeremy Nathans
Peter Sterling

**Essay in eLife (co-authored with Peter Sterling) – March 2016**

eLife 2016;5:e15928

Point of View: How scientists can reduce their carbon footprint

Jeremy Nathans and Peter Sterling

Johns Hopkins University School of Medicine, United States; University of Pennsylvania, United States

Abstract: Cutting down on long-distance air travel is the best way to reduce the emission of greenhouse gases by the scientific community.

Anthropogenic climate change is the single greatest challenge facing our planet and our species. What was once "an inconvenient truth" has become an imminent global emergency that will lead to rising seas, the extinction of species and, very likely, large-scale social instability. Thus far, however, government actions have had only modest effects on reducing greenhouse gas emissions. It is clear that individuals and communities need to take independent action.

Here we propose a set of relatively simple actions that could be implemented rapidly by the world's scientists. While these actions represent only one small step in the right direction, we believe that if the scientific community leads by example, other communities will follow. The basic idea is to dramatically reduce long-distance air travel.

Although aircraft are becoming more fuel efficient, the global aviation industry has an enormous carbon footprint: the combustion of ~5 million barrels of jet fuel per day (Index Mundi, 2016) results in the daily release of ~2.4 million metric tons of carbon dioxide. Moreover, commercial aviation is the fastest growing source of greenhouse gas emissions, and it is projected that the world's commercial fleets will triple their output of carbon dioxide by 2050 (Climate Law Institute, 2015).

The carbon footprint of a scientist

For economy class travel on a commercial airplane, ~1 kg of carbon dioxide is emitted per passenger per 10 kilometers: this means that a flight from the east coast of the United States to central Europe and back (a distance of about 13,000 km) produces 1.3 metric tons of carbon dioxide per passenger. For comparison, a daily round-trip commute of 25 kilometers in a fuel-efficient car produces 1.5 metric tons of carbon dioxide per year. Thus, flying across the Atlantic and back generates roughly the same carbon footprint as a typical year of commuting by car.

To put these numbers in a global perspective, the mean carbon dioxide emission per person per year in the United States is 17 metric tons. Comparable figures for other countries include 9.3 for Japan, 6.7 for China, 5.2 for France, and 1.7 for India (World Bank, 2016). These carbon footprints reflect the total economic activity of a given country, so the carbon dioxide emissions that are under the control of an individual citizen are substantially smaller. Moreover, the per capita carbon footprint is expected to rise substantially in many countries in the developing world over the next 50 years, driven by a broad increase in the standard of living, so citizens in the developed world need to do all they can to start reducing carbon dioxide emissions now.

How does the carbon footprint of air travel compare to the carbon footprint of a typical life sciences laboratory? If we ignore the energy consumed in the heating and cooling of laboratory buildings – values that vary widely depending on locale – we find that most of the carbon footprint is due to refrigerators,

freezers and other large items of equipment. For example, it takes ~18 kW-hours per day to operate a freezer at -80°C, which translates into 4 metric tons of carbon dioxide per year (based on the US average of 1.34 pounds of carbon dioxide per kW-hour; Union of Concerned Scientists, 2012). When lighting, cold rooms, and smaller items of laboratory equipment (such as computers, spectrophotometers and incubators) are included, we estimate that the equipment in a typical life sciences laboratory of 7–10 people would likely generate more than 20 metric tons of carbon dioxide per year.

It is difficult to envision how life scientists could significantly reduce the carbon footprint associated with operating their laboratories since virtually all of the energy is used to run essential equipment. Thus, long-distance air travel would appear to be the largest source of work-related carbon dioxide emission that the scientific community could easily reduce.

To illustrate the magnitude of the scientific community's travel-related carbon footprint, consider the annual meeting of the Society for Neuroscience (SFN), which attracts ~30,000 attendees to the United States from across the globe. By analyzing the cities of origin of attendees at the 2014 SFN meeting in Washington, DC, we estimate the mean round-trip distance traveled per person at ~7,500 kilometers, which gives the meeting a carbon footprint of 22,000 metric tons, roughly equivalent to the annual carbon footprint of 1000 medium-sized laboratories.

## A modest proposal

As a first step in reducing the carbon footprint of the scientific community we propose that all large scientific societies with an annual meeting cut back to one large meeting every two years. To partially compensate, we envision a series of smaller local meetings in alternate years that would bring together hundreds or thousands, rather than tens of thousands, of participants. The proposed change would roughly halve the carbon footprints associated with the largest meetings. We have formally proposed this idea to Dr. Hollis Cline, President of the Society for Neuroscience, and she has agreed to put it before the Society's council. As a practical matter, any proposed changes in the scheduling of large national or international meetings would likely occur on a time scale of at least 5–10 years because societies have to book convention centers many years in advance. This is all the more reason to start the process sooner rather than later.

We further propose that seminars, grant review panels, interviews and other travel-intensive activities be examined with an eye toward reducing long-distance travel. For each of these activities, we should ask whether there is an equivalent seminar speaker or committee member who could travel 300 km instead of 3,000 km. For activities that do not require a face-to-face meeting, such as grant reviews, we should ask whether remote video-conferencing or a conference call could accomplish the same or nearly the same end. Scientists who do not live and work close to major scientific hubs may fear that a reduction in long-distance travel will lead to scientific isolation. Solutions to this challenge might include traveling with an itinerary that includes multiple clustered destinations and making greater use of electronic communication technology.

We appreciate that face-to-face meetings play an important role in the life of a scientific field. However, the cost-benefit balance has shifted: climate-change costs are long-term and they are going to be staggeringly disruptive. This new reality calls for greater flexibility and greater creativity in how we conduct our business. Fortunately, we are more connected now than ever before, thanks to today's technology, so we can offset a reduction in face-to-face meetings by making greater use of electronic communication. For example, when one of us (JN) was invited to lecture in Hyderabad, India, the lecture, together with a question-and-answer session, was delivered in real-time via a remote video-link from a studio at Johns Hopkins University in the US. With video screens simultaneously showing the speaker, the audience and the PowerPoint presentation, the experience was remarkably similar to a live presentation. The entire event took the speaker less time than he would have spent driving to the airport

and waiting to board the plane to India. It also vacated an airplane seat that would have generated 2.6 metric tons of carbon dioxide.

Reductions in long distance travel by the scientific community, if adopted on a global scale, could reduce carbon dioxide emissions by many hundreds of thousands of metric tons annually. Moreover, a demonstration by the scientific community that it is taking concrete action would be an important step in convincing the general public to consider similar actions. Conversely, if scientists – arguably the most highly educated, informed and intellectually rigorous members of society – do not lead by example, then who else will lead?

In summary, the changes that we propose are not small, but they are modest compared to the changes that will soon be forced upon humanity by anthropogenic climate change.

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# Autobiographical items

**David Hogness was one of the founding members of the Department of Biochemistry at the Stanford Medical School. JN worked as a Ph.D. student in his laboratory from 1980 to 1985.**

**Recollections of my time with David Hogness – September 2007**

When I began working in David Hogness's laboratory in January 1980, I was for the most part unaware of the impending revolution in developmental genetics that we now view as the status quo. I had not yet been in the field of molecular biology long enough to appreciate that rapidity of progress or to have witnessed at first hand significant scientific advances. At that time, the Bithorax Complex – into which Welcome Bender and Pierre Spierer had just stepped – was the only "interesting" locus from which DNA had been isolated. From the perspective of a beginning graduate student the isolation of a gene encoding something other that an abundant product seemed a monumental feat, and many late nights were spent discussing how one might approach this problem.

By good fortune, I was taken under the wing of Spyros Artavanis-Tsakonas, a postdoctoral fellow. While in Switzerland in the mid 1970's, Spyros realized that progress in Drosophila molecular biology would depend upon a means of stably introducing cloned DNA into the germline. Dave welcomed this bold assessment and invited Spyros to join his group. At Stanford, Spyros set about microinjecting a variety of selectable and nonselectable DNA's into Drosophila eggs. Injected animals and their progeny were then analyzed genetically or by Southern blotting. Spyros intended to spend two years pursuing this work even though he reckoned that his chances of success might be low. During the nine months that I worked with him on this project and through many days spend hunched over the micromanipulator, Spyros's good humor and well-worn tape recordings of Greek songs kept our spirits up. On a few occasions we observed a faint glimmer of hybridization on Southern blots of DNA from the progeny of injected flies; however, the signals proved to be elusive and we concluded that they were probably artifactual.

It was a special pleasure for us to learn two years later of Gerry Rubin's and Alan Spradling's spectacular success in introducing exogenous DNA into the Drosophila germline using P-element vectors. By that time, I was working on human visual pigments and Spyros was at Yale working on the Notch locus.

At the beginning of my graduate studies Dave and I fully intended that I should work on Drosophila, but events intervened to change those plans. In the fall of 1980, I heard Lubert Stryer and Dennis Baylor describe their recent work on the biochemistry and electrophysiology of photoreceptor cells. For me this was an extraordinary revelation. Here was a system that could reliably detect single photons, that turned on and then turned off the component of a complex enzyme cascade with remarkable precision, and that appeared to resemble the activation of adenylate cyclase by hormone receptor complexes. The subsequent steps of signal processing in the visual system appeared to be even more remarkable: from color opponent cells in the retina to moving edge detectors in the cortex, ultimately to the seat of consciousness. I headed for the library determined to learn more about vision.

Among the articles I read at that time, one in particular aroused my curiosity: George Wald's 1968 Nobel Lecture. In this lecture, Wald described his then recent work on the three visual pigments that mediate color vision in humans. Wald showed that these pigments appear to resemble rhodopsin, the visual pigment responsible for vision in dim light, in consisting of an apoprotein bound to an 11-cis retinal chromophore. He interred, therefore, that differences in their absorbance spectra are the result of differences in the attached apoproteins. Wald also presented evidence that the common inherited forms of variant human color vision ("color blindness") could most easily be explained by mutations in the genes

that encode the difference apoproteins. As I read, I became intrigued by the possibility that these models could be directly tested by isolating the genes that encode the different visual pigments. It is a reflection of Dave's generous nature and broad scientific interests that he encouraged me to follow this idea. He also maintained an infectious optimism that was especially welcome during the first two years of this work when I made very little progress.

Our experimental approach was to first isolate cDNA and genomic DNA clones encoding bovine rhodopsin and then to use these DNAs as hybridization probes to isolate the genes encoding the human visual pigments. This strategy depended on the assumption that all of the visual pigments are members of a family of homologous proteins encoded by the corresponding members of a family of homologous genes. On evolutionary grounds this seemed like a reasonable guess. As it turned out, this hypothesis proved to be correct, and we found that the human visual pigment genes bear a degree of homology to the bovine sequence just sufficient to permit their isolation by this approach. In the course of this work, we observed that the genes coding for the red and green sensitive pigments appear to lie in a tandem array on the X-chromosome, and that unequal recombination produces variation in gene number in color normal subjects. Remarkably, unequal homologous exchanges also account for the genotypes of color variant subjects. Nearly all color variant genotypes differ from normal with respect to gene number and/or by virtue of possessing hybrids genes.

I am pleased to add that our work on human visual pigments has returned an unexpected dividend to the Drosophila community: Charles Zuker and Gerry Rubin have used our bovine rhodopsin probe to isolate the gene coding for the major Drosophila rhodopsin. Their work paves the way for an in vivo analysis of visual pigment structure and function. It also represents a first step in addressing the fascinating question of how during development each photoreceptor cell chooses to express the correct visual pigment gene.

With my departure, the work on visual pigments has quietly ended in Dave's lab. During my six years there, Dave left an enduring mark on vision research and on me.

**Comments at a reception for the Champalimaud Award at Johns Hopkins – October 2008**

I would like to start by thanking Drs. Miller, Sommer, Beleza, Greider, and Huganir for their kind words. I would also like to thank everyone who took the time to come to this event – especially Dr. Beleza who has come all the way from Lisbon.

It is a special honor to share the Champalimaud Award with my good friend and colleague, King-Wai Yau. This is the second year in which the Champalimaud Foundation has focused international attention on innovative vision research and clinical ophthalmology. In an era of increasingly tight funding for biomedical research, the Champalimaud Foundation's bold initiative to support the most creative vision research encourages all biomedical scientists to dream the big dreams. I salute Dr. Beleza and the Champalimaud Foundation for your wisdom and generosity.

The Champalimaud Award explicitly recognizes not the individual scientist but the entire laboratory. This is altogether fitting, because research – at least of the sort that we do – is very much a team effort. A research team's accomplishments reflect the expertise, creativity, and hard work of students, technicians, postdoctoral fellows, and senior researchers; occasionally the principal investigator also makes a contribution. In fact, the team is really much larger than that: it also includes the people in core labs, administration, facilities, housekeeping, animal care, and a wide variety of other jobs. It is a complex ecosystem, and we are very fortunate at Johns Hopkins to having amazing talent and dedication at every link in the web.

Another attribute that makes great research happen at Johns Hopkins is the collegiality that is so much a part of the fabric here. At every level there is an openness and a friendliness that makes it easy to work together or to ask for advice. It can feel like being part of a big family; for some of us, it has been family.

In closing I would like to take this opportunity to salute the many heroes of scientific discovery at Johns Hopkins: not only the scientists at the bench but all of the members of the Johns Hopkins family whose hard work and dedication make great discoveries possible.

**Comments at Stanford Medical School – May 2013**

**In 2013, JN received the Arthur Kornberg and Paul Berg Lifetime Achievement Award from Stanford Medical School.**

It is great to be back at Stanford in the company of so many good friends. I am very grateful and deeply honored to be associated via this award with Paul Berg and Arthur Kornberg, two scientists whom I have long admired and whose discoveries and leadership profoundly influenced biomedical research.

In a lighter vein, I can't help noting that the phrase "lifetime achievement" has a slightly ominous ring. I hope to be at the lab bench for at least a few more years before I hang up my pipettes.

An award of this sort recognizes many people. High on that list are the students, postdocs, technicians, and research associates who have worked with me at Johns Hopkins for the past 25 years and whose hard work, drive, and creativity are largely responsible for whatever progress we have made.

This award also recognizes the deep commitment of the Stanford community to the mentoring of young scientists. Mentoring is like gardening - creating the right environment is essential if one wants to nurture the growth of young plants or young scientists.

I would like to take this opportunity to say a heartfelt "thank you" to the many people at Stanford who created the remarkable scientific environment here, and to those whose collegiality, mentoring, and friendship have been so important, including my medical school and graduate school classmates, the postdocs and support staff who were my contemporaries, and the faculty who were here in the 1980s.

The faculty members in the Biochemistry Department were especially influential. For example, Arthur Kornberg let me know at regular intervals that my education would not be complete without purifying an enzyme. He generally did this by asking: "Well, Jeremy, have you purified an enzyme yet?" I had to confess that I had not. But the larger lesson that I learned from Arthur and the other members of the department was the importance of creating a community in which everyone felt like they were part of the family.

When I was a graduate student, I was very fortunate to work with David Hogness. Dave was fantastic. Dave loved to discuss science and he had an amazing ability to think in a way that was both highly rigorous and highly original. As an advisor, Dave had a light touch - he was helpful, encouraging, and inspiring, but he gave his students a lot of freedom.

Once, at a departmental retreat, a new postdoc overheard Dave say: "The lab I have now is the smartest lab I've ever had." The newcomer looked at me, Phil Beachy, Rick Lifton, John Carlson, and the other members of the Hogness laboratory and thought - as he told me later - "these guys must really be good." However, as Dave's conversation continued it became apparent that he was referring to his new Labrador retriever.

As a student, I was also very fortunate to have Lubert Stryer as an informal mentor. On various occasions, Lubert would call me in the lab and say "I have an interesting idea", and I would come over to his office to hear the latest. Thirty years later, I still recall those conversations as some of the most stimulating of my career.

Let me conclude with the most important "thank you" - to my wife, Thanh, who is here in the audience. Thanh and I met here as first year students 33 years ago and we have been together ever since.

**Comments on the inauguration of the Samuel Theobald Professorship – June 2013**

It is a great honor to be here on this very special occasion. An endowed Professorship represents a unique link across generations. As it is handed from one person to another it represents and enables the spirit of free inquiry that is at the core of every great university. It is especially fitting that we should honor Samuel Theobald, the first Johns Hopkins ophthalmologist, in this way.

There are many people who have made this day possible and to whom I would like to offer my most sincere thanks. First, to the generous donor who made this professorship possible. The donor wishes to remain anonymous, and therefore I cannot thank him by name. Second, I would like to give a special thank you to Peter McDonnell, Director of the Wilmer Eye Institute, for envisioning and catalyzing this professorship. I have learned and continue to learn a lot from Peter, mostly by osmosis - that is, just by watching how he handles things. Similarly, I learned and continue to learn from Mort Goldberg, who still keeps me up to date with the latest papers and also keeps me on my toes with challenging questions. During my 27 years at Johns Hopkins, the Wilmer community has been a source of wisdom, inspiration, and friendship. I cannot resist mentioning that three graduates of my lab - Shannath Merbs, Pradeep Ramulu, and Don Zack - are currently faculty members at Wilmer. I am incredibly proud of each of them.

As you know, my primary appointment is in the Department of Molecular Biology and Genetics. MBG is a remarkable department. It is built on a foundation of mutual respect, collegiality, and a commitment to outstanding science. Under a succession of far-sighted leaders - Barry Wood, Dan Nathans, Tom Kelly, and Carol Greider - it has become one of the most influential molecular biology departments in the world. I would like to extend a heartfelt thanks to my faculty colleagues, the support staff, and the students, postdocs, and technicians in MBG who have made the department what it is today.

The success of any laboratory rests on many shoulders. I am standing here as the representative of the Nathans laboratory. But the credit for whatever success we have had goes to my team mates, past and present. I would like to particularly mention those who have been on the team for the long haul: Yanshu Wang, Amir Rattner, Phil Smallwood, John Williams, and Terry Stromsky.

I would like to say a special thank you to my family: my wife, Thanh, my daughters, Riva and Rosalie, and my parents and brothers. They have made all the difference.

In most of life's endeavors - but especially in scientific research - it takes a lot of sweat to make even the smallest advance. In science, the challenge is compounded by the uncertainty of not knowing, for much of the time, if one is even on the right track. It takes a combination of flexibility, ruthless honesty, irrational optimism, and stubbornness to tease out even the smallest of Nature's secrets. But that moment of insight - sometimes sudden, sometimes gradual - when a scientist realizes that a little bit of what used to be terra incognita is now and forever known is priceless.

Now, a few words about vision research, the area in which I have worked for 35 years. Like many researchers, we have been strongly motivated by the hope that our work will help people who are suffering from or at risk for vision loss. Over the years, much of our research has centered on inherited

diseases of the retina, and during the past few decades our lab and other labs have been able to put the genetic and biochemical basis of many retinal diseases on a sound scientific foundation. But, I am sure that everyone in this room appreciates that these insights represent just one step on a long and challenging journey toward improved prevention and treatment. There is a still a lot of work ahead.

There is a second motivation for our fascination with vision research. The visual system is stunningly beautiful. It is a tour de force of engineering, in which the most intricate anatomy is elegantly wedded to function. In The Origin of Species, Charles Darwin reserved a chapter for potential challenges to his theory of natural selection. Among the most serious challenges was the existence of what Darwin referred to as "organs of extreme perfection". Exhibit A was the vertebrate eye. One and one-half centuries after The Origin of Species was published, I am happy to report that current molecular analyses support the view that the eye has, in fact, evolved step-wise from simpler light sensing structures. Darwin would be gratified.

In closing, let me say that being a biomedical scientist at Johns Hopkins is a great privilege. It is hard to imagine a better way to spend one's professional life. And for that, I am very grateful.

# Transcripts of Lectures

**Presentation to the Johns Hopkins Medical Institutions Board of Trustees – March 2002**

Genetics and Biomedical Research

In his inaugural address in 1961, John F. Kennedy observed that the human species was "standing on the edge of a new frontier". The frontier to which Kennedy was referring was the frontier of scientific knowledge, and he challenged his fellow citizens to explore it for the betterment of all mankind. Forty-one years later we are the heirs to that challenge, and in this talk I hope to give you some sense of the excitement that I and my colleagues feel as we pursue research at that frontier.

While thinking about this presentation, I was reminded of a story told by my Ph.D. thesis advisor, David Hogness. Many years ago, Dave was invited to present his genetics research to the Physics Department at Stanford. In introducing him, Dave's host suggested that the speaker would do well to remember that although those in attendance did not know very much about genetics they were VERY smart. I'll make the same assumption here.

Forty years ago, few people could have foreseen the revolutionary advances in biological understanding that were to come, a revolution that has occurred within the lifetime of practically everyone in this room. We can date the beginning to 1953 when Jim Watson and Francis Crick proposed a structure for deoxyribonucleic acid – DNA - that laid out in a single stroke how biological information is encoded and copied. It is worth spending a minute reviewing that structure and its implications.

First, DNA is a long chemical chain. It consists of a string of chemical building blocks - we call them bases - connected together like beads on a string. There are four kinds of bases and these differ in their chemical structures. We abbreviate them with the letters A, C, G, and T. This much was already known in 1953, and it was also known at that time that DNA was - somehow – the carrier of genetic information. In other words, it carried the blueprint for building the entire organism. The first point Watson and Crick made is that the bases are essentially the letters of an alphabet and, as in any written language, the information is coded by the order of the letters which spell out words, sentences, and paragraphs. So there is a language that uses these four letters, and if we could only understand that language we would, in essence, be able to read the book of life.

Watson and Crick's second point was that the structure showed two complementary strands of DNA mutually intertwined. Wherever one strand had a base of type T, the other one had an A; and wherever one strand had a G, the other one had a C. In this way, each place on one strand fit the corresponding place on the other like a key fits a lock. I think you can see that this structure immediately suggests how the genetic material is copied. Since each strand carries all of the information to specify the other, the two strands can come apart and each one can serve as a template upon which a new mate can be constructed. Finally, implicit in this structure was another very powerful idea: that random changes in the sequence of the DNA bases - essentially random typos in the book of life - are the raw material of evolution and also the basis of genetic disease.

What was missing in 1953 was a connection to proteins. Proteins are another kind of complex molecule, and they are also made of building blocks strung together like beads on a string. In the case of proteins, the building blocks are called amino acids, and there are 20 of them. The 20 different amino acids differ in size, shape, and various chemical properties. Proteins don't encode or store information, rather they

are the machines that do virtually everything in living cells. For example, one kind of protein, called hemoglobin, carries the oxygen in your blood - taking it from your lungs to every part of your body.

A critical aspect of what makes each protein unique is its three dimensional shape: this is determined by the sequence of amino acids along the chain. In a protein, the amino acids fit together like pieces of a giant three-dimensional jigsaw puzzle. (Show hemoglobin model - note this is just the backbone.)

Let me make a very brief digression here and give you some numbers regarding protein sequences. As I mentioned, there are 20 different kinds of amino acids. Suppose we had a protein chain consisting of only two amino acids strung together. How many different kinds of such proteins could there be? This is easily calculated: there are 20 possibilities for the first position, and for each of those there are 20 possibilities for the second position. So altogether there are 20 x 20 = 400 different kinds of chains that are two amino acids in length. What if the chain were three amino acids in length? Then there would be 20 x 20 x 20 = 8,000 different possibilities. For a typical protein of 300 amino acids in length the number of possible sequences is: 20 x 20 x 20, etc. 300 times. That turns out to be a VERY big number. It is a 1 with about 370 zeros after it - even bigger than the national debt. Actually, that number is far larger than the number of atoms in the universe (which is 'only' 1 with about 80 zeros after it). What this means is that the number of protein sequences that exist on earth is only an extremely tiny fraction of the possible sequences. There is still plenty of room for evolutionary innovation.

In the 1960's the code for reading out one kind of information from the DNA sequence was determined. This code - which we call the genetic code - showed how the sequence of DNA letters coded for the particular sequence of amino acids in each protein. It is actually very simple. Three DNA letters in a row code for an amino acid. For example, the three DNA letters ATG code for the amino acid methionine and the three DNA letters TTC code for phenylalanine. The details of how the cellular machinery uses the DNA sequence to direct the assembly of proteins is now pretty well worked out, but in the interests of time we won't go into it here.

Before we relate DNA and proteins to the rest of biology, let me say a few things about the complexity of biological systems. To me the two things that are most striking about biological systems is how well they work and how small the pieces are. To illustrate the second point, let's make a comparison between biological and man-made machines. As a typical example of the man-made variety, let's take an automobile engine. Here is a diagram of the parts of a carburetor. Each part is roughly one centimeter in size, with a range of perhaps a factor of 10 bigger and smaller. The engine itself is roughly one meter on each side, a cubic meter in volume.

How about biological systems? If we take the individual amino acids as the basic machine parts, then the dimensions of the parts are about one ten millionth of a centimeter - about one ten millionth the average size of the car engine parts. Therefore, a living organism packs the complexity of an automobile engine into a cube that is one ten millionth of a meter on each side. Even if we compare man-made objects that are at the limits of current nanotechnology - as seen for example by the gear which is shown on this slide next to the head of a pin - the smallest man-made objects are still thousands of times larger than the biological ones.

This extreme miniaturization means that most biological structures of any significant size are EXTREMELY complex. Take for example the human brain, which measures roughly 10 cm on a side, and is the single most complex biological structure that we know. The preceding calculation predicts that the human brain has roughly one million trillion times the complexity of a car engine.

Given this biological complexity, one might suppose that the blueprint that encodes it all would be very large. It is and it isn't, depending on your point of view. As I am sure you know, the nearly complete sequence of the human genome has been determined by the efforts of both NIH-funded and private

laboratories. There are still a few gaps, but we've got at least 98% of it. Interestingly, only 3 billion bases are required to encode a complete human being.

Is this a lot or a little? It is about one thousand times more than a bacterium has and about 30 times more than a fly. But it turns out that a lot of our DNA is not used to encode proteins - in fact less than 2% of it encodes proteins. Other parts of the DNA are used to regulate when and where each protein is made - for example, we want hemoglobin to be made in red blood cells but not in the brain. Figuring out how the DNA encodes information to determine that each gene is activated at the right place and time is one of the most exciting frontiers in this business because what ultimately distinguishes different kinds of cells - red blood cells and brain cells, for example - is a difference in the choice of which genes are active and which are not. For completeness, I should add that we also know that a lot of our DNA is junk - like obsolete copies of software that fill up your hard disc but will never be used again.

Returning to the theme of miniaturization, it is an amazing fact that two copies of the human genome - one from your mother, and one from your father - are neatly packaged into every cell in your body in a space somewhat less than one one-thousandth of a centimeter across.

Let's relate the 3 billion letters of the human genome to the amount of text we typically handle. Since an average printed page contains about 4,000 letters, it will take 750,000 pages to print the human genome sequence, or 750 volumes at 1,000 pages per volume. Importantly, this information can fit neatly onto one compact disc. And here I want to take the opportunity to note that the biology revolution is inextricably tied to the information revolution, because with this quantity and complexity of genetic information we need the most powerful computing tools we can get. At present, the NIH provides much of this. For example, anyone anywhere in the world with an internet connection can log onto the NIH web site and use the NIH supercomputers to search the human genome sequence for patterns, or compare normal and disease-associated sequences, or compare sequences from various organisms, and so on. This is all done in real time with the results typically coming back to the user within 5-10 seconds.

What can we glean from the human genome sequence with our present level of understanding? First, we have a complete parts list for our species. If we take our automobile analogy, this is like having all the parts of a car spread out on the floor of a huge warehouse. Actually, it is more than just a list of parts because living organisms are self-assembling, so it is really like having all of the parts of the car PLUS all of the parts of the car factory spread out in the warehouse. Actually, it is even more than THAT, because built into the system are a whole series of instructions for responding to external changes, for example changes in temperature, availability of food, infection, and so on.

Neglecting for the moment all these additional complexities and if we simply consider the original analogy with the car parts on the warehouse floor, it is obvious that we will need more than just a catalogue of parts to understand how the system works. In particular, we need to know (1) how the parts fit together and (2) how they function. For example, how is a muscle built from a thousand different kinds of proteins? I think you can also see that if the medical profession, which we equate with the auto mechanic in this analogy, is going to be able to treat disease - or even better prevent disease - then we will need to have a deeper understanding of how the parts function.

The classic genetic approach for getting at the question of how the parts function is to look at what happens when they fail - that is, when individual genes are mutated. To go back to the automobile analogy we could try to identify all of the components involved in braking by studying cars that can't stop properly and determining for each one what was defective. The result would be a sub-list of parts: the brake pedal, the brake pads, etc. We still wouldn't fully understand the system but we would be a step closer. Although we ultimately need a multipronged approach to fully understand a biological system, there is something uniquely powerful about the genetic approach because DNA sequencing techniques leave no doubt about whether the gene sequence is normal or defective.

I would like to also add that in comparing the human genome sequence with the partially complete sequences of other mammals, such as mice, the parts lists are virtually identical. In fact, it is uncanny how similar the sequences are, and it gets even more remarkable as we look further along our little branch of the evolutionary tree. Chimpanzees, our closest living primate relatives, have DNA sequences that are 99% identical to ours. This incredible similarity at the molecular level means that we can learn a lot about ourselves from studying our evolutionary relatives.

Let's shift now to the particular area of research that is the focus of my laboratory: the development and function of the visual system. A significant part of our research program is also focused on diseases that impair vision. The next slide shows the parts of the central nervous system that are devoted to vision. At the front end are the two eyes, and then deeper within the brain are all of the circuits for analyzing the image, comparing it to our memories of earlier images, correlating it with inputs from other senses, and so on.

The next slide shows a cross section of a human eye. Our work has focused largely on the retina, the thin layer of nerve cells that lines the back wall of the eye. If you think of the eye as a camera, then the retina would be the film. The retina is the part that absorbs light, records the image, processes it a bit, and then sends an encoded version of the image along the optic nerve to the brain.

The more I study the eye the more impressed I am with its performance. For example, the retina has a built-in mechanism that adjusts its sensitivity to light from second to second, and it does this independently for different parts of the image. It is what an engineer might call "smart film". As a result, we can see well on sunny afternoons and on moonless nights, situations in which the amount of light striking the retina differs by over a million-fold.

Charles Darwin was also impressed with the eye. In his book The Origin of Species, one chapter is devoted to “difficulties” with his theory - that is, observations that would seem to run counter to progressive evolutionary change by natural selection. One of the gravest difficulties comes from what Darwin calls "organs of extreme perfection", and to illustrate the point he takes the eye as the example. The difficulty for Darwin 's theory is that the eye is so incredibly good at what it does, so perfectly “designed”, one might say, that it is hard to imagine that it is not the product of a supreme designer. After a few pages of handwringing, Darwin eventually brings the chapter to a happy ending by arguing that it should be possible after all to produce an organ of such perfection given enough time and selective pressure.

Now let me describe, briefly, one area in which we are actively working. We are interested in determining the disease mechanisms responsible for macular degeneration. In macular degeneration the central retina - which is referred to as the macula - undergoes a progressive degeneration, and there is a resulting loss of central vision. The central part of the retina is specialized for vision with high spatial resolution. That is why when you read a newspaper your eyes move back and forth in their sockets, sweeping your gaze along the page. To see at the high resolution required for reading newsprint you must image the letters on the central retina. I invite you, while reading, to fixate on one word and then, without moving your gaze, to try reading other words that are more than a few centimeters away. You can’t do it because the spatial resolution of your peripheral vision is too low.

Why is the system built this way? The reason, we think, is because the optic nerve that connects your eye and your brain has a limited number of cables, which therefore limits the amount of information that can be transmitted. The best way to use the limited capacity for information transfer is by having 99% of the retina send a coarse- grained signal - which is just good enough to let you know if something interesting is happening in your peripheral visual field. The fine-grained, high-resolution signal comes only from the central 1% of the retina. We are normally unaware of this design feature in the human eye because eye movements allow us to rapidly image the region of interest on that central 1% of the retina. The down

side of this design feature is that if we lose function from even a millimeter or two of central retina we will suffer an enormous loss in visual acuity.

Macular degeneration is especially common in older individuals - in the U .S. roughly 2 million people suffer from it in one form or another. Just as a point of interest, could everyone in this room who has or had a close friend or relative with macular degeneration raise their hand? A look around the room indicates that this is a disease that touches many lives.

Our approach to this problem is to study those relatively rare patients who have early onset macular degeneration - for example, starting in the teens or twenties. The next slide shows what the retina of one of these individuals looks like when viewed through the ophthalmoscope. The individual with macular degeneration has abnormal yellow deposits in and under the retina and also shows a loss of the pigmented cell layer behind the central retina.

It is interesting that these early onset cases of macular degeneration are almost invariably genetic in origin, whereas the sort of macular degeneration that we see in older individuals appears to have both genetic and environmental causes. Why are early onset diseases more often purely genetic? Most probably because there hasn't been enough time for environmental effects to act, or to act independent of a genetic predilection. Any auto mechanic would be able to appreciate this. If you have two cars with brake problems and one has gone 2,000 miles and the other has gone 200,000 miles, most likely the first car has a problem that came from the factory (equivalent to a genetic problem) whereas the second probably just has old brake pads.

I should mention that this strategy of trying to find the purely genetic forms of a disease is a very powerful approach for two reasons. First, we now have the methods to track down and identify the mutant genes and, second, a full understanding of the genetic forms is very likely to produce important insights into the more common and more complex forms that are harder to analyze.

Our work on early onset macular degeneration has recently led us to identify the function of two genes that cause this disease. One of these genes codes for a transporter protein that we have shown plays a critical role in recycling the chemical that retinal cells use to absorb light. Loss of this transporter leads to an accumulation of the chemical in the retina, and its conversion into a toxic derivative. Interestingly - or ominously, depending on your point of view - the same toxic derivative is accumulating at a slower rate in the retinas of all of us. Therefore, we suspect that this toxic compound may also play a role in producing the late onset forms of macular degeneration.

The second gene that we have studied codes for a new class of ion channel – essentially a miniature gate that allows only particular types of molecules to enter or exit cells. This channel is present in the pigmented cells immediately behind the retina. These cells help the retina in many ways, including providing nutrients and removing waste products. To return again to the automobile analogy, the retina is like a Ferrari - high performance but also high maintenance. It has lots of parts, and many things can go wrong. Apparently, the defect in ion movement into or out of the cells adjacent to the retina leads ultimately to dysfunction of the retina itself. We are now hard at work investigating the mechanism by which that happens.

Let me close on a somewhat more philosophical note. One of the great frontiers ahead of us - arguably the greatest frontier - is to understand how the human mind works. Figuring out how we perceive the world is one small part of that quest, and here vision research can pose deep and, I believe, answerable questions about brain function. Ultimately, the complete explanation will tell us how the mechanisms of perception are encoded within our DNA.

Let me give you two examples. We know a lot about how colors are analyzed, at least at the front end of the visual system. Within the retina, one set of nerve cells computes the relative intensities of red vs.

green colors and a second set of nerve cells computes the relative intensities of yellow vs. blue colors. Interestingly, it is only the relative intensities that the retina tells the brain - the brain never gets to see the raw data. The next slide illustrates one consequence of this design feature, namely the production of afterimages of complementary colors. These nerve cell circuits must be encoded within our DNA, but at present we do not know how.

The second example is more complicated. The human brain has an amazing ability to synthesize complex visual inputs. We are generally unaware of this ability simply because we do it so effortlessly. For example we can recognize faces far better than any computer vision program. Indeed, the computer scientists were among the first to draw attention to these remarkable abilities because they were having such difficulty reproducing them with machines. In the next slide we see a pattern. Can you guess what it is? It is a detail from a painting by Chuck Close, and the last slide reveals it to be an eye. It is made up of elements that are completely foreign to our normal visual experience, yet it is effortlessly synthesized into a uniquely recognizable face when put in the right context. Figuring out how the brain does this sort of thing is truly the next frontier.

**The Vertebrate Retina (iBioSeminars video transcripts) – August 2008**

The Vertebrate Retina Part 1A

I am Jeremy Nathans. I am a Professor at the Johns Hopkins Medical School and an Investigator of Howard Hughes Medical Institute.

This is the first of three lectures on the Vertebrate Retina: its structure, function, and evolution. In this first part, we are going to look at photoreceptors and image processing. Let's start with a look at the visual system in its entirety. It consists, of course, of the eye and a significant fraction of the brain, as indicated by these arrows. That is really too much for three lectures, and so we are going to concentrate just on the eye and the inner workings of the retina within it.

Let's have a closer look at the vertebrate eye. Light enters the vertebrate eye by refraction at the cornea-air interface and again by the lens. The image is formed on the back wall of the eye, which is lined by a thin layer of neural tissue called the retina.

A comparison of the eye to a camera is irresistible. You can see that many of the components are the same: they both have an aperture, and they both have a lens. The image is formed on the back wall of both. On the back wall of the camera there is the film, and on the back wall of the eye there is the retina. The image is inverted, of course, by refraction at the cornea and the lens. But there is a critical difference between a camera and the eye: and that is that the retina doesn't just capture the image the way a film does. The retina also processes the image and extracts from it those aspects of the visual world that are most important to the organism.

This amazing piece of engineering has captured the imagination of scientists for centuries. The performance of the retina is quite remarkable. For example, the retina performs - indeed, the whole visual system performs - extremely well on a moonless night and extremely well on a sunny afternoon, when the ambient light levels differ by a million-fold. The retina is also capable of discriminating objects that differ in their angular position by only 1% of one degree. An amazing performance! In fact, that performance gave Charles Darwin a bit of a nightmare. In his "Origin of Species", he had written a chapter - a critical chapter - that he called "Problems with the Theory", in which he examined what he called "organs of extreme perfection". By this he meant organs that had achieved such remarkable abilities that they seemed to fly in the face of his simple idea of evolution by small stepwise changes - and the star witness for this collection of organs of extreme perfection was the eye. In the end, Darwin concluded that perhaps the eye could have evolved stepwise, but I think it gave him a bit of a headache.

Today, we are going to talk mostly about the vertebrate eye but I want, just for completeness, to note that this is not the only structure that evolution has come up with to capture light and to analyze it. Insects have an anatomically quite different arrangement. Here is a fruitfly. It has a pair of eyes on either side of the head. But each eye is really a collection of hundreds of little eyes, called ommatidia, and for many years that anatomic difference was thought to reflect a very different evolutionally pathway to the production of an eye. However, in recent years it has become apparent that a number of the molecular players are similar – indeed, virtually identical - between insects and vertebrates, although the overall anatomy is quite different. For example, the light sensing proteins, which we will talk about in detail in a few minutes, are nearly identical between insects and vertebrates. Perhaps more surprising, so are the genes that control the development of the eye, including one in particular called Pax6, a master regulator gene of vertebrate eye development.

In insects, Eyeless and its close cousin, Twin-of-Eyeless, function in largely the same ways as Pax6. These genes have dramatic effects on development of the eye. Let me show you one example of how dramatic the effects of these genes can be. This is an experiment in which either the Eyeless gene or the Twin-of-Eyeless gene has been over-expressed in incorrect locations in a fruit fly. On the left we have

over-expression on the legs and these red patches on both legs, left and right, are eyes that developed on the legs, simply because the gene was over-expressed! On the right we see a fly where an eye has appeared on the antenna, where there shouldn't be an eye.

For the rest of this lecture, we are not going to say anything more about invertebrate vision, and at this point we will return to the vertebrate retina, which is the object of our lectures today. Let's look at its overall structure. The retina is a layered structure. It is rather thin, substantially less than a millimeter in thickness. In the outermost layer, we see the photoreceptor cells, the rods and cones. These are up here. The rods are thin cells, and are more numerous. The cones are the thicker cells. Then there is a second layer of intervening neurons: the bipolar, horizontal, and amacrine cells. And finally at the bottom there is an output layer of cells, which send their axons to the brain: these are the retinal ganglion cells, the final arbiters of the information that will flow to the brain.

Let's have a slightly closer look at the photoreceptors cells. Here is a scanning electron micrograph showing the rods and the cones in a salamander retina, and you can see that they are quite unusual-looking cells. The cones are the little ones with these cone-shaped tips, and the rods are the big ones with these barrels, the rod-shaped parts. Each cell has one of these specialized appendages - they are called 'outer segments'. They are really modified cilia, and they hold all of the light sensitive machinery and the enzymes that transduce the light information following light capture.

Let's look again - now at even higher magnification - at the internal structure of one of these outer segments. Here is a transmission electron micrograph. What we see is that the outer segment is filled with membranes and they are layered like a stack of pancakes. There are about a thousand of these flattened membrane sacks within a single outer segment. Why is it built this way? Why are all of these membranes present? In addition, why are they stacked in this configuration? The answer is that the light sensing protein, generically called visual pigment – rhodopsin in the case of rods - is an integral membrane protein and it resides in this membrane. In fact, the membrane is virtually a liquid crystal of the visual pigment.

Here is the three dimensional structure of a visual pigment: this is bovine rhodopsin. You can see it has seven transmembrane domains: those are the cylindrical objects passing through the membrane, which is in the horizontal plane here. Rhodopsin is a G-protein-coupled receptor. All visual proteins are G-protein-coupled receptors. They act by catalyzing the activation of a G-protein, which then transmits the signal further within the cell. We will discuss that in a minute.

One can ask what part of the protein actually absorbs light. Protein side chains do not generally absorb visible light. In some cases, they show absorption of ultraviolet light. The thing that absorbs visible light, which is shown here in red, is the chromophore - 11-cis retinal, which is a different compound, and is joined covalently to the receptor protein. This is what 11-cis retinal looks like in schematic form. It is a vitamin A derivative. We don't make it ourselves; we have to eat it. Vitamin A, or its precursor beta-carotene, comes from a variety of plant sources; carrots are a good source. 11-cis retinal is bound covalently to the terminal amino group of a lysine that is part of the light-sensing protein.

Light does only one thing in all of vision. It isomerizes retinal from cis to trans. In the dark state, which is the unexcited state, there is one double bond in the cis configuration and that is the 11-12 double bond. Photo-isomerization, as shown by the transition from the upper to the lower structure, converts that cis bond to a trans bond. That is it! This happens in about $10^{-12}$ seconds from the moment of photon capture. Everything else that happens in terms of receiving and amplifying the signal happens as a consequence of this isomerization.

What does this do to the protein? If you think like a pharmacologist you can conceptualize the dark form of the visual pigment, with the 11-cis form of retinal, as having an antagonist that sits in the binding pocket keeping the protein in the 'off' configuration. It keeps the protein silent. The isomerization,

which converts the chromophore from the 11-cis to the all-trans form, then activates a series of conformational changes in the attached apo-protein – producing the 'on' state.

There is one new player in the photo-sensing world that has just emerged in the last decade. That is an additional light-sensing pigment that is in the vertebrate eye but not in the rods or cones. This came as quite a surprise. This is a visual pigment, that we call melanopsin. It resides in intrinsically photosensitive retinal ganglion cells, located in the third and output layer of the retina, where one would not have expected to find direct photosensitivity. It turns out that a small subset of those ganglion cells have a response like the one shown here: we see this very slow time course of response to a pulse of light. The square wave is the pulse of light. This very slow response is typical for these intrinsically photosensitive retinal ganglion cells. That is far too slow to be useful for image forming vision - for example, the sort of vision that lets us play tennis or walk around. However, it is just the sort of response that is useful for rather slower visual tasks, for example, constriction of the pupil. When the ambient light increases or decreases, your pupil constricts or dilates accordingly. Another example is entraining neural rhythms to the light and dark variation that occurs over 24 hours, the circadian rhythm. In fact these intrinsically photosensitive retinal ganglion cells mediate exactly those two functions.

Now let's ask a question which has been asked by many vision scientists over a very long time period. What is the absolute sensitivity of human vision? In other words, what is the dimmest light that we can see? This is a question that has been of interest not only to vision scientists but also to astronomers. In the days before electronic detectors or film, an astronomer like Kepler or Galileo or Newton would look through the telescope with the naked eye. So the question naturally arose: "How good is the eye?" For example, are there stars out there that are so dim that we can't see them because the eye is not sufficiently sensitive? Of course, we now know that the answer is "Yes, there are many stars that are far dimmer than can be seen with the naked eye".

In addressing this question you might think it is not that difficult experimentally to obtain an answer. We could simply start with a calibrated light source, so we know how many photons it is delivering per unit time. We will then deliver some stimulus to the eye and we will simply calculate the number of photons required to see the stimulus. To first approximation, that is the way the experiment is done. If you do it with all due preparation - that is, you have the subject fully dark adapted by sitting in a pitch-black room for a half an hour or so, then you deliver a very brief and very tiny flash of light, which is the best stimulus, and you deliver it to the most rod rich region of the retina because rods are more sensitive then cones - you can get an answer that turns out to be a rather small number of photons. About 100 photons must be delivered to the cornea for the person to say: "Yes, I saw the flash of light". That is an impressively small number, but it doesn't get fully at the answer. What we would really like to know is how many photons must be captured by the photoreceptor cells to produce a visual sensation, not how many arrive at the eye from the outside world - because many of those photons, in fact, may not be used at all. Many of the photons that arrive at the eye may be wasted if they pass through the retina unabsorbed. In fact, that is the case: the eye is not 100% efficient in its ability to capture and utilize light information.

In the quest to figure out exactly how many photons need to be absorbed to produce a visual sensation, Selig Hecht, one of the greatest vision scientists, thought of an extremely clever approach. Hecht's method relies on the statistical variation in the number of photons delivered to the eye in one of those flashes - that is, the variation from trial to trial - as a way of determining the minimal number of photons that is required to see a flash of light.

Let's follow this experiment. I am going to give you two numerical examples that will illustrate the method. Imagine that we delivery - in the upper example here - a certain number of photons per flash, and we will say that the average number is three. Every time the shutter opens, on average three photons strike the eye as a result of that one millisecond flash of light. Let's imagine, for the sake of this example, that 5 or more photons are required to allow the person to actually see the flash of light: that is to say, 5/3

as many photons as were delivered on average per flash. If one is delivering on average three photons per flash - and recall that photons emerge from a filament of a light bulb independently and at random – then this number will vary in a Poisson manner - that is, in a random manner. The variation in the number of photons delivered by the stimulus on different occasions will have a bell shaped curve as shown here: some flashes deliver the average of three photons; some deliver more - say four or five; and some delivery fewer - two or one. Because of this variation it will only be the occasional flash of light, say ten percent, that happens to deliver five or more photons per flash. The individual being tested would say perhaps one out of ten times, "Yes, I saw something".

Now, let's look at this lower example. Suppose the experimental set-up is the same as in the first example but the difference is that the subject now requires fifty or more photons to see the flash, and that on average thirty photons are delivered per flash. How will that change the outcome of the experiment? It will change it in the following manner. Because photons emerge from the light bulb filament at random and because that random process has this sort of bell-shaped curve, if the total number of photons in the sample is larger, that curve will necessarily be narrower. That is, the relative fluctuation about the mean for larger numbers of independent events will be less then it will be for smaller numbers of events. Even though the number of photons required by the person to say "Yes, I saw something" is still 5/3 of the average number that were delivered, the fraction of the time that this large number will be delivered to the eye - that is, fifty or more photons delivered to the eye - will be far less than it was in our first example. It might be perhaps one percent or less then one percent of the time. It was this frequency of seeing a flash that Hecht set out to measure.

Let's look at two related curves. These show the fraction of trials in which the subject reported seeing the flash of light as a function of the average number of photons delivered per trial. I think we can see in this pair of curves what would come from Hecht's experiment. If a small number of absorbed photons is required - say five or more - then that curve is rather shallow; it is a broad S-shaped curve. If we deliver on average somewhat fewer than five photons and then progressively increase the average flash intensity, there will be a gradual increase in the probability that five or more photons are absorbed because the number of photons that are delivered per trial has this rather large variation.

On the other hand, if a larger number - say fifty or more photons - is required per trial, then the curve is steeper. I think you can see there is a sharper transition here. With an average of 30 or 40 photons per flash it is rather unlikely that 50 or more photons will be delivered to the retina, whereas with an average above sixty or seventy photons, it is quite likely that 50 or more photons will be delivered to the retina. Hence, the relative steepness of the curve.

Therefore, based simply on how shallow or steep the response curve was, Hecht could determine how many photons were required to see a flash of light. Remarkably, the answer is only five to seven photons - a very small number! So, even though one hundred photons strike the cornea, only five to seven of them are actually used to initiate the visual sensation at the absolute threshold of sensitivity.

Five, six or seven photons correspond to an extremely small amount of energy. Let's get a sense of how small that energy is. We will compare it to the energy that is lost by dropping a dime one millimeter in the Earth's gravitational field. I have a dime here, and I am going to drop it one millimeter onto the palm of my hand. It makes a little 'thud', and I can certainly feel it, but it is not a big stimulus. Suppose we convert that amount of energy into photons. We can ask: "How many photons would that give us?"

That is a straightforward calculation. Here we have the mass of the dime ($10^{-3}$ kilograms), the acceleration in the earth's gravitational field (9.8 meters per second squared), and the distance dropped ($10^{-3}$ meters). The product of those terms gives us $9.8 \times 10^{-6}$ Joules. That is how much energy was lost when we dropped the dime one millimeter. That was, of course, the amount of kinetic energy that hit the palm of my hand.

Now let's figure out the amount of energy per 500 nm photon. This would be a wavelength right in the middle of the visible spectrum. For photons, energy equals hv, where h is Planck's constant, and v is the speed of light (c) divided by wavelength. We can plug in the numbers, as shown down here, and we end up with $4 \times 10^{-19}$ Joules per photon. Now comparing this number to the number that we calculated for dropping the dime one millimeter, we see that the energy equivalent to dropping a dime one millimeter in the earth's gravitational field corresponds to $2.5 \times 10^{13}$ photons! That is, this amount of energy could be divided into billions of flashes of light and a flash delivered to every person on the planet – and it would be an easily detectable flash! That means that the visual system is extremely sensitive at absolute threshold. This is a remarkable property.

Now let's ask if it is possible to look at the single cell level and see the single cell correlate of this incredible sensitivity. At this point I should mention that the flash of light that is used for an experiment of the sort that Hecht did lands on the retina over an area that encompasses roughly five hundred photoreceptors cells. Why five hundred? Because that is the region that is summed by a single ganglion cell to determine its output. If the light is spread over a much larger region of retina, the sensitivity will go down because the information will be carried by different ganglion cells and the signal will not be as effectively integrated. If we look at a region of just five hundred photoreceptor cells, and we deliver the flash of light to just that region, then those signals will converge on a single ganglion cell or a very small number of ganglion cells and the signal will be optimally delivered to the brain.

The fact that we can see as few as five to seven photons reliably over an area that encompasses five hundred photoreceptors must mean that in general a single photoreceptor is responding to a single photon. Of course, most of these 500 photoreceptors are capturing no photons, the occasional photoreceptor is capturing only one photon, and very rarely - hardly ever - is a photoreceptor capturing more then one photon in this circumstance. This predicts that a photoreceptor can capture a single photon and amplify the signal induced by it.

The predicted single photon response has, in fact, been measured in photoreceptor cells by recording the current flowing into a single rod outer segment using the recording arrangement shown here. This large object is a glass electrode. This is its tip. It has an opening down at the bottom. Within that opening, it has drawn up one outer segment from this little chunk of retina, where there are many outer segments sticking out. This horizontal yellow line is the exciting beam of light, which is going to stimulate that photoreceptor outer segment. Using this electrode, where the seal between the outer segment and the recording pipette is extremely snug at the bottom, allows one to measure the current that flows in to the top and sides of the outer segment and then out from the cell body at the bottom.

With this recording set-up, one can observe the response to a brief flash of light. That is shown in the middle trace. This little blip is the light stimulus. The response to that brief flash has a characteristic shape and duration. If the flash is very bright, as we see with the highest of these response curves, the response rises quite rapidly to a final saturating level. It is maintained at that level and then returns back to baseline. As the light gets dimmer and dimmer – as we see in this family of response curves - the response correspondingly goes down. At some point, the response is quite small, and as the light gets ever dimmer we see that the response is either there or not there. It is quantized. Those are the responses to single photons. The capture of a photon occurs only rarely per trial, and when it does occur it is usually only a single photon. Occasionally there are two photons captured and then one can see that the response is roughly twice the size of the single photon response. If that is all there is to it, you might wonder: "Why can't the brain just see a single photon? Why do we need five, six, or seven photons?" The answer is that this is not the entire story.

If you look at the response properties of a rod cell in complete darkness what you see are electrical events that resemble - in fact they are indistinguishable from - single photon events. Here are a series of traces. The upper three traces show the responses of a single rod outer segment in complete darkness. In theory, there should be no activity in darkness, but, instead, you see a little variation in the background: it is not a

completely smooth baseline. Most strikingly, there are occasional responses, little 'blips' that resemble in every respect the responses to single photons. This is not just noise in the recording apparatus. How do we know that? Because in this lowest trace the same rod has been expose to very bright light. The very bright light saturates the response, and you can see that it is quite smooth. It clearly lacks these individual blips and therefore this shows that the noise that we are seeing comes from the dark-adapted rod and it is completely suppressed in the presence of saturating light.

What is the origin of the responses that look like single photons responses? These are thermal isomerizations of the visual pigment, rhodopsin. Occasionally, the 11-cis retinal chromophore - even in the absence of light - will spontaneously isomerize to all-trans. On a per molecule basis, this only happens once every one hundred years. But there are a many millions of rhodopsins per photoreceptor cell, so in a given cell one of those events happens roughly every minute or every half-minute. This makes the problem, from the point of view of the ganglion cell more, complicated.

What does this thermal isomerization mean for the signal that is being sent from the retina to the brain? Recall that the ganglion cells that are sending this signal are each in charge of roughly 500 rod photoreceptors. The ganglion cell now has the task of distinguishing a true signal - that is, a light-induced response - from the thermal noise. We saw that the thermal noise consists of spontaneous events at a frequency of one or two per minute per photoreceptor cell. The ganglion cell is being bombarded by perhaps five of ten of these false signals every second. I think you can see immediately why a true signal, derived only from a single absorbed photon, could never be seen over that background. What the ganglion cell is looking for is several photoreceptor responses within a very small time interval, say ten or so milliseconds: that would produce a signal that rises above the noise.

We see, for example, in this central panel - here just drawn schematically - what the ganglion cell input looks like: it is this noisy signal coming from many photoreceptors cells. But if there is a flash of light - as shown in this upper trace here - at one moment in time, which induces a series of photoreceptors responses and brings the input to the ganglion cell above the noise by some criterion, then the ganglion cell will respond by firing action potentials - a couple of action potentials are shown here - which upon receipt in the brain may register in consciousness as a signal above the noise. Again, at each step there is a signal-to-noise issue because, of course, the ganglion cell occasionally fires an action potential when there is no light, simply in response to the random input and when the threshold has been reached to initiate an action potential. The system is built to be a coincidence detector, and five to seven photons are required to bring the signal above the noise to an extent that it is statistically significant. That is the very best the retina can do in the context of photoreceptors that are not completely noiseless.

Now let's ask, by looking inside the photoreceptor, how can it detect a stimulus as weak as a single photon? Of course, because of the quantum nature of light, this is the smallest stimulus that the photoreceptor could detect. If we take an engineer's view of signal amplification in sensory receptors, we can imagine different ways in which the photoreceptor might be built to respond to this signal. Then we can ask: "How do those different ways measure up for detecting very weak signals?" On the left, I have illustrated the very simplest possible response that one could have. Here the receptor R is converted to an activated form R*. This is the entire response; there is nothing more in this instance. A little flash of light, shown by this blip, would elicit an immediate response - as shown by this step function - of receptor activity. That is a possible way to build a receptor, but it doesn't have any amplification built in, in the sense that a single initiating particle – such as a photon - doesn't lead to the activation of multiple particles in the responding cell. So, in this case, we have only a one-to-one correspondence between input and output. This is an un-amplified system: it is rapid but not very sensitive.

We could make the system more sensitive – as shown in this central panel - by imagining that the active receptor R* is a catalyst. This is the classic way that biological systems amplify signals: by initiating the formation of or unveiling a catalyst, which then catalyzes the reaction indicated here as A being converted to A*. This has the virtue of amplification, because for every catalyst R* that appears in response to the

stimulus, there will be many A to A* conversions. Here, we see A* appearing as a function of time: that is this ramp function. After a flash of light we can appreciate that although there is a bit of a delay - it takes a while for many of these final activated compounds called A* (whatever they are) to accumulate – A* could accumulate to rather large levels. There could be hundreds or thousands of A*'s, and that would be a way of amplifying a signal on a per-particle basis.

Let's take that logic one step further. Suppose, as shown on the right, A* is itself a catalyst so that there is an initial catalytic conversion of A to A*, and then each A* converts many molecules of B to B*. Now we have a second stage of amplification. If B* is the final signal that activates the cell's response, then that would have a time course as shown on the top curve. There would be an even greater delay in the response because it takes a while for the A*'s to accumulate and then for the B *'s to accumulate in turn. But the reward for that delay is an enormous amplification in generating the product of B*'s catalytic activity - perhaps thousands, tens of thousands, or hundreds of thousands of such molecules generated for every R to R* conversion.

So how does a photoreceptor actually respond? It turns out that this last strategy – with two stages of amplification - is the one used in the vertebrate eye.

In this case rhodopsin is the initial catalyst. It is a G-protein coupled receptor and it catalyzes the activation of multiple G-proteins called transducin, shown in green here. Then the active transducin activates a cGMP phosphodiesterase shown in blue. In the dark, the phosphodiesterase is inactive, the transducin is inactive, and the rhodopsin is also inactive. cGMP is present at quite high concentrations. cGMP, the internal messenger, acts directly on an ion channel in the membrane - a sodium and calcium permeable channel - and maintains it in an open state. The effect of photon absorption is to activate rhodopsin – shown as a red ball - that then activates a large number of transducins. Although only one is drawn here, there are many dozens of activated transducins. Each activated transducin then activates a phosphodiesterase, which, in turn, hydrolyzes hundreds to thousands of cGMPs per second. The result is that the cGMP level drops and that drop then leads to the closure of the ion channels. In fact, you can think of the ion channels as essentially a third catalyst: it is catalyzing the transfer of ions from one side of the membrane to the other. A single ion channel, on a per particle basis, allows the passage of many ions. So really, there are three stages of amplification in this system. This is what has allowed a rod photoreceptor to respond to a single photon - this enormous per particle amplification.

## The Vertebrate Retina Part 1B

Let's look at the arrangement of photoreceptors within the retina and explore the significance of that arrangement for the functioning of the system. Here is an en face view of a primate retina. Each of these white spots is a single rod photoreceptor cell. These are the closely packed ones. And the clear spaces, each with a single white spot in it, are the cone photoreceptor cells. You can see that it is essentially a sea of rods with cones interspersed like little pebbles.

This is what the peripheral retina looks like, the region that is off to the side. But the retina overall is not a homogenous structure with respect to photoreceptor topography. In the primate retina, including the human retina, if we were to map the density of the different photoreceptor cell types across the width of the retina from one side to the other, we would see a very distinctive distribution. For example, the rod photoreceptors - these dots here – are very abundant in the peripheral retina. The cone photoreceptors – plotted down at the bottom - are relatively rare in the peripheral retina as we saw in the previous slide. But towards the central retina, and especially at the very center of the retina called the fovea, the cone density rises to a very high peak and the rod density correspondingly goes down to essentially zero.

That is a very striking arrangement. Why is it arranged that way? It turns out that the retina of a primate, like ourselves, is really a two-stage structure. We have a high acuity zone of the retina - this very central

zone, which encompasses just a tiny fraction of the retinal surface area, less than 1 percent - and the rest of the retina exists simply to alert the central retina that something interesting has happened. Whenever we look at something that we are interested in, we turn our eyes towards that object. We do that because we want the object to be imaged on the central region of the retina.

Let's look at one consequence of this specialization within the retina, and that is the eye movements that allow different regions of the world in which we are interested to be sequentially imaged on the central retina. And there is no better example than reading text. If you are reading, it is possible to monitor the accompanying eye movements. You will see that as we look here on the horizontal axis at eye position and on the vertical axis at time - if we look at the way the eye moves - we will see that there is a series of stops and starts. The eye is initially focused on one location, and then there is a rapid movement to a new location, a brief pause at that place, and then a rapid movement to yet another location, and so on, as we read from word to word across the page. And, of course, when we get to the end of a line, then we reset all the way back to the beginning of the next line.

Why are we doing that? Why can't we just stare straight ahead and read? The answer is that when you are reading you need to see the words and the letters at high acuity, and the only way to do that is to have their images fall on the very central retina. So your eye must be continually moving to image the object of interest on the most central region, the fovea. The rest of the retina exists simply to get our attention and tell us about an object that we might want to image on the fovea. For example, if you see a fly in your peripheral vision buzzing around the room, that will grab your attention and you will perhaps turn your eye toward the fly, but you won't really get a good look at it until you turn your eye towards it.

Let's look at eye movements in a somewhat more natural context. This tells us something not only about the eye but also about the brain. Let’s see which regions of a scene grab our attention. Here, for example we are looking at eye movements associated with looking at faces. The top two photographs are the images that were observed and the bottom data points indicate where the eyes were pointed during viewing of these images.

When looking at a face – for example, this young lady’s face - you can see that the eyes of the observer tend to look at her eyes. They also look at her mouth, they look at her nose a little bit, maybe around the face. If we look at a face in profile, again, you can see - from where the eyes are pointing - that we tend to look at the edges of the image: the nose, the eyes, the chin, the mouth, and so on. We largely neglect the central regions: the cheeks, the neck, and so on, that are of perhaps lesser interest and where less is going on. This is a highly selective viewing strategy, and it means that we are sampling the world in a way that is far from random and far from complete. We are sampling just subsets of any given scene.

The fact that the central retina is the only place where the image is seen with high acuity means that if you are going to examine a non-moving object and you are doing it in the context of head and body movement - perhaps because you are walking, or running, or just trying to stay still but you are not entirely still – then there must be a mechanism that allows the eye to stabilize itself in the context of this moving structure, that is, the rest of the body. In fact, that mechanism exists and it is a very powerful one.

Here is an example showing how that sort of mechanism compensates for head and body movements during walking. Again, on the horizontal axis we have the angle of the optical axis in degrees, and we have plotted here in red the head movements associated with walking. Of course, there is some swaying back and forth with each step. As time goes on - moving up the chart - we see that the head movements (in red) and the eye movements within the head (in green) are nearly mirror images of each other. That is, the eye is moving within the socket to almost perfectly compensate for the back and forth movement of the head! This is completely unconscious: we do it without thinking about it. But the result is that the eye is pointing nearly perfectly straight ahead during the entire walk by virtue of this moment-to-moment sense of where it is deflected. If it is deflected a little to the left, it will move to the right. If it is deflected

a little to the right, it will move to the left. And this, of course, keeps the world looking relatively still despite the fact that we are moving around.

Let me say one final thing about the arrangement of photoreceptors within the retina and how it relates to the distribution of the different cone photoreceptors. We have not yet talked about the different kinds of cones. We are going to talk in detail about that in the next lectures. In the human retina, let's just for the moment note that there are three different cone classes: one is most sensitive to longer wave light, one is most sensitive to medium wavelengths of light, and one is most sensitive to shorter wavelengths of light. The medium and longer wave length receptors – I will call these M and L – are, in fact, rather similar to one another with largely overlapping absorbances, whereas the shorter wave receptor - which I will call S - is quite different. It absorbs at wavelengths quite far down toward the short end of the visible spectrum. And as a consequence, any given image that contains wavelengths throughout the visible spectrum – and which, therefore, would be exciting all the different photoreceptor cells – will, when it arrives at the retina, not be perfectly focused at all wavelengths.

Let's think about why that is. It is because any lens, including our own lens, has some degree of what is called chromatic aberration. That is, the image being focused for a given wavelength is not going to be focused perfectly for some other wavelength. And so, for example, as shown here in this upper image, suppose this word "red" – shown in red letters - is focused perfectly on the retina: that is, it is sharply focused and a point in the outer world comes to a point on the retina. Then blue light coming from the same region of space would be focused in front of the retina, so that the word "blue" here, as shown on the right, would be a bit blurry, a bit out of focus.

How does the retina deal with this problem? It turns out that in the very central fovea the S cones have been excluded. Only M and L cones populate that region. This is the region with the very highest acuity. And what the retina has done, what the eye has done, is simply eliminate the short wavelength end of the spectrum for that most high acuity zone of the retina. So by taking a narrow cut of wavelengths we are effectively getting a sharper image - of course, at the price of having a less colorful image.

Now, let's talk about how the image is processed in the retina. We mentioned at the very beginning of the first lecture that the retina is different from a film in a camera in the sense that it is not just detecting the image and sending that detected image to the brain, but it is processing it and extracting from it those aspects that are of greatest interest to the organism.

Let's look at one of those feature extractors here. This can be illustrated with this classic illusion, the so-called Hering illusion. I hope you can see that at the intersections where these white streets come together there are illusory black dots. Actually, the black dots are not seen on the intersection that you focus on, but on the ones that strike your peripheral retina. I will leave it as a homework exercise to figure out why that should be so.

If you can't see these black dots as clearly as I can, I invite you to produce an illusion of just this sort on a home computer. You can do it either with black squares and white streets in between, or the reverse. If you do it with white squares and black streets you will see little white dots at the intersections of the streets. This illusion has been known for well over a century, and it turns out to be fully explained by a distinctive type of spatial organization of the receptive fields of ganglion cells.

At this point we should define "receptive field". It refers to the zone of primary photoreceptor input that influences the output of the retinal ganglion cell. The classic retinal ganglion cell receptive field is shown here. There is a little zone of retina – we are looking now en face at the retina - where illumination excites the ganglion cell, and would therefore increase the firing of action potentials. Then there is an annulus - like a doughnut - around this central zone where light activation of photoreceptors inhibits the ganglion cell.

The ganglion cell is essentially a contrast detector. The ganglion cell is looking for spatial differences in illumination across the retina. Let's see how this explains the illusion. Here, I have shown superimposed on a little region of the Hering illusion one of the receptive fields of a ganglion cell. In the center, the ganglion cell is looking at the light that falls at one of these intersections between white streets. You can see that, for this particular cell, not only is the center being illuminated, which would tend to excite the cell, but a rather substantial region of the surround, on the right and left sides and above and below, is also being illuminated. So the result would be that this cell would be substantially suppressed by that illumination of the inhibitory surround.

What happens if we look at a ganglion cell that is a little off to the right? Its center is also fully illuminated, but now you can appreciate that a bit less of the surround is illuminated than was the case for the first cell. If we look at a cell that is even further off to the right, we see that the center is illuminated but now the surround is only minimally illuminated - just this horizontal region here is receiving light. This cell would be substantially more active because the central region that is fully illuminated is countered by only a modest amount of inhibitory illumination coming just from the left and right sides.

As a result, the brain would perceive - or the retina would perceive - this zone of white street as brighter relative to the zone over here. Because the ganglion cells that are seeing the street that is off to the right side or off to the left side would have greater overall activity than would the ganglion cell that was centered over this intersection here. And that is the source of the illusion of blackness, that sort of fuzzy blackness at the intersections between those streets. I should add that this idea of center-surround ganglion cells was predicted by this illusion many years before those cells were actually identified electrophysiologically.

Now this brings us to a larger question related to image processing in the visual system, and here we are going to move beyond the retina into the brain. If what the retina and the brain are looking for, among other things, are differences between one region of the image and another region, as illustrated by those center-surround ganglion cells, then it stands to reason that schematic images of the sort that bring out those differences might resonate in some way - might have a special meaning - in terms of their information content for our visual system. And that is exactly the case.

For example, we see here on the left a photograph of a hand with the fingers about to snap, and on the right we see a schematic, just a line drawing, of the same kind of hand. The fingers are about to do like this (snap). And we immediately recognize in this simple line drawing what is going on.

But it is actually kind of surprising that we should recognize this image of a hand so readily. After all, on a pixel-by-pixel basis, this schematic image bears very little resemblance to the photograph. The schematic shows black lines that outline each object: each finger and the palm of the hand. But the real world isn't like that at all! In fact, the real world is made of shapes with shadows and complex changes in illumination - as shown by that photograph – that are very different on a pixel-by-pixel basis from this schematic.

Why is the schematic so immediately recognizable? Almost certainly, it is because the schematic is essentially the processed version that our retina and our brain has created from the real image. By giving it this schematic, we feed the visual system a version that is already part way up the visual chain of command.

Let's see another example of this. Here, in this self-portrait by Pablo Picasso, we see the remarkable effectiveness of simple portrait sketches. Why is this so immediately recognizable as a face? In fact, it is recognizable as Picasso's face. Again - even though on a pixel-by-pixel basis it is very different from a real human face - it has abstracted the information in just the way that our brain abstracts it.

There are other things that the visual system is interested in besides changes in intensity over space. It is also interested in changes over time, and the combination of time and space. Let's look at an example of changes over time.

Here are the responses of a retinal ganglion cell in the rabbit retina to an object moving in various different directions. The directions of motion across the receptive field are indicated by the arrows in the center here, and the responses that go with each of those directions of motion are indicated by the cluster of action potentials recorded from that cell that are indicated adjacent to the corresponding arrow.

I think you can appreciate that motion in the upward direction, or directions that are close to it, are especially effective. Motion in the downward direction gives essentially no response. This is a cell that is interested in movement and, in particular, in movement in a particular direction.

Having cells of this kind makes perfect sense because, of course, things that are moving in the world are of interest to the organism. If you are a rabbit, you are interested in things like hawks that might be moving. And so having cells that respond selectively to motion - as opposed to simply a world that is unchanging - has obvious selective value. We can all appreciate that in our own everyday experience. For example, if a fly or some other object is moving in the peripheral visual field, that immediately catches our attention, and it does so in a way that non-moving objects do not.

Now this brings us to a potential paradox. As we saw a few minutes ago, the head and body are generally moving around in space as we walk or go about our daily business. And even though there are compensatory eye movements, which work quite well to keep the eyes largely oriented in space despite those movements, the compensatory eye movements are not perfect, and so the eye is constantly wiggling around back and forth in space and therefore the image that falls upon the retina is constantly wiggling back and forth in the reverse direction. If our retinas were composed of direction selective cells of the sort we have seen here, and these cells are the ones that are supposed to tell us what is moving out there in the world, we would have a problem that these cells would be constantly stimulated simply by the motion that is referable to head, body and eye motion - that is, to self motion.

What is the solution to that problem? It turns out that the solution is a more clever set of cells! Again, they are motion selective cells, but they respond only to local motion and not to global motion. For example, if we deliver to one of these cells - within its receptive field - a grating of alternating black and white stripes that are moving from left to right - so they are just flowing across the visual field - the cell gives a very brisk response, if that is all that is being presented to the retina. In this example, the surrounding region of retina is being presented simply with a non-moving gray background. The cell loves this stimulus and responds vigorously.

What if we simply unmask the rest of the retina and show it the same set of bars moving from left to right? The receptive field of the cell - this central circular region - has not changed at all in terms of the stimulus being delivered to it. It is completely unchanged. The only thing that is different is that now the surround is receiving exactly the same stimulus. What happens? The cell immediately falls silent!

This is a cell that wants to see a little region of the world moving against a background that is not moving. And if everything moves at the same time, that is not an interesting stimulus. This is perfect. This is just the kind of cell that would tell a rabbit, for example, that a hawk is flying across the sky, but the cell would not respond if the rabbit had turned its eye a little bit and the trees and bushes and all the other images that were impinging on the retina had moved across the retinal surface. It tells the rabbit just what the rabbit wants to know.

There is a very beautiful illusion - the so called Ouchi illusion, named after the Japanese artist who initially derived it - that nicely illustrates this affect of local motion sensitive ganglion cells on our visual

system.  I have shown the Ouchi illusion here at two different magnifications, because depending on how you are viewing this lecture one or the other might be more effective.

In the Ouchi illusion, there are a series of horizontal black and white bricks that encompass a surrounding zone and constitute most of the image.  In the center, the circular center, there is essentially the same thing except it has been rotated 90 degrees.  I think you can appreciate that the central region appears to float around and bounce back and forth in a way that is somewhat different from the surround, as if it is almost autonomous from the surround.

The origin of that illusion of motion is the small spontaneous eye movements that we experience all the time.  Our eyes are constantly jiggling around in their sockets, and because of that jiggling the direction-selective ganglion cells are differentially activated by the center versus the surround of this illusion. For example, if the eye were to make a small horizontal excursion, these horizontal brick stimuli would be less provocative to those ganglion cells, on average. Why? Because a small horizontal movement leaves much of the visual field with the same stimulus that it had before the movement: the same little retinal region that was stimulated by a black zone when the eye was at the first location, will, if the eye now moves a tiny bit horizontally, still be stimulated by a black zone in the new location.

But the vertically arranged bricks will have a relatively larger effect for a given horizontal eye movement, because that little movement will be more likely to shift the gaze from a black zone to a white zone or a white zone to a black zone.  The reverse is true for vertical eye movements.  That difference causes the visual system to make this segregation of the central circular zone from the surround and it gives it this sense of bouncing back and forth, this sense of autonomy, that grabs our attention and makes this illusion so effective.

To continue with our theme of looking at how the visual system extracts information from the scene, we can ask whether having two eyes gives us some special advantage over an organism that might have only one eye.  The answer is “Yes, having two eyes does confer a special advantage”. In particular, it allows us to determine the depth of an object - that is, its distance away from ourselves - using a mechanism called stereoscopic depth perception.

Let's see how that works. Suppose that we have two points in the visual world - one here on the right and one here on the left.  You can see, by simple geometric optics, how these would be imaged on the retinas of the two eyes, shown down at the bottom.  Of course, the left point is imaged on the right side of the retina, because the image is reversed when it is imaged on the retina.  Similarly, the right point is imaged on the left side of the retina.  Those two images fall on what would be called corresponding points.  There are corresponding points for the right spot and there are corresponding points for the left spot.  There is nothing surprising here.

Now let's ask: “What if there is a pair of points that differ not by virtue of their positions left and right, but by virtue of the fact that one is further and one is nearer to the viewer?”  If you think about it, what the geometric optics tells us is that the innermost point is imaged further to the periphery on the left retina and also further to the periphery on the right retina.  That is, the corresponding points for this closer object lie on opposite sides of the corresponding points for the further object.  And the more distant point here is now imaged on points that are closer in - more nasal - on the retina.

That is now a bit more confusing, perhaps, for the brain to figure out.  What the brain has to do is figure out that the images for the nearer point - on the left retina and on the right retina – that those two images are really representing the same object.  This is called ‘the correspondence problem’.

Because the image of the nearer object falls on these different sides of the image of the further object, it must be nearer.  The nearer object can be detected as nearer by virtue of the fact that its corresponding points are lateral, and the further object can be detected as being further by virtue of the fact that its

corresponding points are more nasal. As it turns out, this is a very difficult computational problem, and it is not yet fully understood how the brain's stereoscopic depth system works. But it is a very powerful system, and it gives us very accurate depth perception.

As we consider further how the brain analyzes the visual scene, we eventually reach a point where the information is so complex that the analysis does not proceed with an assumption-less series of steps, but rather a series of steps that involve imposing some order that is derived from our previous experience of visual information.

Let me give you an example of this. Here we see a way in which we analyze depth from shading - and we have included in that analyses a hidden assumption. The hidden assumption is that this three-dimensional object has been illuminated from above. That is a natural assumption because, in general, the sun - the classic source of illumination - is above. And so, when we see an object, in general the shadows are below. A round object can be analyzed, in part, based on the pattern of its shadows, with that usually correct assumption that the sun is above it.

Just to illustrate this type of analysis, we have here two images of cuneiform writing. In fact, these two images are the same image. The one on the right differs from the one on the left only by virtue of its having been rotated 180 degrees. You can appreciate that the one on the left looks as if the cuneiform is coming out at us from the plane and the one on the right looks like the cuneiform is receding into the plane. The reason for this is that when we see the shadows on the left we immediately assume that the sunlight is from above and therefore since the shadows are below, the objects are sticking out at us. And on the right side, it is the reverse. Again, if we assume the illumination is from the top, the locations of the shadows would tell us that the objects have receded into the plane. That is obviously a learned assumption. It is an unconsciously learned assumption, and it is generally a correct one.

Let's look at another way in which learned responses affect the way we analyze a scene. Of course, we move around in a world of three dimensions, and we are very tuned-in to the depth of three-dimensional scenes. We see some objects as closer, some as further away. In this drawing, we certainly get a strong sense that the walls form a zigzag pattern, coming out toward us and then receding. The images of the gentlemen who are pictured here - by virtue of their different sizes - reinforce that sense.

But now if we look at these heavy black bars - one that is here on the right and the other one to the left - we get a strong sense, because we have assumed they are at different depths, that the bar that is to the right is smaller than the bar that is to the left. In the context of this three dimensional scene, that is perfectly correct. But, in fact, if you measure the size of these two bars in this particular image - you can simply put a ruler next to one bar and a ruler next to the other bar - they are exactly the same size! What is most striking is that even after you know this, and even if you hold two rulers next to these black bars and you prove to yourself that they are the same size, you will have a very difficult time convincing your visual system that this is true! The sense of a differential in size is very strong and very persistent. And again, it is a learned sense, and it is learned in the context of depth perception in the real world.

Let's look at one particularly famous example of the way in which we impose order on a scene. This is a commemorative vase. It was made to honor Prince Phillip and Queen Elizabeth, and not only is it a beautiful vase, but on one side is the profile of Queen Elizabeth - that is, the shape of the vase makes her profile - and on the other side is the profile of Prince Phillip. That is the nose right there, and here is a nose right here.

One striking thing about this vase, as you view it and look for those profiles, is that the sense that it is a white vase or the sense that it is two faces looking at each other seem to be mutually exclusive. That is, you can see it one way or you can see the other way, but it is hard to see it both ways, or see the two ways fully - to see them in a dominant way - at the same time. Again, this is just an example of the visual

system imposing some order on the scene. It is trying to choose which of those two somewhat exclusive ways of looking at the scene is the correct one.

Let's look at one final example. This is a series of four sketches that Pablo Picasso drew of a bull, one of his favorite subjects. In going from the upper left to the lower right we are seeing an increasingly abstract version of a bull. Yet the striking aspect of this set of drawings is that, despite the abstraction, we immediately recognize it for what it is.

Like those simple line drawings that we saw earlier, I think this begs the question of why that should be so. Why is the visual brain so good at identifying these sets of rather abstract images as representing a bull? And like those line drawings, I think our conclusion would be that what Picasso has hit upon is that these almost child-like drawings are really the internal representation of the bull: we have created a simplified and abstracted version in our heads - our memory trace of a bull – and it resembles this kind of drawing and therefore resonates immediately with it.

## The Vertebrate Retina Part 2

I am Jeremy Nathans. I am a professor at the Johns Hopkins Medical School and an investigator of the Howard Hughes Medical Institute. This is the second of three lectures on the vertebrate retina: its structure, function, and evolution.

In this lecture we are going to look at human color vision and its variations. Why should we study color vision? One reason - the reason I like most - is because it is beautiful! We see a world of color out there, as seen in this upper photograph, and, if we were deprived of that color, the world would be a far duller place.

The story I want to tell you is really a centuries-long story. It begins in 1665 in the dormitory room of Isaac Newton, who was an undergraduate at Cambridge University at that time. Newton did a very simple, yet profound, experiment. He drilled a hole in his wooden shutter to admit a beam of light, he passed that beam of light through a prism, and then he asked what happened to the light beam. The answer was that the beam was split up into its component colors - the colors of the rainbow - from red, which is the least refrangible, to violet, which is the most refrangible, and in between, orange, yellow, green, and blue.

That had been known for some time. But Newton appreciated the physical significance of that phenomenon - that is, that white light was a summation of different lights, and that those lights could be separated physically in an objective fashion, and that their properties could be objectified in the sense that each kind of ray had a particular angle of refraction when passed from air to glass and then from glass back to air again. Furthermore, Newton realized that this method could be used to purify the individual rays of light to obtain spectrally pure samples with which to work. So, for example, by blocking off all but the orange ray of light, as shown here, Newton was able to obtain a beam of spectrally pure orange. Nowadays, we would do this with a tunable laser to obtain a spectrally pure light. Newton appreciated the power of this purification method, and he used it to good effect. In particular, he used it to recombine lights of different colors.

Now I can't resist showing you Newton's original sketch, his quick pen sketch of the experiment. It is reversed left to right from the image I showed you earlier. Here is the beam of light coming in the window. It is refracted by the prism, and then various beams are obtained from it by using their specific angles of refraction.

Newton performed the following very simple but profound experiment. It is diagrammed here with projectors, as we might do it today, whereas Newton did it with mirrors and the beams of spectrally

purified lights. Newton asked, "What if you combine together a spectrally pure red and a spectrally pure green light? What would it look like?" The answer is it looks like neither; it looks yellow! That is, the superposition of red and green looks just like a spectrally pure yellow. But it is not physically identical to a spectrally pure yellow, and Newton proved this by passing this yellow, such as we see here, through another prism. A spectrally pure yellow, identical to it in all appearances, was also passed through a prism. And what he saw was that the lights behaved quite differently. A spectrally pure yellow retains its same initial angle of refraction and remains a single homogenous beam when passed through a prism, but a synthetic yellow, such as we see here - one obtained by a superposition of red and green lights - splits up into its component red and green lights, each with its own original angle of refraction when passed through a prism. Newton realized that this meant that human color vision is imperfect, in the sense that it can not distinguish certain physically distinct combinations of lights.

As far as we know, Newton never investigated the physiologic basis for that phenomenon, although he worked on the physical rules that govern the recombining of lights with different angles of refraction. [Today, we would refer to the lights by their different wavelengths, instead of their angles of refraction as Newton did.]

Newton had remarkable physical insights into the color vision system. Let me share one of these with you. This appeared in Opticks, Newton's wonderful book describing his early experiments. Here Newton asks, "May not the harmony and discord of colours" - that is, the similarities and differences of the colors - "arise from the proportions of the vibrations propagated through the fibres of the optick nerves into the brain, as the harmony and discord of sounds arise from the proportions of the vibrations of the air?". This is a remarkable insight at a time when it was not at all clear what the physical nature of light was. Newton was suggesting - by analogy with sound waves - that light might consist of some sort of wave.

I should add that Newton - also in Opticks - discussed the evidence that light has a particle-like characteristic. In fact, he comes down somewhat in the middle and says that light is both particle-like and wave-like, a remarkable judgment given that this was more than two centuries before the quantum theory emerged to tell us that in fact light does have both particle and wave properties.

The physiologic underpinnings of the color mixing results of the kind that Newton saw were not understood until the 19$^{th}$ Century. We owe its first clear description to Thomas Young, the universal genius who worked on many things, including the Rosetta Stone and vision. In the Bakerian Lecture of 1802 before the Royal Society of London, Young suggested the following as a model for how color vision might work. He writes as follows, "As it is almost impossible to conceive each sensitive point of the retina to contain an infinite number of particles" - that is, an infinite variety of receptors - "each capable of vibrating in perfect unison with every possible undulation" - that is, every possible wavelength of light, because at this point it was clear that light had wave properties - "it becomes necessary to suppose the number limited, for instance to the three principal colours, red, yellow, and blue, and that each particle is capable of being put in motion more or less forcibly by undulations differing less or more from perfect unison."

This very prescient statement hit the nail exactly on the head, because what Young is saying here is that each of the three receptors would have a broad bell-shaped curve. There would be a place where the receptor is maximally sensitive, where it is matching the so-called "undulation" of the stimulus, and then there are other parts of the spectrum where it would be less sensitive, because the match was less perfect. By having that sort of broad sensitivity, a limited number of receptors - the three receptors that he is postulating - would be able to cover the visible spectrum, and by comparing their degrees of excitation one could determine the color appearance of any given light. That is exactly right!

The physiologic evidence - behavioral evidence - from testing humans that support this model was not forthcoming until another 50 years, and it came from two equally remarkable scientists: Hermann von

Helmholtz, shown at the left; and James Clerk Maxwell, shown at the right. They are both shown here in their 20s. Helmholtz at the time of this photograph had just invented the ophthalmoscope and revolutionized ophthalmology. Maxwell, shown to the right, is holding his famous color top. He was an undergraduate in this photograph. He had been interested in color for many years, starting as a teenager, and he had devised a series of tops with different color patterns that he could spin at high speed to produce a uniform mixing of colors.

We now know - if we fast-forward 150 years - that the Young model is exactly right, and that there are, in fact, three light sensors and they have broad bell-shaped sensitivity curves. These curves have now been identified by a number of methods, and here is one of them. In this case, the individual proteins that constitute these receptors and their 11-cis retinal chromophore have been joined together, and the absorbance spectra determined in a spectrophotometer. We see that 'Rho', which stands for rhodopsin, the receptor in rods, is this curve, peaking at about 500 nanometers. This one is not involved in color vision; I put it here just for completeness. It is involved in dim light vision only. But it has the same overall shape, because - in terms of their photochemistry - all of these different visual pigments work in the same way.

The other visual pigment curves - the longer wave (the L) curve, the medium wave (the M) curve, and the short wave (the S) curve - are offset by substantial numbers of nanometers from one another and from the rhodopsin curve, and together they span essentially the full range of the visible spectrum, just as Thomas Young predicted.

What does this get us in terms of color vision ability? We can ask that in a number of ways. One way we could ask that question is simply by asking, "At any given wavelength along the entire visible spectrum, how different do two lights have to be to tell them apart?" The answer to that question is shown here. On the horizontal axis is wavelength, and on the vertical axis is the wavelength differential - the "delta lambda", the differential between two lights that one needs to discriminate them. You can appreciate that the curve is not a simple flat curve; it goes up and down, there are hills and valleys. There are some places, for example right here, where a difference of perhaps half a nanometer is sufficient to distinguish two lights, and other places where a difference of about six nanometers is required.

This curve of hills and valleys can be completely understood by reference to the original absorbance curves of the pigments. For example, if we ask how we sense a light of 600 nanometers, we see that it differentially excites the long and medium-wave pigments, whereas a light of 595 nanometers, a little bit blue-shifted relative to 600 nm, has a different ratio of excitation of those two pigments. And that is a sufficiently great difference so that we can tell them apart.

I should add that this set of visual pigment absorbance curves also explains Newton's color-mixing data in a very simple way. For example, if we have a sum of red and green lights, that sum gives a degree of excitation of those three different sensors that is the same as that produced by a spectrally pure yellow light. The system cannot tell the two apart, because, in the end, a light detector is really just a photon counter. Consider a light of just one wavelength – the type that is produced by a laser – and its effects on a single type of cone photoreceptor. Once a photon is captured, there is no way for the photoreceptor to determine or communicate any information about the wavelength of that photon. Was it a long-wave photon that was captured inefficiently? Or was it a shorter-wave photon that was captured more efficiently? That information is completely lost within the system. The result is that for any particular class of cones, a pair of lights that gives the same total number of photons captured per unit time will be indistinguishable.

As part of his experimental approach to analyzing human color vision, Maxwell developed a conceptualization of color perception that is extremely useful, and is shown here. Maxwell conceptualized color space as a 3-dimensional space in which the three axes shown here - the L, the M, and the S axes - correspond to the degree of excitation of the three classes of cones. For example, a white

light, which equally excites all three cone classes, is shown by the corner of this cube here and by the vector coming from the origin in this direction. A light of any particular wavelength would be represented by a distinctive vector in its own unique direction. In Maxwell's conceptualization, our color vision is three-dimensional; our color vision has three degrees of freedom. If an individual were to have only two receptors, that individual would have a two-dimensional color space. For example, if one is missing the L-receptor, then the color space would consist of the M- and S-axes and the plane defined by them, but not the three-dimensional S, M, and L space.

Now let's talk a little bit about the chemistry of color reception, and, in particular, the ways in which different wavelengths of light might be selectively absorbed by the different visual pigments. We saw in the first lecture the overall structure of a visual pigment: it is a G-protein coupled receptor, it has seven transmembrane segments, and it sits in the membranes of the outer-segment. As you may recall from that first lecture, the actual light-absorbing part is a vitamin A derivative called 11-cis retinal. That is true for all of the human pigments; they are all built on this same basic architecture, and they all use the same 11-cis retinal chromophore.

The difference between the pigments is a difference in the proteins, and what the proteins do is they impose a somewhat different electronic environment around that retinal chromophore, which has the effect of tuning its absorbance spectrum to either longer or shorter wavelengths. One can think about this spectral tuning challenge as really a question of how to modify the π-electron system of the retinal chromophore by modifying the surrounding amino acid side chains.

We can learn something that, at least, constrains the possible mechanisms of spectral tuning by examining the basic photochemistry of retinal itself. The critical point with respect to spectral tuning is that the degree of π-electron delocalization within retinal determines its absorbance spectrum. Retinal - being a conjugated polyene, as shown here, with six double bonds - has a substantial amount of resonance, and therefore delocalization of electrons. I have shown below just one resonance structure that one could draw. This is not a particularly favorable one, because it places a positive charge on this carbon here as a result of moving the π-electrons over towards the nitrogen, which now has a free electron pair. This resonance structure, even though it is relatively unfavorable, will contribute to some extent in the equilibrium ensemble of all resonance structures.

Just to get a sense of how substantial this resonance effect is in the absorbance spectra of these kinds of compounds, let's look at the two model compounds that are shown here: a polyene at the top, and a cyanine at the bottom. These are drawn with the same number of double bonds that retinal has, that is six. You can see - if we look at this polyene at the top, where the chain ends in carbons, and the resonance structure that I have drawn just below it, in which one carbon now carries a positive charge and the other carries a negative charge – that this resonance structure would be quite unfavorable because it involves a charge separation, in addition to the general unfavorability of placing charges on carbons.

And so, in general, polyenes have very little π-electron delocalization. We know this for a fact, because when one looks at the crystal structure of a polyene one sees that the lengths of the bonds are highly alternating: half the bonds that are long, the canonical single-bond lengths; and the other half, in between them, are short, with double-bond lengths. And so, this back-and-forth, long-short-long-short-long-short pattern of bond lengths tells us that the single bonds have nearly exclusive single-bond character, and the double-bonds have nearly exclusive double-bond character. To go along with that, the absorbance spectra of polyenes are at quite short wavelengths. For example, this one is down in the ultraviolet, with the absorbance maximum at about 360 nanometers.

At the other end of the spectrum - so to speak - for π-electron delocalization, would be a model compound of the sort shown down here. This is a cyanine - again six double bonds - but now we have an NH or $NH_2$ at each end. At one end there is a positive charge, at the other end there is a free electron pair. You can appreciate that the sort of resonance structure that is drawn below - in which each single bond has been

switched to a double bond and each double bond has been switched to a single bond - is simply a mirror image of the one above. Now the free electron pair is on the right and the positive charge is on the left, but everything else is the same in chemical terms. Therefore, these two structures must be equal in their energies, they make equal contributions to the mixture of resonance states, and the π-electrons are maximally delocalized in a cyanine-type compound. Again, we know this is true because crystal structures of cyanines show that all of the bond lengths are the same: they are midway between the lengths of single and double bonds. Going along with that, we see that the absorbance maximum of a cyanine is at quite long wavelengths; in this case it is 750 nanometers, far to the red. This would be a very deep red-absorbing compound.

With these two model compounds we see a difference in absorbance that spans essentially the entire visible range. All visual pigments that are known in nature have absorbance spectra somewhere between the extremes defined by these two model compounds. In essence, what visual pigments are doing is they are creating, with the retinal chromophore, some sort of hybrid between a polyene and a cyanine - a hybrid in the sense that the electrons are delocalized to a degree that is intermediate between the delocalization seen with a polyene and the delocalization seen with a cyanine. And correspondingly, the absorbance spectrum is intermediate between the extremes shown here: 360 nanometers and 750 nanometers.

Now, that focuses our thinking a little bit, because really what we can imagine the protein must do is make the chromophore look more polyene-like or more cyanine-like. How it does that we don't know in complete detail at this point, but we have a few clues. First, we have the amino acid sequences of the proteins. We can look at those sequences, as shown here where the proteins are splayed out in two dimensions with each dot in each of these schematics indicating an amino acid difference. Here, for example, we are comparing the M-cone pigment, the middle wave-sensitive pigment, with rhodopsin. Here we are comparing the S- or short-wave pigment with rhodopsin. Here we are comparing the middle wave pigment, the M-pigment, with the short-wave pigment; and here, in the lower right, we are comparing the middle-wave pigment with the longer-wave pigment, M versus L.

You can appreciate that the pigments have the same overall structure - they are seven transmembrane G-protein-coupled receptors, and there are obviously many amino acids that are identical, as shown by the open circles, which indicate identities. But there are also, in three of these pair-wise comparisons, many amino acid differences.

You can also appreciate that there is an asymmetry here. The M versus L comparison shows that these two pigments are extremely similar to each other. There are only about 15 amino acid differences. This number depends on which variant one compares, as there are a few allelic variations that can make that number a bit bigger or smaller. But, roughly speaking there are 15 amino acid substitutions that distinguish the M and L pigments out of a total of 364 amino acids. That asymmetry among the pigment sequences is going to be the focus of much of the remainder of this lecture and the next one.

Let's see what that sequence differences looks like in a dendrogram format. Here we are looking at sequence divergence among human and mouse rod and cone pigments. We have picked the mouse as a representative non-primate mammal. And here let me note that the non-primate mammals have rods very much like our rods, and only two types of cones, whereas a subset of primates, like ourselves, have three types of cones. Let's look at these amino acid differences: here we are plotting on the horizontal axis the degree of sequence divergence in the typical dendrogram-type plot, and on the vertical axis we are plotting the wavelength of maximal absorbance of the corresponding pigment.

Let's walk through this, starting with the mouse example. Mouse rhodopsin, like typical mammalian rhodopsins, absorbs maximally at about 500 nanometers, and its sequence is rather different - that is, this dendrogram line, this horizontal line, is rather long - compared to the mouse middle-wave pigment, the only example that the mouse has of a longer wavelength-sensitive pigment. And it is also quite different

from the mouse shorter-wavelength pigment, which absorbs in the near ultraviolet, at wave-lengths somewhat shorter than the S-pigment that we have.

In the case of the human pigments, we see that humans have a rhodopsin that is typical of mammalian rhodopsins, and we have a shorter-wavelength pigment, and these differ substantially in sequence. And then, in what must have been a very recent evolutionary event, there has been a split on the branch of the tree to give the long- and a middle-wavelength pigments, whereas our immediate mammalian ancestors did not possess that pair of pigments.

When the genes for the L and M pigments were first identified, not only were their sequences found to be very similar – that, of course, is the source of the sequence comparison that we just saw – but also the genes were found to be adjacent to one another on the DNA. Here is the arrangement of the human L pigment gene, shown with a red arrow, and the M pigment gene, shown with a green arrow. That is not a surprising arrangement, given their recent evolutionary history. Genes that duplicate are not infrequently found to be adjacent to one another. We imagine that, at some point in evolution, there was an erroneous recombination event that mis-paired two homologous chromosomes at meiosis, and as a result we obtained a chromosome – or, more precisely, our ancestors obtained a chromosome - with two copies of the same gene adjacent to each other on the DNA.

I have drawn here one aspect of that ancient arrangement, which I will justify in the next lecture: and that is that the original pair of visual pigment genes that underwent this recombination were not actually identical - one was already an L-pigment gene and the other was already an M-pigment gene. That is, they were already different from each other at the time of the duplication. As I said, let me reserve that story for the next lecture.

If we look at modern-day humans, although we see this arrangement of a single L and a single M pigment gene on some chromosomes, in fact, only about 20 percent of human X-chromosomes – it turns out these genes are on the X-chromosome – actually have that arrangement. When DNA from a large number of humans was examined to look at the arrangement of the L and M genes it became apparent that the basic arrangement of one L gene and one M gene, as shown at the top here, is actually not the most common arrangement in the population. In fact, most X-chromosomes have one L gene and two M genes, some have one L gene and three M genes, and there are a few that have four or five M genes. All of these X-chromosomes, as far as we can tell, confer perfectly normal color vision. These various gene arrangements almost certainly arise because the L and M genes are highly homologous to one another and are capable of homologous recombination at meiosis. We will discuss that in just a minute.

This type of recombination gives rise to a number of variations in gene structure. The sort of variation that appeared first, in terms of scientific attention, was the kind that affected color vision and has been called, perhaps incorrectly, "color blindness." "Color blindness" doesn't mean a complete inability to see colors. As the term is generally used, it means simply a reduction of color vision from trichromacy - from having three receptors - down to having only two. Perhaps the most famous dichromat was John Dalton, the great British chemist who, in his first scientific paper in 1794, described his own color vision in meticulous detail. Dalton was a dichromat, and he reported that what other people called red or orange or yellow or green appeared to him to be just a single kind of color, differing only in intensity.

Let's see what the world looks like to people who are missing one of the three receptors. I am showing here a photograph of a fruit stand that was processed so that we see what it would look like to a normal trichromat - here on the upper left - or to any of the three types of dichromats. On the upper right is a protanope's view; that is someone missing the long-wavelength sensor. On the lower right is the deuteranope's view; that is someone missing the middle-wavelength sensor. And over here on the lower-left is a tritanope's view; that is someone missing the short-wavelength sensor. I think you can appreciate that, as Dalton reported, without the long or medium-wavelength sensors the color of the fruit looks very much washed out. That is, the longer wavelength colors - the ones that particularly characterize the

ripeness of fruits; the green, yellow, orange, and red colors - are not distinguishable readily by an individual who is missing either the long or the middle-wavelength sensor.

What is the origin of these not uncommon color vision anomalies? It turns out that they arise from unequal recombination between the genes in the L and M tandem array. This recombination occurs quite readily because the genes not only are adjacent to one another and not only are they in a head-to-tail tandem array, but they also have retained a very high degree of sequence identity: approximately 98-percent identity at the DNA level. And so, as a result, mis-pairing can occur at meiosis of the kind shown here. For example, a region distal to this M-pigment gene is nearly identical in sequence to a region just distal to this L-pigment gene, and if those two regions were to pair at meiosis and a recombination event were to occur there, we would get the two meiotic products shown at the bottom: one in which only a single L-pigment gene remains, and the other in which an additional M-pigment gene has been acquired. Suppose that the chromosome shown at the top is inherited by a man. Since this is on the X-chromosome - and for that man this is, of course, the only X-chromosome that he has - it would cause dichromacy. This gentleman would be missing the M-pigment and would have only the S- and L-pigments. As far as we know, as I mentioned earlier, people with extra pigment genes - generally extra M-pigment genes - have perfectly normal trichromatic color vision. In fact, current evidence indicates that when there are multiple M-pigment genes, only the first M-pigment gene in the array is expressed, and more distal M-pigment genes are not expressed.

What if recombination occurs at an intragenic location - that is within the genes - rather than between the genes. If this region of the M-pigment gene pairs with a corresponding region of the L-pigment gene - and, again, these regions are almost identical in sequence – homologous recombination would create meiotic products in which there would be hybrid genes. For example, one product in which the M-pigment gene was lost would retain not a normal L-pigment gene, but an L-M hybrid. The reciprocal arrangement would be present on the other chromosomal product of this recombination.

Again, the color vision of these individuals would be affected. Of course, the man who inherits the chromosome shown at the top would have the L-M hybrid instead of either a normal L or a normal M gene. In the case of the individual who gets the chromosome shown at the bottom - recall that I just mentioned that only the first two genes in the array are expressed - this person would express the L-pigment gene, and that would be a normal gene. But the M-L hybrid would now be expressed instead of a normal M-pigment gene. And that hybrid, we have come to realize, would, in general, have an absorbance spectrum different from either of the two parental pigments. This hybrid – and this is also true of the hybrid diagrammed here - would be shifted in its absorbance spectrum, and the individual down here would be an anomalous trichromat: someone with three cone pigments, but not the normal set of three. This person would make different judgments when asked to quantitatively mix different colored lights.

More complex events are also possible, because many of the starting arrangements involve arrays that have multiple M-pigment genes. For example, if we start with one array that has two M-pigment genes and a second array that has only one, and envision these kinds of recombination events - in this case intragenic recombination events that one might encounter - we can, for example, see a meiotic product that has a hybrid gene, an L-M hybrid instead of the L-pigment gene, paired with an M-pigment gene. This person would also be an anomalous trichromat, in this case having replaced the normal L-pigment gene with a spectrally shifted hybrid. And the person down below would be the reciprocal kind of anomalous trichromat, having a hybrid M-L pigment gene and an unexpressed M-pigment gene in addition to a normal L-pigment gene. These are quite common in the population. Eight to ten percent of human X-chromosomes have some sort of rearrangement that affects trichromatic color vision, and, therefore, the eight to ten percent of males who carry those types of chromosomes have a color vision anomaly.

There are also more subtle variations in color vision. Let me show you the one that is the most common. This is a single-nucleotide variation that, among males, divides the apparently color-normal population into two distinct perceptual groups, and among females into three perceptual groups. This is a single nucleotide difference in the L-pigment gene, which results in a single amino acid substitution: a serine versus alanine difference at position 180.

We can study this variation in a psychophysical test by mixing red and green lights - here the result is plotted on the horizontal axis as a ratio of red to red-plus-green intensity; and, on the vertical axis, the number of individuals who had a given test result. The mixture of red and green lights is being compared to a standard spectrally pure yellow light, the same way that Newton did his color mixing experiment.

Let's look at the male curve at the top; males are at the top, females are at the bottom. Some males require more red in the mixture to match the standard yellow, others require less. The distribution is bimodal. In the female set, there are some who test like the males who require more red, some who test like the males who require less red, and others who are in the middle. Those are the heterozygotes in the middle. What we are seeing is the effect of this polymorphic variation on the absorbance spectrum of the L-pigment. This is now shown here, determined by producing the recombinant proteins and reconstituting them with the retinal chromophore. The serine version, the one that has serine in position 180, is a little bit red-shifted - that is this upper curve - compared to the absorbance spectrum of the pigment with alanine at position 180. There is a four or five nanometer shift, and it precisely accounts for this variation in spectral sensitivity between individuals who have either the alanine version or the serine version of the L-pigment.

So even though we think, perhaps simplistically, of the world of trichromats as a single unitary group of individuals with respect to their color vision, that is not so. Individuals are seeing the world somewhat differently based on this genotypic difference. Although each of them is internally consistent, if you gather them together in a laboratory and ask them to mix colored lights quantitatively, you will see that they divide up into these distinct perceptual groups.

We saw at the beginning of this lecture, and also in the last slide, how human visual pigments can be produced in the laboratory and their absorbance spectra measured directly after they are joined to 11-cis retinal. That is a wonderfully direct technique and it gives us a very precise measure of the absorbance spectra of the pigments.

Now we would like to ask, if we go back to the living human eye, can we analyze the pigment spectral sensitivities in the same precise way? In this example I will show how males who have only a single visual pigment gene on the X-chromosome provide a perfect group for this sort of study. These men have lost, by homologous recombination, all but one of the visual pigment genes on the X-chromosome. What remains behind is either a normal L-pigment gene, because they have lost the M-pigment genes by homologous intergenic recombination, or a single L-M hybrid gene, containing either more or less of one or the other the parental contributions, depending on the exact point of recombination. The other genes in the array have been lost by recombination.

These subjects are, in a sense, the perfect ones to study, because they have only two cone pigments to examine: the S-pigment and the single remaining longer-wavelength pigment. For simplification, one can design the study so that the S-pigment is not interfering with the sensitivity measurements for the longer-wave pigment. To do this, one can use longer-wavelength test lights, and also shorter wavelength background lights to selectively desensitize the short-wave cones. We now have - at least at the longer-wave end of the spectrum - the very simplest arrangement one could possibly have. We have someone who has just a single X-chromosome, and on that X-chromosome just a single visual pigment gene, and we are going to ask: "What is that pigment's spectral sensitivity?"

The result is shown on the next slide. The spectral sensitivity is determined by a method called "flicker photometry". It is a completely safe and non-invasive method. The individual views a screen on which is alternating - at about 20 times per second - a light of a standard wavelength, say 600 nanometers, and with it, in alternation, a test light with a variable wavelength. The test light could be at 610 nanometers, 620, 630, 640, 650 and so on in 10 nanometer increments up and down the wavelength axis. What the subject has to do is to adjust a dial that controls the relative intensities of these two lights so that the sense of flicker is completely eliminated.

Let's ask how that could possibly happen. After all, these are two differently colored lights - lights of different wavelengths that are being presented, alternating one with another. How could the sense that they are flickering back and forth not be seen? Remember, these subjects have only a single visual pigment at the long-wavelength end of the spectrum, and we have suppressed the S-cone pigment so that it is irrelevant to this measurement. And I should add that the rods have also been suppressed by the high intensity of the lights being used here. So, for that one remaining pigment, if the number of photons captured per second from these two different lights is the same, then at that point - for that individual - there is no sense of flicker. It just looks like uniform illumination! That is the sense that is obtained when the dial that determines the intensity ratio is set to just the right location. This method gives the relative efficiency of photon capture for those two different stimuli. If this is done for each of the different test wavelengths along the whole wavelength axis, then we can plot out the full sensitivity curve.

And here are these data. Shown in green we see the curve of sensitivity for the M-pigment. This is obtained from individuals who have an L-M hybrid, but the L-M hybrid consists almost completely of M sequences, and in particular it consists of M sequences in those regions which are critical for the spectral difference between L and M pigments. So, de facto, these are individuals who have only an M pigment and no L pigment - and here is their sensitivity spectrum in green.

Shown in yellow and red are the two different variants of the L pigment, with alanine at position 180 or serine in position 180. I think that you can appreciate that the pigment with serine at position 180 is offset to the right compared to the alanine at 180 version - just as it was in the in vitro spectrum. This is a very satisfying result: in the living human eye we can see the full spectral sensitivity of the pigments that underlie normal color vision in the human population.

My only regret in describing this experiment is that one of the most interesting dichromats, John Dalton, didn't live long enough to participate. Dalton was born in 1766. I think if he had been born two centuries later he would have been an eager participant in this experiment. Dalton maintained a lifelong interest in color vision and color blindness. And even though he didn't participate in this experiment, you may be interested to know that he made substantial contributions to the science of color vision, and, in particular, to understanding color blindness even after his death - which seems surprising!

During his lifetime, Dalton suggested that perhaps the source of his color anomaly was a selective filtering out of longer wavelengths of light by some colored medium, either in his vitreous - the fluid within the eyeball - or perhaps in the lens. And so, he stipulated in his will that when he died his eyes should be cut out and a little hole cut in the back of each eyeball. By viewing the world through that hole, it would be possible to tell whether the light was being filtered by some sort of colored substance within his eyes. That test was duly performed upon his death, and the result was that except for a little bit of yellowing of the lens, which is to be expected in someone who is somewhat older, the path was not colored. There was no filtering at all by the hypothesized color filter. And, therefore, Dalton's colorblindness must have been due to some difference within the retina or possibly within the brain. This was a major conceptual leap in understanding the origins of colorblindness, and it would have been a substantial contribution if nothing more had been done with his eyes.

In fact, Dalton continued to make contributions to the world of colorblindness research, and 150 years later his eyes, which had been preserved by the Manchester Literary and Philosophical Society, were

examined by DNA analysis. A small tissue sample was taken for that analysis, and it was shown that Dalton was, in fact, missing the M-pigment gene. He was a dichromat of just the sort we have seen before, with only an L-pigment gene and an S-pigment gene.

I think Dalton would have been very pleased with that result.

## The Vertebrate Retina Part 3

I am Jeremy Nathans. I am a professor at the Johns Hopkins Medical School and an investigator of the Howard Hughes Medical Institute. This is the third of three lectures on the structure, function, and evolution of the vertebrate retina. In this third part we are going to focus on the evolution of trichromatic color vision.

Let's consider the requirements that an organism needs to fulfill in order to evolve a new dimension of color vision. Here I will use the term "dimension" in the way Maxwell used it. We saw in the last lecture that Maxwell envisioned a three dimensional space - a color space, a perceptual space - where each dimension corresponded to the degree of excitation of a single type of photoreceptor cell. We can ask what one needs to do to add an additional dimension to that color space. That is exactly the evolutionary step that we are going to consider in this lecture - the transition from a simple, or simpler - dichromatic color vision to the trichromatic color vision that we humans enjoy today.

If we ask what is essential in making that evolutionary step, I think we can divide the answer into three parts. First, the organism needs to evolve a new light-sensing visual pigment. This would presumably be encoded by a distinct gene: the gene would encode a protein with a sequence that differs from those of the preexisting visual pigment proteins. Second, that gene needs to be expressed in a distinctive set of photoreceptor cells, distinct from the cells expressing the visual pigments that were preexisting in that organism. And finally, if those two steps are fulfilled, the organism still needs one thing more: it needs the neural circuitry to extract the information from that new receptor and compare it to the information that it is receiving from the preexisting receptors.

As we proceed in this lecture, we will consider each of these three steps and what we know about them and how we think they might have happened.

To begin: how do we know that an animal has color vision? At some level, you have to ask the animal. Of course if the animal is a human that is simple. You can set up a color vision test of the sort that Newton set up, as we saw in the last lecture, in which, for example, two spectrally pure lights are superimposed and their appearance matches a third light. We can ask a person: "do they match or do they not match?" And if they don't match we can then give the person a dial and let them adjust the intensity of one or another of those lights until a match is made. That is the classical method of human color vision testing.

For a nonhuman animal, where one does not have the advantage of verbal communication, we have to set up a test that will determine whether the animal can make those kinds of chromatic discriminations. The test is of the sort shown here. This is a little monkey who has the task of deciding which one of these three images looks different from the other two. This particular slide is unusual. We don't usually show them pictures of people. We show them just a blank panel of one or another color or one or another intensity and the animal decides which of the three panels looks different.

Here, this little monkey is going to decide which one of this set of three panels stands out. It is the one on the right, obviously: it is in color, and the other two are in black and white. She will press a lever underneath the bowl that corresponds to that panel and she will get a little candy reward in the bowl for

figuring out the right answer. This sort of test would be repeated on many trials, and the location of the picture that is different would be randomly changed in its location among the three different locations.

Importantly, we would also vary the intensities. Remember, in the real tests we don't use portraits like this, we just use blank panels of solid color, and we would vary the intensity of the colors at random. And that is a very important point to make because we want to make sure that the animal is not cueing on intensity but is cueing strictly on color. And the animal has to be smart enough and also have the color vision ability to realize that the test can be figured out by determining which color looks different independent of intensity differences.

Now we are going to focus on evolution in the primate lineage. I want to remind you that primates are quite diverse, although we think of them as just one little subset of mammals. Here we see three representative primates: gibbons on the left, a gorilla in the middle, and a bush baby on the right. This diversity is really enormous. For example, the bush baby on the right could easily fit into the hand of the gorilla in the middle. Within the primate lineage, color vision is also diverse, and that diversity correlates in an interesting way with the habitats of the primates.

Here, we need to take a brief detour into the geological history of our planet. Recall from what we know about plate tectonics that the continents were not separated for all time as they are now. South America (the New World) and Africa (the Old World) were once contiguous but they have been moving steadily apart. That has been going on for about 150 million years. About 50 or 75 million years ago there was a complete separation of all of the animal species on these two continents in the sense that there was no contact between them. In particular, the new and old world primates were free to go their separate evolutionary ways, and, as you will see in a minute, they have gone their separate ways with respect to their color vision.

In the case of the evolution of trichromacy within the primate lineage, we can ask: What advantage is there to trichromacy? Why not stick with the dichromacy that characterizes all of the non-primate mammals? Although I don't think we really know the answer to these questions, there are some ideas that are quite plausible. One of the most plausible is that it is easier to detect fruit among foliage – and, in particular, the ripeness of the fruit - if one has trichromatic color vision. We got a sense of that in the preceding lecture when we looked at an image of a fruit stand as seen by a normal trichromat and by various of the types of dichromats in the human population. Dichromats clearly have a more difficult time judging the ripeness of fruit. For animals that get a substantial fraction of their food from fruit, as many primates do, this could be a significant selective pressure.

It is also possible that there are other visual tasks that could be performed better with trichromatic color vision. Some animals, including some primates, are brightly colored, and it is a general pattern that those animals that have bright coloration - be they birds or fish (tropical fish, for example) - also have excellent color vision to see that coloration.

The answer is not known, in terms of what the real selective pressures are for trichromatic color vision, but it is widespread among primates and we presume there is some positive selective value to it.

Before proceeding further, let's briefly revisit a slide that we saw in the previous lecture. This is to remind ourselves that the basic mammalian arrangement - as shown by this dendrogram in the center for the mouse pigments - is one in which there are just two cone pigment genes. There is a longer wavelength one, an M pigment in the mouse; and a shorter wavelength one that happens to be UV sensitive in the mouse. In humans and other Old World primates, like gorillas and macaques, we have seen a split in the longer wavelength pigment lineage - a very recent split - so that now we have both M and L pigments in place of just a single pigment. But those pigments are still very similar in their sequences.

Let's now examine one of the earliest clues to the origins of primate trichromacy. That clue was gleaned

by looking at the way in which color signals are analyzed in the retina. If we look at the basic dichromat arrangement, this is the arrangement typical of non-primate mammals, it is quite simple: they have a shorter wavelength cone, an S cone, and they have a longer wavelength one – I will just call it M/L, the precursor of our M and L pigments. These two cone types feed, in an antagonistic way, into a circuit that is essentially a blue versus yellow circuit - a shorter wavelength versus a longer wavelength circuit - which then goes to the brain. This circuit might have, for example, an excitatory input from the longer wavelength side and an inhibitory input from the shorter wavelength side, and the output. The ganglion cell that is the output of this little circuit, is essentially a differential analyzer for longer versus shorter wavelength lights.

That is a basic circuit that is present in all mammals. We have essentially the same circuit in our retinas. If we look at the primate retina - the Old World primate retina, a retina like ours - we see that the circuitry has changed remarkably little. The circuit that I showed you on the previous slide has just been enhanced by adding the M and L cone inputs to the limb that previously received the ancestor of those cones. But it makes no distinction between these two new cone types. M and L cones are treated equivalently as regards this short versus longer wavelength circuit. Ultimately, after summing them at the first stage, they are compared in an antagonistic fashion - plus versus minus - in a second stage. This results in essentially the same sort of output that we saw before: a blue versus yellow type output.

There is a second circuit, though, that is involved in comparing M versus L signals. This circuit is again an antagonistic one. One of the cone signals is excitatory - shown here as the L signal; the other is inhibitory - the M signal. But there is a curious feature of this circuit. It would appear to be a new circuit, one that was added on later but not present in the more primitive mammals. But it is actually not a new circuit!

This circuit preexisted simply as a circuit involved in spatial vision. In our ancestors it used a single cone type - the precursor to the M and L cones - and it compared the signal in the center of the receptive field to the signal in the surround. This signal is achromatic – a non-color signal – and it tells the organism something about intensity differences in one place versus another place.

It appears that the same circuitry - essentially unchanged as far as we can tell - has now been co-opted to tell us something about color as well as about spatial intensity. In fact the two pieces of information, the two kinds of information, are now convoluted within this system. And it is not entirely clear exactly where and how those signals are de-convoluted. But this observation - this finding that the circuitry within the retina seems to have changed little if at all in the transition from dichromatic to trichromatic vision - is a striking one. And it argues that the principal evolutionary event - and perhaps the only evolutionary event - in making this transition was the acquisition of a new kind of cone.

I want to mention one additional thing about this retinal circuitry. You can appreciate there is an asymmetry here in the sense that the circuit does not compare S versus M, or S versus L, or L versus M in a symmetric way. It could have. Because of the pair-wise comparison of 'S versus M plus L' and 'M versus L' we have essentially a pair of axes for color comparisons. One can think of them as an X-axis and a Y-axis in a two dimensional space.

This has resulted in an interesting psychophysical phenomenon when we view the different wavelengths of light. One can display different lights in order according to their wavelengths: short wavelengths at the ultraviolet end, proceeding through the blues, the greens, the yellows, the oranges, and the reds, as we go to longer wavelengths. This is essentially a linear physical stimulus going from short wavelengths to long wavelengths.

Interestingly, the visual system - our visual system - converts this linear scale to a circular scale. We have all appreciated this in kindergarten when we first started playing with crayons. If you draw the colors in what seems to be their natural order - natural in the sense that the gradations between neighboring colors

is minimal - we naturally arrange them in the order red, orange, yellow, green, blue, violet. But then we think violet and red are somewhat similar because there is a purple transition between them, so we connect the colors into a circular pattern.

Why do we do that? Why do we make a circle out of what is physically a linear input? The answer is: because we are using this pair of axes to do our color comparisons in the visual system. We are basically looking at red versus green - that is, the L versus M dimension - in one comparison; and we are looking at the short wave or blue versus the sum of red and green - blue versus yellow - in the other dimension. And simply by dividing the world along these two dimensions – red/green and yellow/blue - we naturally create a two dimensional system in which we psychologically complete the circle. That is really an aside, but it is a natural outcome of the way in which we analyze color.

Now, let’s talk a bit about the details of visual pigment sequences and the implications of those sequences for the evolution of primate trichromacy. In the previous lecture we looked briefly at the sequence differences that distinguish the different human visual pigments from each other, and we remarked on the surprising – the striking - similarity between long and middle wavelength pigments, the L and M pigments. And if we look at those comparisons in greater detail, and then ask functionally what is the significance of the various amino acids that differ between L and M pigments, what we see is that there are only three major players relevant to the spectral sensitivity, the differential spectral tuning of L and M pigments. There is an amino acid at position 277 that can either be phenylalanine or tyrosine, one at position 285 that can either be alanine or threonine, and one at position 180 that can either be alanine or serine. In fact, the difference at position 180 is the one that is polymorphic in the L pigment gene pool. Together, these three positions are responsible for virtually all of the spectral difference between the L and M pigments.

If phenylalanine is present at position 277, if alanine is present at position 285, and alanine at position 180, then the pigment will absorb maximally at 530 nanometer: it will be an M pigment. If tyrosine is present at position 277, threonine at position 285 and serine at position 180, then the pigment will absorb maximally at 560 nanometers: it will be an L pigment. Those three positions are of interest because they have been seen in both New and Old World primates, as we will discuss in just a minute.

At this point, I need to take a slight interlude and say a few words about the X-chromosome and the significance of X-linkage, because X-linkage turns out to loom very large in this story. In all mammals, males differ from females in their chromosomal constitution. Males have an X-chromosome and a Y-chromosome and females have two X-chromosomes. The genes on the X-chromosome, of which there are many thousands, must be expressed in both males and females at the appropriate level. Yet females are endowed with twice the number of copies of those genes as males have. How does one avoid expressing twice as many copies of the corresponding messenger RNAs in a female compared to a male? If one did express twice the number of transcripts, that would be disastrous: it would wreak havoc with development.

Mammals have hit upon a peculiar solution to this problem. There is a selective inactivation of one of the two X chromosomes in each cell in the female body. Just for completeness, let me say that not every gene on the X chromosome obeys this rule, but most of them do. At an early point in development, when an embryo consists of a few thousand cells, each of those cells decides with essentially a molecular coin toss which of the two X-chromosomes will be inactive and which will remain active.

The result is that all female mammals are mosaics, as shown here for this cat. This female cat has an X-linked coat color variation, and she is a heterozygote. You can appreciate that there are patches of her coat that are one color and patches of her coat that are another color. For the most part, the colors are haphazardly mixed, but there are also some places where there are small regions that are solidly one or the other color. This mosaicism can play itself out in any number of ways with X-linked genes. And in

the context of the visual pigment genes in New World Primates, it plays itself out in an especially interesting way.

As it turns out, New World primates have trichromatic color vision only among females. Male New World monkeys are dichromats. And among the females in those populations, only a fraction are trichromats - roughly two-thirds. The way this works is that these New World monkeys have a single X-linked visual pigment gene. They do not have the gene duplication that we have. But that one gene is polymorphic in the population. And the different alleles encode variant visual pigments that have different spectral sensitivities.

For example, for one typical New World monkey species, we see that there are three visual pigment alleles: one is maximally sensitive at 535 nanometers, rather like our M pigment; another at 550 nanometers, roughly midway between the M and L pigments; and the third at 563 nanometers; quite close to our L pigment. By comparison, our Old World arrangement - as we saw in the previous lecture - involves two genes, or more than two in some cases, in tandem on the X-chromosome. They encode pigments with peak absorbances at 530 and 560 nanometers.

The striking finding - when one looks at the sequences of New and Old World primate pigment genes - is that the New World monkeys are using exactly the same three amino acid differences to differentially tune the spectral sensitivities of their pigments as we Old World primates use to differentially tune the spectrally sensitivities of our pigments.

Just to recap, at these three critical sites, we use alanine, phenylalanine, and alanine in our M pigment, and serine, tyrosine, and threonine in our L pigment. The New World monkeys do exactly the same thing. Their pigment that has an absorbance spectrum half-way in between M and L has alanine, phenylalanine, and threonine - which means it is a hybrid of M and L sequences, just as you might have expected. This is quite a striking finding, because we know from site-directed mutagenesis and from sequencing the genes from different vertebrates that this is not the only way to tune these pigments. There are other ways - other amino acids can vary and can give rise to spectral tuning to either shorter or longer wavelengths. The fact that New World and Old World primates use exactly the same amino acid variations to tune their visual pigment spectral sensitivities argues that this is not a coincidence and it is not likely to be a convergence on the same solution, but rather these pigments arose from a common ancestor.

We suspect that the common ancestor had the New World gene arrangement. In other words, this allelic variation preexisted among our ancestors, among the earliest primates that pre-dated the separation of New and Old Worlds. As shown schematically in this next slide, we can envision a timeline - with time going from left to right - in which non-primate mammals - shown at the very top - have gone their separate route and remained dichromatic. Along the primate lineage - or the proto-primate lineage - we see at some point, before the split between New and Old World, this polymorphism appearing in the X-linked visual pigment genes. And then, there is the split of New World primates, who have maintained that system, and Old World primates. At some point in the Old World primate lineage, there has been the acquisition of the M and L gene duplication that we now enjoy.

This harks back to the previous lecture, when I mentioned that we believe the duplication occurred between variant sequences that were already different - that is, between a preexisting L-like pigment and a preexisting M-like pigment. This is an exception to the way that we think that gene evolution usually occurs. The classic mode of gene evolution involves, first, the duplication of a gene to make an identical copy and then, over time, the acquisition of mutations within that copy or perhaps within the parental copy to change both sequence and function. That is "duplication followed by divergence". That is the classic mode of gene evolution and it has been documented in many, many instances.

What we have here is the reverse. This is "divergence followed by duplication". It begs the question of

whether there might be other examples of this sort of gene evolution.

What I have just described addresses the first of the three challenges for evolving a new dimension of color vision - the production of a visual pigment with a novel absorbance spectrum. We think that this happened initially by allelic variation, and it has been cemented in the Old World lineage by gene duplication. Now, let's consider the second of the three requirements: expression of the new visual pigment gene in a class of photoreceptor cells distinct from the classes that are expressing the preexisting pigments.

The first clue to how this might work for the L and M pigments came from studying those rare humans who are missing both M and L sensitivities. These individuals have what is called "blue cone monochromacy". They have normal blue, or S, cones with which they can see the world, and they have normal rods. Since the rod system does not contribute to color vision and the S cones are the only cone system that they possess, they cannot compare the S cone output with any other cone type. Therefore, these individuals are monochromats. They have a fully monochromatic color world: that is, just a one-dimensional color world where there are only changes in intensity. They have no sense of color at all. This is true color blindness.

It turns out that blue cone monochromacy is X-linked, as are the common dichromacies and anomalous trichromacies. In fact, blue cone monochromacy arises from sequence variation at the L and M gene locus.

There are two basic mechanisms for blue cone monochromacy. The first - which I will describe here just for completeness, but which is really not that relevant to our story - is the one you might have guessed based on what I have presented thus far. We can start with the wild type gene arrangement - and one example is shown here at the top, with one L and two M pigment genes. By the homologous recombination that we considered in the previous lecture, this arrangement can be reduced to just a single gene within the array. And that can either be an L pigment gene or it could be an L/M hybrid gene. This is not news to you at this point. The male who carries this gene arrangement would be a dichromat.

But, then, that gene could suffer an additional mutational event. Like any gene, it could suffer some sort of mutation that disrupts protein structure or function and, as a result, this individual would now - by virtue of these two mutational steps - be missing all functional long and medium wavelength pigment genes. This is what is seen in about half of blue cone monochromats. Blue cone monochromacy occurs at a frequency of about one person in 100,000, and about half of blue cone monochromats have the sort of mutational event I have illustrated here.

The other half, though, are more germane to the lecture today. Those are the gene arrangements that have, in one step, suffered a mutational event that has eliminated the expression of the L and M pigment genes. Interestingly, in many cases, that mutational event has not affected the coding regions of those genes at all.

Here is an example of a normal array: one L and two M pigment genes. This is a typical array. Here below is the array with a deletion of sequences upstream. That deletion, as far as we can tell from analyzing those individuals, has completely eliminated the expression of all the genes in the array. There is a critical sequence upstream of the genes that is involved in their expression. This is not completely surprising in the mammalian gene expression business. The upstream region would be called an enhancer: a sequence at some distance from the gene that it controls. Presumably there is some sort of assembly of promoter and enhancer sequences and their associated proteins that controls transcription.

We know that the upstream sequence is important in the control of gene expression because if we produce a transgenic mouse that carries the human upstream sequences - the promoter region of the L pigment gene plus the upstream region with this enhancer-like region, which we infer is important from the

analysis of blue cone monochromats - we can see that this combination of sequences can drive the expression of a reporter - in this case lacZ, the beta-galactosidase gene, from E. coli - in cone photoreceptor cells in the mouse retina. That is what these blue cells are: these are cells that have been stained with the beta-galactosidase substrate X-gal. In this transgenic mouse retina, that substrate is now converted into a blue precipitate, indicating the location of cells expressing the beta-galactosidase transgene. If exactly the same type of transgenic mouse is produced with sequences that are missing the upstream segment - just the kind of deletion a blue cone monochromat might have – then there is no expression of the transgene in the retina. So this upstream sequence is essential for gene expression.

The mouse experiment that we just discussed, as well as the DNA sequences of this region obtained from many mammals, reveal that, in fact, this upstream region - which we are now going to call a "locus control region" because it is controlling the locus of L and M pigment genes - is highly conserved among mammals. It is present in dogs, cows, cats, and other species. And it is also present in us. Here is the locus control region, shown schematically as a little purple ball. Although we don't know the details, we presume that in ancestral mammals - the ones with just a single visual pigment gene - or in New World primates today, where there is a single gene but the gene is polymorphic, somehow this DNA region acts on or with the adjacent promoter to activate transcription in cone photoreceptors.

Importantly, the locus control region is located outside of the region that was duplicated in evolution to create the L and M pigment genes. We humans and other Old World primates have only a single copy of the locus control region, as do non-primate mammals. And, therefore, one presumes that this locus control region acts on the L pigment gene promoter in L cones and on the M pigment gene promoter in M cones. That is a reasonable assumption, although I should say it is more of a model than a summary of data. This model makes a simple prediction, and that is that the pairing of the locus control region either with the L pigment gene in L cones or the M pigment gene in M cones is a critical event in the development of those cones, and in the decision to become either an L or an M cone. At present we know of no other molecular differences between those two cell types, so the possibility exists that this is the only difference that distinguishes these cones from each other.

With that idea in mind, let's consider for a moment how that M vs. L decision might be made. And now we are really considering models for which we don't have firm data, but I think they constrain the way in which we might think about the process. We could imagine that in an ancestral dichromatic mammal and in present-day New World primates, there is a single transcription factor - shown by this black ball, this ancestral transcription factor - that mediates the pairing of the locus control region with the single nearby promoter. There is really no decision to be made here. There is only one gene that is available for expression. And that pairing would facilitate the expression of that one gene in the one kind of longer wavelength cone that this animal has.

In primates like us - Old World primates - there are two different genes, an L and an M pigment gene. In the context of this model - what I will call the standard model – we can envision transcription factors specific for either the L or the M cones - and these are shown as red and green balls, respectively- and those specific transcription factors would orchestrate the pairing of the locus control region with the appropriate promoter. That would be the standard model that one thinks about in considering the differential expression of genes in any particular set of distinctive cells, say in kidney cells versus liver cells. It would be orchestrated by cell type-specific transcription factors in those cases.

Now let's consider a simpler model and one that has a different set of predictions - and that is a stochastic model of cell type-specific gene expression. In this model, we imagine that the ancient transcription factor - the ancestral transcription factor, this black ball, that mediates the pairing in dichromatic mammals and presumably also New World monkeys – is, in fact, the same transcription factor that we humans have. In that case, the pairing in L cones and M cones is simply determined by a molecular coin toss. It can involve pairing of the locus control region with either the L pigment promoter or the M pigment promoter. Once the pairing has occurred, presumably it will be stable, and there are various

molecular mechanisms that one can envision for stabilizing it: DNA methylation, for example, or other epigenetic modifications.  We imagine that the initial choice is made without reference to any other decision-making process.  Once the choice is made, that is what sets the destiny of that photoreceptor as being either an L or an M cone.

That is a very simple model.  It makes a number of predictions, and one prediction that it makes is that the decision to express a visual pigment gene in one cone or another, in either L or M cones, is actually a decision process that any mammal can perform.  It doesn't need a special transcription factor family that is specific for L or M cones.

That idea has been tested by placing a version of the human L and M pigment gene array, with the locus control region, into the mouse genome.  Here is the construct that was inserted into the mouse genome.  There is a locus control region at the left end; followed by the L pigment promoter shown in red, followed by one enzymatic reporter (alkaline phosphatase), which produces a brown histochemical product in those cells in which it is expressed; followed by an M pigment promoter and the beta-galactosidase or lacZ reporter, which we have seen before and which gives a blue product in those cells in which it is expressed.

This DNA construct was inserted into the mouse genome at exactly one copy and then the retina was examined, and - lo and behold - it was observed that not only was the expression exclusively in cone photoreceptors - that was expected - but the cones were either brown or blue and only very rarely were they both.  That is, the mouse appears to be quite capable of doing this molecular coin toss, deciding which of the two genes to express, and expressing them in a mutually exclusive fashion.  The fact that New World monkeys use X-inactivation - which we know is a stochastic mechanism - to make the L vs. M cone decision argues that stochastic mechanisms in general are plausible mechanisms for generating an L/M cone mosaic and extracting information – again, in ways which we don't fully understand - to generate trichromacy.

Now let's take this one step further.  If it is possible for a mammal that has never experienced trichromacy to produce a mosaic of L and M type cones in its retina simply by being presented with those genes in its genome, let's ask: "Could that mammal - if given a new visual pigment gene - immediately use it for color vision?"  That experiment has also been done in the mouse.

Here is a mouse that has had a human long wavelength visual pigment gene inserted into its genome.  She is a female, and she has, on one of her X-chromosomes a normal mouse pigment gene, an M pigment gene, that absorbs maximally at 510 nanometers.  On her other X-chromosome, she has a human L pigment gene, which encodes a pigment that absorbs maximally at 560 nanometers.  Here she is been given the mouse version of that color vision task that we saw earlier for the little monkey.  In this case, she has to decide which one of these three panels, shown here, has a light that is different from the other two.  If she decides correctly, she gets a little drop of soy milk, which she is drinking right now and which is coming from above the panel that looks different.  There is a little tube here that will produce a drop of soy milk when she guesses the correct panel.  Of course, the test is repeated many times over, the location of the differently colored light is varied randomly among the panels, and the mouse is asked - by measuring how many times it gets a drop of soy milk, which is measured electronically - "can you see the difference between the colors even if we randomize intensity?"

When this test was initially done, the mouse was simply asked whether it could see longer wavelength lights more efficiently now that it had a human L pigment gene, compared to a normal mouse.  And the answer is "yes".  A heterozygous mouse with both M and L pigments required less long wavelength light compared to a control mouse with only the M pigment.  That was not surprising.  It just shows that the human L pigment works in the mouse retina, and can transduce signals and tell the brain that it has captured light.

But the more telling experiment is here, where we are looking at discrimination between lights of different wavelengths. Here we have a three-way forced choice task of just the sort we saw the mouse performing. Because there are three panels and one of the three is correct, an animal that cannot pass this test will simply guess on every round and get it right - as shown by these data points down here – one third of the time. So these data points represent mice that cannot pass the test, but they have realized quite quickly that it is better to guess than to do nothing, because even if they guess they'll get a drop of soy milk a third of the time.

But how about a mouse that has the engineered human pigment, as well as the normal mouse pigment? These, of course, are female mice because this gene is on the X-chromosome, and females have - by virtue of X inactivation - created a mosaic of the different cone types within the retina. We now know that it is a rather fine-grained mosaic. That kind of mouse can discriminate test lights - shown here - that vary in their wavelengths from 500 to 600 nanometers from a control standard light of 600 nanometers quite substantially better than chance. Roughly 70 or 75 percent of the time, when that test wavelength is 500 or 520 or 540 or 560 or 580 nanometers, the mice can tell the difference between the test wavelength and the standard control wavelength. Again, intensities have been varied randomly so that the animal cannot cue on intensity; it must be seeing the color aspect of the stimulus.

When the test wavelength gets very close to the standard, when it is at, say, 590 nanometers, very close to the standard at 600 nanometers, then the mouse begins to fail the test. And, of course, when the two are exactly the same wavelength, the mouse fails completely and it is just guessing at what the right answer might be.

This experiment has a number of interesting implications for color vision evolution and, perhaps, brain evolution in general. In the context of the evolution of trichromatic color vision, what it says is that there is a plasticity that is naturally built into the mammalian brain that allows it to take an input - a novel sensory input - and make sense of it in the context of preexisting sensory inputs.

From the point of view of brain evolution in general, I think this points to what is probably the winning strategy for brain evolution: which is to have the system built with a degree of plasticity that allows it to take advantage - perhaps immediate advantage - of genetic changes that affect parts of the system – say, the front end of the system, the receptors themselves - and to extract information that is useful even though the only genetic change has been in the receptor and not in the neural wiring.

From the point of view of the evolution of trichromatic color vision, this would argue that the first primate who acquired an additional genetic change to create a novel visual pigment immediately saw a world of color that no primate had ever seen before.

**One Amazing Second in the Life of Your Brain (iBio101 video transcript) – April 2011**

I am Jeremy Nathans. I am a Professor at the Johns Hopkins Medical School, and an Investigator of the Howard Hughes Medical Institute.

This entire lecture is devoted to understanding a simple task that will take less than one second for you to perform. At first glance, the process seems so simple and so commonplace that we might hardly think it worth commenting on. But I hope that by the end of the lecture you will agree that what has happened inside your head during that one second is truly amazing.

Let's introduce the task. I will say "three plus two" and you say what it equals. I suspect that it has not taken you very long to say "five". We can do simple tasks like this with what seems like almost no effort. But let's now ask: What actually happened inside your head during that one second? We can divide the process roughly into the following parts: you detected the sounds, you decoded their meaning, you held the numbers (as well as the instructions about what calculation to perform) in your memory, you performed a mathematical calculation, you formulated your linguistic response, and you generated the sounds that constitute speech. Listed that way, it sounds a bit more complicated. Let's dissect it step by step and see what is involved.

Consider the sound waves that have emerged from my mouth and have arrived at your ear. Sound waves consist of alternating compressions and rarefactions of the air. Air is like a spring – it can be compressed and it can expand. That pattern of compressions and expansions arrives at your ear as a complex series of waves. They enter at the outer ear canal, and they cause this very thin membrane – called the ear drum because it is like the head of an acoustic drum – to vibrate back and forth. That vibration is transmitted to a series of three tiny bones that are connected to each other and reside in the middle ear.

The bones of the middle ear conduct vibrations from the ear drum to a much smaller vibrating layer – the oval window - at the base of the cochlea, which is Latin for snail. The three bones that conduct the vibrations through the middle ear are the three smallest bones in the human body. Here is a photograph of one of them, the stapes, placed next to a coin. It looks like a tiny horse's stirrup, and in fact 'stapes' means 'stirrup' in Latin.

Here is a cross section through the cochlea, the structure shaped like a snail. The spiral tube is divided into three parallel channels by thin flexible dividers. It is all filled with a salt and water fluid – there no air bubbles – and it is surrounded by bone. All along the lower divider of the central channel - from the base of the spiral to the apex (apex is just a fancy word for tip) – is an extraordinarily delicate and beautiful structure called the organ of Corti. This houses the sound sensing cells.

What happens to the vibrating motion that was transmitted from the eardrum to the oval window? The oval window forms the base of the upper channel and it is connected to the stapes, which moves back and forth like a piston, reproducing the pattern of vibrations of the eardrum; the lower channel has its own flexible base, called the round window, which freely moves back and forth. The rest of the surrounding material is bone – it is not flexible. When the oval window is pushed inward, the fluid inside the upper channel pushes on the flexible divider separating it from the middle channel, which in turn causes the fluid in the middle channel to push against the divider to the lower channel, which makes the round window bulge out into the middle ear. Now imagine these movements occurring thousands of times per second as the vibrations of human speech arrive at the eardrum. The result is that the two flexible dividers vibrate up and down.

But there is an important detail here: along the 3 cm length of the cochlea each region vibrates preferentially to only one particular frequency or pitch. At the base of the cochlea the lower divider - called the basilar membrane – is narrow and very stiff – it is tuned to vibrate to high frequencies. At the apex, the basilar membrane is wider and not so stiff – it is tuned to vibrate at lower frequencies. In going

from the base to the apex, the width and stiffness of the basilar membrane gradually changes so that for each frequency within the range that we can hear – from about 500 vibrations per second to about 15,000 vibrations per second - there is one and only one point along the cochlea where the basilar membrane vibrates the most. In a sense, the cochlea is like the keys on a piano: the frequencies are laid out in order in a one dimensional array – the brain's job is to look at the locations of neuronal activity along the cochlea as a function of time to read out the pattern of frequencies that make up the sound.

How do we detect the sound waves? We detect the fluid vibrations. There is a very sensitive detector apparatus that is mounted in this central chamber – it is called the organ of Corti. It has a series of delicate sensory cells – called hair cells - and if we look on the next slide at the organ of Corti at high magnification, we see this series of cells. This image shows the organ of Corti cut in cross section, and it is seen through a microscope.

The cells are sitting just underneath the tectorial membrane, which is essentially a lid on top of the cells. As the organ of Corti moves up and down, the lid, which is connected to the top surface of the cells, moves back and forth just a little bit: the back and forth motion is coupled to the up and down motion of the entire apparatus. That back and forth motion is the thing that is detected by the sensory cells.

Here we see the V-shaped sensory apparatus of each of these hair cells. The tips of the little cilia that constitute the V-shapes touch the tectorial membrane, which lies on top of the sheet of cells. As that membrane moves back and forth, it pulls these little V-shaped objects back and forth with it.

Let's look at even higher power at one of these sensory cells. This image is actually from a different part of the inner ear, the part that detects motion of the head, rather than sound, but the operating principles are the same. Here we see that the bundle consists of a series of individual rods that stick up – the technical name is stereocilia. The rods can pivot at their bases. When the tip of the bundle is pulled back and forth, the entire bundle to pivots back and forth.

You may have noticed that the heights of the individual stereocilia increase in going from one side to the other. If the bundle is pushed toward the taller stereocilia, the cell is activated. If the bundle is pushed in the opposite direction, the cell is inhibited. What do we mean when we say the cell is activated? Activation occurs when charged atoms – they are called ions – flow through channels in the surface membrane. When the hair bundle is at rest most of the channels are closed. Movement of the hair bundle in the direction of the tallest stereocilia opens the channels and movement in the opposite direction closes the channels.

How is channel opening controlled by hair bundle movement? A critical clue came from looking at the hair bundles with an electron microscope – a microscope that can image at very high magnification because it uses electrons rather than light to create an image. Tiny threads connect the tip of each stereocilium to the side of its neighboring stereocilium, and either one or both ends of these threads are connected to the ion channels. As the bundle moves to the right, the shearing movement stretches the thread – which can stretch like a rubber band - and that tension on the thread opens the channel. In this cartoon the thread is shown connecting directly to a door on the channel that can swing open – this is conceptually right, but we don't yet know what the channel door really looks like.

This system is so sensitive that it can detect a movement of the hair bundle of less than one billionth of a meter – the diameter of a large atom. This is less than one thousandth the length of the stereocilia. If we imagine an individual stereocilium enlarged to the size of a 100-story building, this movement would be equivalent to a swaying motion at the top of the building of about half a meter.

Unfortunately, in a system as intricate as the inner ear, many things can go wrong, either as a result of injury or disease. Many people have severe hearing loss due to defects in the middle ear or the cochlea that cannot be corrected by simply amplifying the sound with a hearing aid. For these individuals, the

cochlear implant - a triumph of bioengineering - offers hope for substantial recovery of hearing. The cochlear implant has two parts. The first part is an external microphone that detects sound and converts it into a radio signal. The second part is implanted inside the bone – it receives the radio signal and converts that information into a pattern of electrical impulses in a series of wires that are bundled together and terminate at different locations along the length of the bundle. The wire bundle is surgically wound along the spiral of the cochlea. Because the cochlea responds to different frequencies – or pitches – at different positions along its length, the electrical impulses along the cochlear implant bundle can accurately mimic the normal pattern of electrical activity – low frequency sounds activate signals in the electrode at the tip of the cochlea and high frequency sounds activate signals in the electrode at the base of the cochlea, and intermediate pitches activate intermediate locations within the cochlea. Here is what the cochlear implant looks like from the outside. World-wide about 200,000 people now use a cochlear implant.

How is the activation of a sensory hair cell communicated to other nerve cells? Nerve cells, also called neurons, use a mixture of electrical and chemical signaling. When information moves long distances, and in particular when it moves along the thin cables called axons, it moves as an electrical wave. We won't go into the details of this mechanism, but let's take a moment to see what happens when information is passed from one neuron to another. The points of close contact are called synapses – two of them are shown here in this cartoon. In general, information flows in one direction at a synapse, and the cell that is sending the information has within it packets of chemicals called neurotransmitters. The neurotransmitters are released into the tiny space between the sending and receiving cells and this release is triggered by the arrival of the electrical wave. The cell that is sending the information is called the pre-synaptic cell, and the cell receiving the information is called the post-synaptic cell. If we look with the electron microscope at a very thin slice of nervous system tissue, we can see how close together the cells are at the synapse – the separation is about 50 billionths of a meter. The receiving cell has specific neurotransmitter receptor proteins in its surface membrane – proteins that upon binding the released neurotransmitter change their shape to either open an ion channel or communicate in some other way to the cell that the transmitter has arrived. The whole process of sending a signal from one neuron to its neighbor takes about one thousandth of a second.

But synapses do much more than simply convey signals. They can change over time – a property that neuroscientists refer to as "plasticity". Synaptic plasticity appears to be a central mechanism – maybe THE central mechanism – for learning and memory. In the present case, you have remembered that your task was to state the sum of two plus three. Of course, to perform this task you have must also have learned and remembered the meanings of the words that allowed you to understand the instructions, and the rules of addition that allow you to know that the sum of two plus three is five. Even if we don't know exactly what went on in our brains when we remembered all these things – and we don't - it is obvious that something must have changed.

Some of the most incisive discoveries in the quest to understand the mechanisms of learning and memory have come from studying simple organisms, such Aplysia, a baseball-sized sea slug. Although it has a very simple nervous system, Aplysia can learn and remember simple things, and it is possible to record the electrical responses of individual neurons while its nervous system is learning, remembering, or forgetting. I want to describe two important discoveries about synapses that apply to animals as different as mammals and sea slugs. First, the strength of synapses can change rapidly, as shown here for a series of identical electrical impulses delivered from a pre-synaptic cell to a postsynaptic cell. I will call each brief period of neurotransmitter release a stimulus; the figure shows seven identical closely spaced stimuli. As you can see the response of the postsynaptic cell is increasing with each successive stimulus. Somehow, the synapse has been altered – it can remember! For some synapses, a series of stimuli like the ones shown here can produce a change in synaptic strength that lasts for many hours. Recent experiments indicate that the strength of the response is modulated by changes in the number of neurotransmitter receptors in the surface membrane in the post-synaptic cell.

The second important discovery is that the number and location of synapses can change, even in a fully mature brain. The image on the left is from an adult mouse brain, and it shows one branch – called a dendrite - from a single neuron. There are a series of little bumps sticking out: these are the sites where synapses are located. The image on the right is of the same branch but taken a few weeks later, and you can see that the arrangement has changed – some old bumps have disappeared and some new bumps have appeared. This sort of structural change could mediate memories that last for weeks, months, or years.

We humans like to think that, with our big brains, we are better than our nonhuman relatives at all kinds of mental tasks. Let me show a video of a chimp that casts some doubt on this assumption. The chimp in this video has learned a relatively complex task. First, she has learned to distinguish the appearance of the numbers one through nine. Second she has learned to play a little video game in which the nine numbers are flashed for a fraction of a second on a touch screen and then, after the numbers have disappeared, she tries to touch – in order – the places on the screen where the numbers were. That is, she first touches the place where number 1 was, then the place where number 2 was, then the place where number 3 was, and so on. If she correctly touches all nine locations, she gets a little snack as a reward – you will see her dipping her finger into the snack food at the end of each session. Let's watch her playing the game, first in slow motion and then at the real speed. You may be interested to know that young people, such as college students, are better at this game than older people like me, but that this chimp is better at it than the average college student. It is also interesting to consider how smart this chimp must be just to figure out each of the steps required to play the game - after all, her handlers couldn't explain the rules to her. Everything she knows about this game had to be learned by trial and error with a little snack as a reward. I invite you to try teaching one of your friends something new and complicated using as your only means of communication a reward or no reward instead of language.

Now let's return to the flow of information in our "two plus three equals five" task. As the electrical signals initiated by the complex sounds that comprise our speech are transferred from the ear to the brain and from one brain area to another, they activate neurons that respond optimally to different features of the sound, including pitch, loudness, and location in space. But how these different sound elements are decoded to produce linguistic meaning is still largely unknown.

However, we do know something about where in the brain these processes happen. One hundred year ago, the localization of function to different brain region relied on studying those unfortunate people who suffered an injury to one or another brain region. The method was simple: define the mental function that was affected and then, after the person died, determine which part of the brain was injured. Needless to say, this method is not very efficient. But new techniques have transformed this area of investigation and one of the most powerful is a method called functional magnetic resonance imaging – fMRI for short, which measures how the flow of blood to different brain regions changes from moment to moment. In the same way that blood flow increases to a muscle that is working hard – for example, the flow of blood to your legs increases when you run – so the flow of blood increases to those brain regions that are working hard. Here we see an MRI scanner – it consists of a large round magnet and a bed with a plastic head holder. The subject lies down on the bed, slides into the hole in the center of the magnet, and then performs various mental tasks while the scanner monitors regional blood flow in the brain.

The next slide shows a conventional MRI image – not the kind that reveals blood flow, just an image that shows all of the structures. The MRI technology can generate an image derived from a thin slice at any angle one pleases – in this case right down the middle of the head. As you can imagine, this imaging technology has revolutionized the practice of neurosurgery. Thanks to MRI the neurosurgeon has a very good idea of what he or she will encounter before the operation begins.

The next slide shows a set of four blood flow images from fMRI – here the brain is viewed from the side with the front toward the left. The colors show those locations with the greatest increase in blood flow when the subject performed four language related tasks. Each of the four active regions resides within the cerebral cortex – the large folded sheet that covers most of the outside of the human brain. When we see

words, the back of the cortex processes that information, and when we hear words, a more anterior region processes the information. When we think about words, the frontal cortex is working, and finally when we speak a very particular area along the side of the cortex is activated. It is clear that multiple widely separated regions of the cerebral cortex are involved in processing language.

Let's look more closely at two regions of the cortex: one, called Wernicke's area, that is especially important for understanding words and sentences, and the second, called Broca's area, that is especially important for generating speech. These regions largely overlap the two regions shown on the preceding slide that are activated when we hear words and when we speak. Interestingly, Wernicke's area and Broca's area are usually located only on the left side of the brain, although in a minority of people, these areas are either on the right side or on both sides of the brain. Individuals with damage to Wernicke's area can speak fluently, but the combinations of words that they choose have little or no meaning. In addition, their ability to understand what other people are saying is severely diminished. By contrast, individuals with damage to Broca's area can understand speech – this is easy to demonstrate by asking such a person to do something like touch his or her nose - but they speak haltingly and with great effort. In rough terms, Wernicke's area is responsible for formulating the meanings of words and sentences, whereas Broca's area is responsible for controlling the complicated planning of muscle movements that produce speech. Not surprisingly, the two areas are connected by a large bundle of nerve fibers, with information flowing from Wernicke's area to Broca's area.

Now we are about one half of a second into our task: you have heard and understood the phrase "two plus three", you have remembered the instructions, and you have come up with the correct answer, "five". Broca's area is now preparing the right pattern of neural activity so that you can say the word "five". At this point, let's note that the location of Broca's area does not appear to be accidental: it is just in front of a thin strip of cerebral cortex, called the motor cortex, that controls the body's muscles.

There are many muscles in the human body - some large and some small - and the precision with which they are controlled varies enormously. Your leg and arm muscles are powerful but not precisely controlled. But the muscles that control your fingers, your vocal cords, and your lips and tongue are under very precise control. This allows us to use our hands for all kinds of difficult tasks that we can't do with our feet, even if we could hold things with our toes: tasks like typing, threading needles, painting pictures, playing the violin, and doing surgery. Similarly, the high precision muscular control of breathing, vocal cord movement, and the shaping of our tongue and lips gives us the ability to produce complex sounds. In keeping with these differences in precision of muscle action, if one maps out the location and size of cerebral cortical areas devoted to controlling muscular movements for different parts of the body, one finds the peculiarly distorted body map shown here. Those muscles that are controlled with high precision require a lot of neurons, which occupy a large cortical area. Incidentally, a similarly distorted map is seen for touch sensation over the body surface: the lips and finger tips are far more sensitive than the back, and they are given a correspondingly larger territory in that region of cortex devoted to the sense of touch. These motor and sensory maps were delineated by electrically stimulating small regions of the cerebral cortex in patients who were undergoing brain surgery. In some neurosurgeries, the patient is awake during the procedure and then the surgeon can ask the patient what he or she experiences when the different regions of the brain are stimulated.

Now back to our task. The neurons in Broca's area instruct the neurons in the adjacent motor cortex that control speech, and the neurons in the motor cortex instruct the neurons that synapse directly onto the muscle fibers. Here, I am simplifying things quite a bit because other brain regions, such as the cerebellum – a special region at the back of the brain - also play an important role in coordinating complex muscular movements, including the movements that generate speech.

Signaling from nerve to muscle works in very much the same way as signaling from one neuron to another: there is a synapse from one neuron onto one muscle fiber, and neurotransmitter molecules – in this case acetylcholine molecules - are released by the neuron and bind their receptors on the surface of

the muscle cell. The receptor on the muscle - shown schematically here - is an ion channel that opens when acetylcholine binds to it. Sodium ions, which are present at high concentration outside the cell flow through the channel, thereby making the interior of the cell more positively charged. That increase in positive charge in the cell interior is sensed by another set of channels that conduct calcium ions, and the calcium channels open in response to the increase in positive charge. The result is that calcium flows into the muscle fiber. The increase in calcium then triggers the protein machines that use chemical energy in the form of ATP to drive muscle contraction. With all of the right muscles contracting, you exhale, the air passes through your vocal cords, and the flowing air is shaped by your mouth and tongue to generate the pattern of vibrations that we all know as the sound "5".

The entire process that we have just outlined takes about a second from start to finish. You may have noticed that the different steps were not described in comparable levels of detail. This reflects our current state of knowledge: we know a lot more about the workings of the inner ear and the neuromuscular synapse than about more complex neural processes like decoding language, doing a mathematical calculation, recognizing faces, composing music, or falling in love, which are still largely or completely beyond our understanding. So even though a lot of progress has been made over the past 100 years in understanding brain function, there is much more still to be discovered.

With this scientific challenge in mind, let's look at the big picture, and ask the following simple question: just how complicated is the human brain? Here is a picture of the human brain, viewed from the side. It doesn't look that complex from the outside, but as soon as we look inside, we get quite a different picture. For example, here is a map of the major connections between distant areas as seen in a single slice viewed from the front. This image was produced with a special MRI method called diffusion tensor imaging. Each thread here represents thousands of axons, the individual wires that connect different neurons. It is obvious that the wiring is very complex. If we think of the brain as something like a computer, we can ask the sort of question that an engineer might ask, for example: how many parts does it have? The next slide gives some of the numbers for neurons and synapses, the basic building blocks of the nervous system.

As impressive as these numbers are, they tell only part of the story. For example, if we take a close look at individual neurons, we see that each one has a complex and distinctive architecture, and, in fact, each neuron acts like a small computer. It is also remarkable how all of these complex structures are packed into such a small space. Here is a picture from the brain of a mouse that has been genetically engineered to have differently colored neurons. We see that there is almost no wasted space: the neurons and their various branches are very precisely and very tightly packed.

Another aspect that is impressive from an engineering point of view is how small all of the components are. Each cell body is about one one-hundredth of a millimeter wide and the individual branches that emerge from the cell body are roughly one ten-thousandth of a millimeter in width.

How does this degree of miniaturization compare to the smallest human-made devices? Engineers have made impressive progress in miniaturizing computer chips, which are the most complex objects that humans manufacture. Here is a computer chip with roughly a billion circuit elements – the penny underneath the chip gives you an idea of how small it is. If we look at the chip in the electron microscope we see that the individual elements are about 50 nanometer – that is, 50 billionths of a meter - in width, about the same scale as the individual parts of a synapse. Although this is an impressive feat of miniaturization, the brain is still far ahead because computer chips can only be manufactured as two-dimensional objects – all of the transistors and other circuit elements sit on a flat surface. By contrast, the brain efficiently uses all three dimensions and therefore packs far more circuitry into a volume of space than a computer.

Thinking about the production of computer chips brings us to a related engineering question: how is the brain built? Or more specifically, what type of instructions determines the brain's structure and how are

those instructions read out? We know that the information for building each individual organism is encoded within the DNA of that individual - this is as true for us as it is for sea slugs. But genetic information does not represent the organism that it codes for in the same way that a blueprint represents a house or a car.

Here we see a typical blueprint. It represents an object as an image with a series of accompanying comments – and this is certainly a logical way to present information. But Nature doesn't use drawings. Instead, the genetic information in DNA is present as a long string of chemical groups, which we can think of as the letters in an alphabet. In the case of DNA, the alphabet has 4 letters – A, C, G, and T. The order of these 4 letters not only codes for the individual building blocks of each living organism, but it also codes for the way in which these building blocks are assembled, the interactions of millions of these building bocks in the form of cells, the response of the organism to changes in its environment, and much more. To see how conceptually different this is from the blueprint approach, imagine trying to build a car from solid blocks of metal, rubber, and plastic with a book of instructions that contains only text but no pictures. It won't be easy.

In this lecture, we have discussed some things that we understand, but we have also highlighted many things that are still beyond the frontier of current knowledge. I'd like to leave you with three big questions related to brain development and function. First, "How is brain structure and plasticity encoded in the DNA?" Plasticity is one of the most distinctive attributes of brain structure and function, and without it we would be unable to learn anything. The mechanisms for this plasticity must be encoded in our DNA. Second, "What are the cellular and molecular representations of thoughts and memories?" That is, what exactly has happened inside your brain when you think "2+3=5"? And third, "How do genetics and experience interact to make each brain structurally and functionally unique?" This question gets at the heart of what each of us considers his or her unique identity. Indeed, it is interesting to contemplate how it is that each of us remains uniquely ourselves while our brains are continuously changing with each fresh experience.

The answers to these and related questions will likely emerge bit by bit over many years – and the insights that they provide will fundamentally shape how we see ourselves, as individuals and as a species.

**On Creativity (iBioMagazine video transcript) - December 2011**

Today I would like to talk for a few minutes about creativity in science, something that all of us working scientists think about, but which is a bit of a slippery concept. We wonder where it comes from, and we wonder how to enhance it and cultivate it. It is worth discussing because it is really at the core of the scientific enterprise. So, what is creativity? What is a good idea? What makes an idea a good idea? I think there are a number of things that go into it. In my field – which is experimental science, experimental biology – most of the ideas relate to experiments. Very few of them are strictly conceptual breakthroughs. Many of us spend a lot of time mulling over our data, mulling over our experiments, thinking about how to make the next creative breakthrough. Today I would like to share with you what I do in trying to cultivate my own ideas. Maybe you will find it useful.

First, I write ideas down. I have been doing this for 30 years, since I was an undergraduate. I find that in writing things down it forces me to think more deeply about the idea itself. In many cases it has the sad result that I conclude that it was not a particularly good idea after all. Writing helps one to think of related ideas and, in the act of writing things down, not infrequently a new idea emerges. It also provides a nice longitudinal record so you can look back and see that - maybe a year ago, two years ago - there was this kernel of an idea and now that you know something more or something new has happened in the field, the idea can evolve in a new and maybe significant way.

Related to that, I try as much as possible to talk to other people about my ideas. Again, many of the ideas are not particularly original or are not practical or for one reason or another are not going to go very far, but simply talking with others about them is stimulating, it is fun, and to the extent that additional people are thinking about it from a different angle and bringing their experiences to bear on it - the idea matures. That social aspect of the turning over of ideas is very important. It has certainly been very important for me.

Another thing that goes into the mix when thinking about creative ideas is the eclectic body of knowledge that each of us has. It is very important to cultivate one's body of knowledge as a working scientist. Not to just read the same things that other people are reading, but to think perhaps about technologies that are different, to think about fields that are a little bit orthogonal to the ones that you're working on, and in that way you develop your own unique intellectual fingerprint - something that is distinct from what other people have brought to the field. In many cases it is the connection between disparate areas that one person can make – and that may not be obvious to others in the field - that is the crux of a good idea.

Another thing that I have tried to do over the years is to study what I consider to be the good ideas of other scientists to try to get some sense of how they addressed a challenging problem. Of course, for those really great ideas – the ones that have changed the history of science - there is a sense of inevitability to them, a sense of finality in some cases, that doesn't really do justice to the process that created them. The struggle, initially when it was not obvious, is the more interesting part. Let's take, for example, Einstein's theory of special relativity. This is an incredibly beautiful idea. It is very simple. It is one of those ideas that - once you understand it – you think it's almost obvious. It is the only way it could have been. But it was not at all obvious at the beginning. Einstein had to jettison a series of assumptions that were so deeply ingrained - about the nature of space and time, for example - that they weren't even appreciated to be assumptions. That is a very important lesson. One of the great lessons of Einstein's insight is that one should very rigorously examine those things that are the assumptions upon which your ideas are built, because the assumptions may not be right. They may not be completely wrong, but they may not be exactly right.

One aspect of good ideas, which at first blush is not intuitively obvious, is that they resemble jokes. A good idea is like a good joke: they both have a spark; they make a connection. They require a certain suspension of one's conventional thinking, a willingness to – it's a hackneyed phrase, but I will say it – think out of the box. To think of things in a somewhat different way. It also requires a playfulness to

have good ideas. An ability to be almost childlike in your appreciation for the newness of Nature – to see things through fresh eyes.

That playfulness has been captured by many scientists over the years. Newton had one of the nicest ways of seeing it in himself. He said late in life that when he looked back on his career, he thought that he was just a child playing on the beach and looking for the next pretty pebble. In many ways that is the essence of scientific creativity.

http://ibiomagazine.org/issues/november-2011-issue/jeremy-nathans.html

**Lasker Lessons in Leadership (Advice for Young Scientists) at NIH – November 2016**

I thought that what I could do most usefully today is to say a few words about what I have learned over the years. I brought some notes. No PowerPoint.

Let me start with a little bit of autobiography. I was an undergraduate at MIT and then an MD-PhD student at Stanford. I got interested in vision research by a happy accident. I heard a couple of lectures about vision when I was a second-year medical student. The visual system is very beautiful, and I started reading about it. After the second of those lectures, I ran to the library. This was in the days before the Internet, so you had to go to the library and get the journals off the shelves. I started reading about vision, and as a result I completely switched my research project.

I had a wonderful thesis advisor, David Hogness. Dave knew a lot about genetics and molecular biology and he could sniff out a good problem. He thought that vision was interesting and he said, "go for it", and so I did. Dave was extraordinarily generous and insightful and I am eternally grateful for that. I also had the good luck to be in the right place at the right time. I was surrounded by smart people – people who were smarter than me. Over the years, I have had great mentors - people with perspective and wisdom who helped me along at every stage of my career.

So, what have I learned in 35 years of working in a lab? I think the main thing is the incredible thrill of discovery. That doesn't mean necessarily a gigantic discovery. We haven't made any gigantic discoveries: nothing like the double helix or relativity. But we have made a number of little discoveries. I am proud of every one of them and I take pleasure in every one of them. One of the things I would urge you to do is to take pleasure in every little victory. If you run a pretty protein gel, and the bands are sharp and they look straight – YES! That's great. It's gorgeous, even if it doesn't actually show the band you wanted to see. That is all right. It is a beautiful gel.

Related to that, the main goal here is not to necessarily revolutionize the world. That is very rare, very unusual. The goal is to chip away at Nature's secrets, and, as you all know, Nature does not give up her secrets easily. Every little secret that you find, every little brick that you add to the great wall of science, is a victory.

I think being part of something bigger than your self is one of the great motivators for a scientist. That is the motivator for all great religions. If you are a poor fruit vendor in Cairo, what do you have to look at in life? What is its meaning? I think the greatest meaning very often comes from your religious affiliation. For scientists, meaning in life can come from being part of this quest by our species to understand the world around us. If you can add a little bit to that grand quest, that is great. It means you are part of the same club as Newton, Einstein, Curie, Watson, and Crick.

Related to this, here is a quote from Galileo that I will paraphrase. His comment was that he would rather discover a tiny fact than debate the great issues of the day without discovering anything at all. That really captures it.

So, pick a good problem. It doesn't have to be the double helix, just choose a piece of the world that you want to uncover. And nail it. And once you have done that, it is forever. That is one of the things that science shares with all of the great religions – there is a kind of immortality that comes from having discovered a truth that lives forever.

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Now back to reality. The other thing I have learned is that most experiments do not work. Have you learned that? This comes as a shock because when you are an undergraduate, you are reading in your

textbooks about translation, transcription, DNA replication, and so on. And all of the experiments work, and great discoveries are made.

Then you get to the lab and you realize… hmmm, actually most experiments do not work. Where were those failed experiments in the textbooks? They weren't there.

Most experiments do not work for technically trivial reasons; they do not fail for grand reasons. They just didn't work because you forgot to add the right buffer or the right percentage of ethanol, and you have to do it again the next day.

That is one reason to take pleasure in every little victory. You have to keep yourself going. It is also a motivator to look hard at your data and hard at your experiments. There are various levels of looking. The main thing is not to be fooled by seeing what you want to see and falling in love with your hoped-for result, because very often the result is just a technical artifact. Look hard at that gel and ask yourself: "Is that band really the right size, or do I just want it to be the right size?"

Get other people to look at it, too. The highest compliment anyone else can pay you, as a scientist, is to take their time and effort to look at your data or think about your ideas. If they stop doing that and just pat you on the back and say "Yes, that is great, keep going", then you are in trouble. To get other people to really critically evaluate your work is the name of the game. Everyone brings a different point of view, everyone has a different fund of knowledge or a way of looking at things. I can't tell you how many time this has happened, when I have been in a mental rut, when I have been thinking of something one way, and I mention it to someone else and they say "Why don't you try this…" Duh! Of course, I should have tried that, but it just didn't occur to me. So, don't keep your thoughts secret, share them around. If you think you have a great idea and you don't want someone to steal it - just forget about that – just blab the idea all around, and you will get feed-back and it will improve. In some cases, it might get shot down, but if that happens it will save you a lot of time.

I spent some years on the Scientific Advisory Board at the Merck Research Laboratories. Ed Scolnick was the head of it in those years - a brilliant scientist. [He was here at NIH at the beginning of his career and worked on Ras and cancer.] Ed used to ask of the members of the scientific teams who were presenting their work, "What is the killer experiment for this program?" And by "killer experiment", he meant a single experiment that – if it gives a particular outcome - will kill the program. Scolnick asked this because, if the team was wasting time on something that was not going to work, he wanted to know about it as soon as possible. That was his thinking.

There are always opportunity costs. You could always be doing something different, and if that something different is better, then you want to know about it sooner rather than later. So, I am constantly thinking about that, and my students hear this from me at regular intervals. Even though we think this project is a good project, let's not kid ourselves. Is there any reason to think that this project is a dud? If so, is there any experiment we can do - and sooner rather than later – that will kill it off, so that we can move on to something else?

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Another point is mental toughness and endurance. Science is a marathon; it is not a sprint. You have to be in for the long haul and you will take a lot of pounding. I think it is a lot like boxing – not that I have ever boxed – and you are going to get knocked down. The question is, can you get back up? If you can stand back up, you are still in the game.

For example, you will get knocked down by reviewers who are going to say that your paper is not that good. But you know, in your heart, it is good. Yes, the reviewers may have some good points, but don't

take them too seriously. You have to maintain confidence in yourself. If you did a good piece of work, that is the absolute judgment – what counts is your judgment of your work.

The same is true at every level. If things that you are working on do not seem like they are going well, you have to try and maintain an even keel. There are downs and there are ups, and if you are in a down, you have to say to yourself, "this is temporary, there is going to be an up after this down".

Related to that, science is very much a social business. There are very few people - maybe a few mathematicians – who can do it as a solitary business. But that is not how biology is done, and it shouldn't be. It is very important to be supportive of each other. If you are working at your lab bench and the person sitting at the lab bench next to you is having a hard time, be encouraging. Part of the sociology of science is this mutually reinforcing helpfulness. There is not only the practical part - looking at data, listening to ideas, and coming up with something useful – but also just being encouraging. Give him or her a pat on the back. It will be reciprocated, and at some point you will need it.

As an addendum to that, I'll say something about both science and interpersonal relations, and also about parenting for those who have or are going to have children. My general philosophy about interpersonal relations is to always be nicer than you have to be. You don't have to be nice in every situation, but it is better to be nice.

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Now back to science. One thing I would recommend is to try and master the basics: the foundational knowledge – physics, chemistry and mathematics – that is the basis of everything. Obviously, it's a huge world. There is a vast scientific literature now; it is hard to even master your own immediate area. But try to read broadly and think about the fundamentals.

Here is an example. You take a tube of ATP out of your minus 80 freezer, and you thaw it, and you are going to use some of it to do a ligation reaction. Should you vortex the tube to mix it when you thaw it out? Or is it OK to just pipette 10 microliters out of the tube without mixing the contents? [A student in the audience gives the correct answer: vortex the tube.] You got it. The solution is not uniform because it has salted out: the last regions to freeze are the little micro-domains of higher salt, so the ATP, the sodium chloride, the buffer, and whatever else is in there is not uniformly distributed in the tube. You have to vortex your tubes when you thaw them – it is basic chemistry. Knowing that basic fact makes a difference. Your ligation is either going to work or not work, and it depends on whether you vortexed your tube of ATP.

Another example. When you centrifuge a sample, don't just stick our pipette in the tube without looking at it. Is there a pellet? Is the pellet too big or too small? Maybe something came out of the solution that shouldn't have. If you look at the pellet, then the next time you do this procedure, see if it looks the same. File that information away: this is what the pellet is supposed to look like when the procedure works. Later on, if you see a pellet that looks different and the procedure does not work you may think, "Ahh, something was wrong with that pellet."

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Thus brings us to techniques. I am a big fan of techniques, in part because techniques drive science. Think about what the world would look like without PCR, DNA sequencing, confocal microscopy, monoclonal antibodies, western blots – the list goes on and on. It would be a different world. Techniques – or perhaps we should say technology - drives so much of science. Although I myself am not a techniques-centric scientist, I have enormous respect for people who develop techniques and for people who are masters of technique.

In large part, science is a craft – it is like woodworking or painting or surgery. When I was a medical student, saw a cardiac surgeon doing a bypass operation. It was like watching a violinist play the violin. Every motion was perfect, and there were no wasted motions. He knew exactly where to make the cuts, and he knew exactly how to do everything. It is the same way at the lab bench when you see someone who is an ace at protein purification or microscopy. You know you are watching an ace, and you realize just how incredibly talented that person is. I have great respect for those people.

Honing some of that in one's self is critical. Obviously, one person can't do everything well – there are too many different techniques. But you should try to become an expert in the techniques you will really need. When you become really good, you will be able to do things that other people can't do, and, as a result, you will be able to make difficult experiments work.

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Who writes down their ideas? [Some hands go up.] That's great. I do this, too, because, first, I don't want to forget the idea. But there is more to it than that. The act of writing forces you to think more clearly and more critically about the idea. As you write it down you may think, "hmmm… that is a bit half-baked", or "this is not going to work", or "this is not really very original". There are all kinds of ways in which ideas don't pass muster. But if you write down the idea then you can easily revisit it later. Also, you can talk to people about it. The idea may mature – very few ideas emerge perfectly formed. They generally do not arrive in their final mature state.

It is very difficult to have good ideas if you have only a small number of ideas. The way to have a few really good ideas is to have many ideas, most of which will not be so good. You will have to sift through them, looking for the good ones.

Also, just the exercise of thinking of ideas is like a mental workout in the gym. It gets your brain going, and you improve as you go. I have been writing down my ideas since I was an undergraduate, and I have half a file cabinet filled with pieces of paper with ideas. Of course, most of my ideas have not amounted to much: they are unoriginal, and when I dig deeper I realize that other people thought of this already and they've actually gone way beyond my initial idea. But a few of my ideas have been better.

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Let's talk about picking a good research question. That is a real art form, and it is really hard. You might say to yourself: I am looking for a thesis project or I am going to start a postdoc or I am going to start my lab – what are some really good questions to work on? That is different from doing the science, because in doing the science you are mostly down in the weeds just trying to get this or that to work. But seeing the big picture from 5 miles up and picking a good question is different. You do not have to do it very often, but you have to do it well.

Here is one way of looking at it – it's not the only way, but I think it is useful. Consider a Venn diagram with three circles, and each circle partially overlaps one of the others and there is a region in the center where all three overlap. The part in the center is pretty small and that is the sweet spot.

What are the circles? Circle #1 is what is interesting and important. That is a big circle. Obviously, different people will have different views about what is interesting or important. Presumably you want your research to be in that circle, as you conceive it. Circle #2 is what is technically feasible. Circle #2 only partially overlaps circle #1.

To see an example of what is in circle #1 but not in circle #2, we could ask: "What is the most fascinating biological discovery that could possibly be made?". I would argue it is finding life elsewhere in the universe. If we find life on another planet, that would be a total game-changer – especially a game-

changer philosophically. But I would argue that today it is not technically feasible to look for that directly. Astrophysicists are looking for exo-planets and that is the first step. But it is a much bigger step to look for life on those planets.

Now what is the 3rd circle? The third circle is what is not obvious. In other words, the things that other people haven't thought of. There are lots of scientific questions that are interesting and technically feasible, but a lot of other people have already thought of them – these areas are already well-populated. The sweet spot is something that is interesting and feasible, and no one else has thought of it, or at least very few people have thought of it.

That is a hard sweet spot to find. I am constantly thinking about that. I am partly thinking about it for my students: what is a good thesis project? How do you find that spot? One way to find it - and I think this is one of the best ways to approach this challenge - is to try to enlarge one of the circles to make the sweet spot bigger. The circle that one can enlarge most usefully is circle #2 - the technically feasible circle. Perhaps there is a question that is interesting and not obvious, but is not quite feasible with current technology. Then we can ask: Is there something we can invent - a technique or an approach - that brings it into the realm of what is possible?

This is a well-trod path in science. Look at astrophysics. Astrophysics is driven by the engineers who build better telescopes. At first there were only optical telescopes, but then people started looking at x-rays, radio waves, infrared, and ultraviolet. And now we have the Hubble Space Telescope that can collect images from beyond the Earth's atmosphere. Every time you open up a new region of the spectrum, you reveal new ways of looking at the universe. The same is true in biology. For example, if you are working on a new bacterium, if you can figure out how to get DNA into it and alter its genome, then you have opened up this bacterium to study.

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Let's talk about data. Data is sacred. Don't lose it. If you have done an experiment – for example, you have collected images on a microscope or generated DNA sequences - archive it so that it won't be lost.

Data is sacred in another way. Whatever you put out there, whatever you ultimately communicate to the world, the part that is immortal is the data. The data has to be right. You don't want to put something out there that is an artifact. Sometimes you can't necessarily know; all you can say is: "I did this experiment in this way and here is what I saw". Perhaps the result will turn out to be trivial or irrelevant. But as long as someone else does the same steps – A, B, C, and D - exactly like you did them and they get the same result, then basically it is true: that is the result.

Of course, we are all aiming for something higher than that. We are aiming for a piece of data that will explain the world in some way. The important point here is that even if our explanation is not quite right - for example, if we get a result and we don't really understand it - that is OK. We have to distinguish between the data and our interpretation of the data. For example, if there are three bands on a gel and we do not know what they mean, maybe someone else will look at the gel and come up with the correct explanation. That's what I mean by saying that the data is sacred.

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Let me make a few observations about the sociology of science.

The first observation, which you have probably noticed already, is that here in the U.S., we have a finely-honed Darwinian system. It is a competitive system. It is competitive at every level. It is competitive to get into college; it is competitive to get into graduate school or medical school; it is competitive to get a

postdoctoral fellowship; it is competitive to get grants; it is competitive to publish; it is competitive to get tenure; and on and on. The only part that is not competitive is retiring.

I think this is not going to change. From the point of view of the scientific enterprise as a whole - and certainly from the point of view of the people who are paying for it (the taxpayers) – it is working pretty well. The taxpayer gets a great deal: they get smart, motivated, hard-working people who are not making that much money. What could be better?

Of course, this profession also has a lot of pluses. Even on the worst days, being a scientist beats driving a taxicab. Being a scientist is a wonderful way to spend one's career. It is stimulating; you are with smart and interesting people. You have freedom and the possibility of creativity, which not many jobs have. The baggage that comes with it is worth it for the pleasures of science.

One challenge - because it is a competitive system – is that there are a series of things that are not optimal from our point of view. One of them is the training system, which is a bit of a Ponzi scheme, a pyramid sales scheme. By that, I mean that many trainees enter at the beginning, but the system has a far smaller number of positions for more senior researchers at the other end. This is a numerical fact; it is a fact based on the money. There is a limited NIH budget. Suppose that the typical lab needs a million dollars a year. With a 30 billion dollar annual NIH budget – let's say that half is clinical and the other half is basic research – that is 15 billion dollars divided by a million, so there is enough NIH money for a total 15,000 labs in this country, or, if we stretch the money, 30,000 labs at the most. But there are more than 15,000 postdocs and more than 15,000 graduate students in this country. And each lab has a long lifetime.

At steady state, I should be training one graduate student or one postdoc who will take my place. But that is not how the system works. I cannot run my lab with one student and one postdoc. Everyone who is running a lab has the same dynamic tension. They are trying to bring in trainees because that is what makes the gears turn. But those trainees have their own expectations, and they want – at least many of them want – to have a career like their mentor's. But that is a mathematical impossibility for the vast majority of them.

Is this system ethical? I would argue that it is not inherently unethical, but I think we should be completely honest with our trainees. When you are applying to graduate school, there should be a disclaimer on the school web site that says: "click here and read the ground rules of this business before you fill out this application". It should tell applicants what the numbers are – that there are this many students in the pipeline and this many NIH grants. I think if everyone is informed, then no one is kidding themselves about the odds going into it.

There is at least one good reason why this system should continue the way it is. Because if we had a system that limited entry into biomedical science at the first step, we would be saying to a large number of 21 year olds: "You can not even try to be a biomedical scientist". It is much fairer to say to every 21 years old, "If you want to give it a try, then give it a try". If you want to apply to graduate school or work as a technician for a couple years or be part of the program here at NIH, then there are openings and we are ready for you to try it. After all, almost no one at age 21 really knows what they are good at or what they are interested in or what their true passion is. So we should give everyone a chance.

Having an open system is even more profound than that. If you train in science, you have great training for many different careers, not just working in a lab. Most importantly, you will know how to think.

Here, I cannot resist going back to the election. [The previous day, Nov 8, 2016, Donald Trump was elected President.] We have just had a demonstration of an absolutely disastrous political outcome. The next four years are going to be a complete disaster – there is no getting around that. This happened because of the vast ignorance of our fellow citizens. It is not just the voters. It is the media, and it is

people in positions of power and influence who simply cannot think straight. I hate to say it, but many of these people are running the country.

Look, for example, at the Iraq war. Almost no one in a position of real influence asked in the run-up to that war, “How reliable is the data that Iraq has weapons of mass destruction?”. Obviously, there were people who were saying that there were weapons of mass destruction, but many of those people had an ax to grind with Saddam Hussein. Almost no one here said, “What really is the data?”. Even people like Colin Powell - who is no idiot - swallowed it hook, line, and sinker. He gave a speech before the U.N. presenting pseudo-data – it was total bullshit. That was a multi-trillion-dollar war with many thousands of American casualties and hundreds of thousands of other casualties. That is where you go when people cannot think.

The bottom line is: if science teaches you nothing else, it teaches you to think. It teaches you to look at the data with a critical eye. And that is absolutely essential in every realm of modern society: it is essential to government, it is essential to business, and it is essential to every kind of leadership.

So, I would urge you to think broadly. It is great if you spend 10 years in the lab and you do some great science but then you do something else later. I am totally supportive of any student in my lab who does something else because I know they will do it better for having the scientific training. So, I would urge you to look around and see where you can make an impact. The bottom line is: the goal of our professional is to make an impact, to make the world a better place. It doesn’t necessarily have to be in the lab, and your training will allow you to do it.

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Let’s talk a little bit about competition. Because the system is Darwinian, it is hard not be aware of the competitive aspect. If you are applying to graduate school, and you would like to get into Caltech or another place that is hard to get into, you’re competing with other people. It is hard not to compare yourself with other people. You go to an interview and the person next to you has a stack of papers that they did as a high school student, and you say to yourself, “Holy crap, how am I going to get in?”.

This never lets up, so my point about it would be: try not to play that game. It is a game that you cannot win. There is always someone who is better, and you are not going to come out feeling good. The way to look at it is that everyone has his or her own unique path. You are creating a sculpture – the sculpture is yourself and you have to create your own path, a path that is truly yours and is different from everyone else’s.

I would include in that unique path, collecting and cultivating a distinct fund of knowledge. Don’t just read all the papers that everyone else is reading. Everyone reads Nature, Science, and Cell. If you do that too, you will have the same fund of knowledge as everyone else has. Where the real advances are made is when people bring eclectic knowledge to the table. Flip through catalogues. The New England Biolabs catalogue has got all kinds of fascinating tidbits about biochemistry. The Molecular Probes handbook – now it’s online - is beautiful. It is like a textbook – there are all kinds of useful tidbits in it.

Now I am going to go off on a tangent about eclectic knowledge bases – but it’s part of not being in the competitive mix and making yourself unique. When you are doing computer searching the real drawback is that it is too focused. When you put in your key words, you just get papers about that topic. But if you flip through the journals you will bump into things that you would otherwise not bump into. One of my colleagues, Paul Talalay, said the most important article is the one that is next to the one you are looking for – it is on a totally different topic, but that is the one you need to bump into.

So, I would urge you to browse widely. I do not read that many articles carefully. That is, I do not read every word. I like to read abstracts, but even more than that I like to look at the data. I love looking at

figures, so I won't bother with the introduction, discussion, results – any of that stuff. I just go straight to the figures just filing it away, just letting it soak in. I find that extremely useful. I have a very good memory for that stuff. I am very bad with names of people and places and roads, but I am really good at remembering data. And these little tidbits come back at interesting and useful moments.

Now back to competition. You cannot win the competition game, but you can learn about great scientist and see what their paths have been. The Nobel Prize web site has a lot of this information. There are wonderful autobiographical essays for the Nobel laureates, and they all have fascinating journeys. There are many people who you would never guess would be successful in science.

Eric Betzig is a great example. He won the Nobel Prize this past year in chemistry for super-resolution microscopy. He was a physicist at Bell Labs and then got interested in the auto parts business. His family was in that business. He went to Michigan and for about 8 years he tried to break into the auto parts business. Betzig had some ideas about manufacturing auto parts in a better way. But commercially, it was a flop; he couldn't break into the business. So here was a guy who was unemployed, and he had an idea for super resolution microscopy – he was incubating this for a long time. With his friend, Harold Hess, he built a prototype microscope in Harold's living room. You can see the pictures; the sofa is here and the microscope is right next to the sofa. Then Betzig heard about the Janelia Farm campus that Howard Hughes Medical Institute was building – it was basically a mud pit, it was just being built. Betzig said "I would love to work here" and they said "you're hired" - and the rest is history. So here is a person who had a very unconventional path, and he still has many wonderful and unconventional ideas about what science is like.

Let me close the discussion about comparing oneself to others with a quote. This is from Isaac Newton. He is looking back later in life and describing his time as an undergraduate at Cambridge University. He refers here to the year 1665 when he was 22 years old. He says: "In November, I had the direct method of fluxions [that is what we today call differential calculus, which he invented as an undergraduate], and the next year in January I had the theory of colors, and in May I had entrance to the inverse method of fluxions [that is what today we call integral calculus, which he also invented as an undergraduate], and in the same year I began thinking about gravity extending to the moon and from Kepler's rules, I deduced that the forces which keep the planets in their orbits must be reciprocally as the squares of their distances from the centers from about which they revolve." That was a pretty good year. And none of us is going to beat it. So we should just take pleasure in Newton's discoveries, and think, "That is beautiful, it is truly inspiring".

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Reading great scientific papers is the ultimate education. And not just papers, but also books. Read the really great science, the really original science, which is rare and should be treasured. I'll just list a few books that I highly recommend.

One is Isaac Newton's Opticks. Opticks was published in 1704 as a popularization of Newton's work. It was a best-seller. It is very readable, and is one of the greatest physics books ever written. You see this creative mind at work. Newton describes his own experiments. They were done with very simple materials. He has amazing insights into the physical world. It is completely understandable, with just 6th grade math.

Another one is Jean Perrin's book Atoms. Perrin was a physicist in the early part of the 20th century, and with a series of relatively simple experiments he proved the molecular nature of matter.

There are also various advice books that are worth looking at. One is Peter Medawar's Advice to a Young Scientist. Medawar was an immunologist. He was the one of the discoverers of immune tolerance

and rejection. Ramon y Cajal wrote a similar book, and it has pretty much the same title: Advice for a Young Investigator.

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A few other items of general advice.

Keep your mental balance and perspective. Don't become a lab troll. Don't work 90 hours a week in the lab. That is not going to be good for your mental health. You have to do other things. Read books, go to the movies, take up a sport. Most importantly, make friends, connect with people, fall in love. Doing things beyond science will enrich your science and it will enrich your life.

You have to work hard in this business. It is not a 40-hour a week business unless you are a genius. Maybe there are some people that can do this with 40 hours a week, but I can't. It is more like a 60- or 70-hour a week business. But you have to carve out time for other things, and you have to keep your balance.

Related to that, time management skills are really important. Maybe they are less important when you are young, but when you have children you need to spend time with your children, so you have to be careful with your time. Time is one resource that is finite. When I was a student, I used to schmooze with people for 15 minutes when I got into the lab. I don't do that so much anymore. I may do that for a few minutes, but I have work to do. Especially when my children were little – they are now grown, so it is a little bit more relaxed - but when my kids were little, I had to pick them up from daycare at a certain time and I had to be out of the lab at a certain time. Without being too cut-throat about it, you just have to be keep your eye on the clock and be efficient in how you are using your time.

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Let's talk about the factors that are needed for success in science. I think there are three of them: one is under your control, one is partly under your control, and one is almost completely out of your control.

The factor that is under your control is hard work and motivation. That is totally under your control. I have always thought about myself, that I may not be the smartest person in the room, but I am very often the hardest working person in the room. I know how to get things done by working hard, and that has been useful.

The second factor is brain power, intellectual power. I think it is fair to say that there is an element of this that is God-given. You know it when you see it. When I was an undergraduate, I started out doing physics, and I thought I was pretty good at it. I was taking hard courses and getting A's, and then in my sophomore year I realized that the students who were really good at physics were not in my classes. They had placed out of the classes that I was taking. That was an intimidating realization. There are some kids who are just incredibly sharp and there is something innate about that. But I also think you can hone this mental ability, especially as related to biology, and that is one of the things that attracted me to biology. So, as an undergraduate, I drifted downhill from physics to chemistry and biology.

I like biology because to be a good biologist, you do not have to be an Einstein. You can be just an average person and be a very good biologist. In retrospect, when I look back and when I talk to physicists, I realize that most physicists are not Einsteins; they are doing some kind of experimental physics that I probably could have done. But the larger point is that you need to find a niche where your kind of intelligence and your kind of talent is the right fit, and it can take a bit of sniffing around to find that.

The third factor, the thing that is least under your control, is luck. I think we've all seen this: the graduate student who is working at the next bench – the one who can't even run a straight gel - ends up getting the most amazing result. How did that guy get that result when I've been plugging away for a year and I can't get anything to work? You know it isn't fair, but there is no fair or unfair here. It is just luck.

I think you can try to make luck work in your favor. Pasteur had a phrase in this respect. I'll tell you the experiment that led to it. Pasteur was looking at chicken cholera. Chickens, like us, can get cholera and this can be a devastating economic problem for people who are raising chickens. Around 1860, the French government asked Pasteur to look into this – he was the leading microbiologist in the world at that time. So, Pasteur was culturing the chicken cholera bacterium and inoculating chickens with it and reproducing the disease in the lab. One day he did an experiment and he used a culture that he knew was a little too old. He thought that maybe he should throw it out but he decided to see if it would work. He inoculated the flock and the chickens survived - they didn't get cholera. Okay, so, Pasteur blew it: the bacterial culture was probably too old and the bacteria had probably died. He thought, "I'll do the experiment again with a fresh culture, but let's not waste all these birds since they cost a lot of money; let's just inoculate the same birds and see if they become infected". He started with a fresh culture, he knew the bacteria were fine this time, and he did the inoculation - and the birds did not get cholera!

Now here is the critical part. Pasteur realized that this was a really important result – that the initial inoculation must have done something to make the birds resistant. He had inadvertently vaccinated the birds and they were now resistant to infection by the cholera bacillus. Pasteur's comment about this chance discovery was: "Luck favors the prepared mind." His mind was prepared. He was thinking. His mental gears were spinning. After the failure of the second inoculation, he could have thrown out the whole flock and said, "Let's just do the whole thing over again exactly by the protocol: start with fresh birds and a fresh culture, and follow the protocol." But he didn't. So, that I think is an example of the kind of luck you can make for yourself, and Pasteur was a master at that.

Those are the three factors, and the trick is to get the stars to align as best as you can.

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Let me close by asking why we do scientific research. It has a lot of challenges and a lot of frustrations, and it takes a lot of effort. But I think it is a wonderful life. You get to see incredible beauty. Not the kind of beauty you see when you go to a museum, but you get to see Nature's beauty – this incredible beauty all around us, and if you don't peel away the layers, you don't see the full beauty.

A classic example is Newton's investigation of the rainbow. People had been looking at rainbows for thousands of years but did not know what produced them. Newton realized that there is refraction of light by the water droplets and he figured out precisely and mathematically from the angles of refraction of the different rays of light exactly what the arc of the rainbow should be, where the different colors should be in the rainbow, and so on – a complete physical description of the rainbow. Some people have said, "That takes the beauty out of it". In my view, Newton's explanation puts the full beauty into it, because now we see a rainbow not just as a beautiful artistic phenomenon but also as a beautiful physical phenomenon, and we fully understand it.