Sun’s Rotation

by Bryan Sun

“It’s sort of like all your classmates are on the school bus.” An older and wiser M.D./Ph.D. student was telling me about third year in the program. “You’re standing at the bus stop and everyone at the back of the bus is waving at you as they pull away.”

So that’s what it’s like, I thought. It didn’t sound good. It was my second year, and I was feeling pretty positive about things, feeling swept up into the medical school momentum. Objects in motion tend to stay in motion. And so I went in to talk to Nancy Andrews about this. “I can’t get off the bus,” I said to her. “Not just yet.”

Though, maybe not exactly in those words.

“Well, we’re thinking of having the M.D./Ph.D. students do one clinical rotation in the summer before their third year,” she said. “Would you be interested, if we offered it to people in your class?”

I signed on the dotted line.

Seven minutes into my summer medicine rotation at the Mass General, I thought about lab. In a sweetly reminiscent way, like you might remember the pain of running a marathon. Not that I’ve ever run a marathon, but I’m sure that’s what it’s like.

“You can expect to have one full weekend off per month…” the course director was saying. A few of my classmates nodded in relief.

“…next you will learn how to do provider order entry forms, and then you can go meet your team and get started.”

continued on page 3

Lowenstein Reflects Midway through a Career in Academic Medicine

by Daniel H. Lowenstein, M.D.
Carl W. Walter Professor of Neurology and Dean for Medical Education

It was a true honor and a privilege to deliver the first Eva Neer Memorial Lecture at the annual MD/PhD retreat in Waterville Valley last October. A number of people have asked me to share some of the remarks that I made at the beginning of the lecture concerning my impressions of the experience of being a physician-scientist. I began by noting that, at this point, I may well be at the midpoint of a career in medicine, and I feel very fortunate to have explored many aspects of the broad landscape of the health sciences. I entered medical school thinking that I would set up a small family practice clinic in Sandwich, New Hampshire - in large part to live near my best friend. Little did I know that academics, and especially neuroscience, would capture my attention from the very first semester of medical school, and that my career would take me rather far from the imagined peace and serenity of the New England countryside.

Now, after experiencing medical education at Harvard, residency training in neurology at UCSF, bench research, clinical research, patient care, university service, teaching of medical students and graduate
From graduate school through residency and post-doctoral work, David Altshuler and Joel Hirschhorn, both graduates of the Harvard MD/PhD program, have taken similar paths. Working on the same floor in the HMS Department of Genetics as graduate students, both developed an interest in human disease genetics. After receiving their degrees in 1994 and 1995, respectively, they both pursued residencies in the Boston area, with Dr. Altshuler working in internal medicine at MGH and Dr. Hirschhorn in pediatrics at Children’s. Subsequently, they both performed fellowships in endocrinology, followed by post-doctoral work in Eric Lander’s lab at the Whitehead Institute. Today, they share an office in the Genome Center at MIT. Drs. Hirschhorn and Altshuler have published together on two occasions. Their most recent mutual accomplishment is an article in Nature Genetics.

Published in September of 2000, Drs. Hirschhorn and Altshuler’s article makes an important contribution to the field of human genetics by playing a guiding role for genetic association studies, which have been commonly viewed as unreliable due to their frequent irreproducibility. Drs. Hirschhorn and Altshuler investigated 16 published genetic associations to type II diabetes, representing virtually all such associations known for the disease, and were able to verify only one, that of the Pro12Ala SNP in the PPARγ gene. SNPs are single nucleotide polymorphisms, which are single base-pair positions in genomic DNA where two alternative alleles occur at a frequency greater than 1% in the human population. They have generated considerable interest because they are valuable as genetic markers for association studies to determine genes involved in common multigenic diseases, for which linkage analysis has not been very successful.

Genetic association studies have been performed for decades but have been plagued by irreproducibility. Hirschhorn and Altshuler explain that one of the most significant problems is population stratification, which occurs when patient and control groups are inappropriately matched, with one group coincidentally displaying a higher frequency of disease variants. To avoid population stratification with PPARγ, Hirschhorn and Altshuler used a family based control called the transmission disequilibrium test. “In this test, if an allele contributes to disease, the probability that an affected individual inherited the allele from a heterozygous parent should vary from the expected mendelian 50:50 ratio,” explains Altshuler. “The association of a neutral polymorphism due to stratification displays no such deviation.”

The human population has limited genetic diversity, reflecting the fact that it expanded rapidly 7000 generations ago from a small founding population in Africa. Most of the genetic variation is due to common alleles with modest effects. While infrequent variants are responsible for the rare mendelian diseases, common multigenic disorders, such as diabetes, cardiovascular disease, cancer, and mental illness, have been attributed to high frequency, low risk alleles. A classical example includes the ApoE ε4 allele, which is present in 25% of the population, and remains an important risk factor for Alzheimer’s Disease. In their paper, Drs. Hirschhorn and Altshuler found a 1.25-fold increase in type II diabetes risk associated with the more common Pro12 allele of PPARγ, whose frequency in the population is 85%. While this translates to a small effect on the individual, it has a significant impact on the human population as a whole, since the allele is carried by billions of people resulting in a population attributable risk of 25%.

Association studies, which correlate the prevalence of polymorphisms with clinical phenotypes in a population, are different from positional cloning (linkage) efforts, which analyze transmission of genetic variants within a family. Linkage analyses have been useful for taking a genome wide approach toward the discovery of rare mendelian traits. However, they usually fall short when analyzing common, multigenic diseases with high frequency, low risk alleles. Lack of sufficiently large informative families and too much multilocus etiology in these cases often prevents any single locus from standing out.

All association studies to-date have relied upon a candidate gene approach, in which previously suspected loci were tested for correlation with disease. Performing genome-wide association studies without prior knowledge of candidate genes, however, is the Holy Grail. Drs. Altshuler and Hirschhorn are both pursuing further tools to facilitate reaching this goal. Altshuler has developed a new technique, called reduced representation shotgun sequencing (RRS), for discovering human SNPs. RRS was published in Nature this past September and has been adopted by a joint academic/industrial venture known as The SNP Consortium (TSC), who have already reached their goal of discovering 300,000 SNPs using the technique. With the generation of SNPs well underway, methods for their genotyping have now become the rate-limiting step for genome-wide association studies. To address this problem, Dr. Hirschhorn has developed a new array-based method for inexpensive high-throughput SNP genotyping, called SBE-TAGS, which was published this past October in PNAS. Both techniques are important developments in the use of SNP libraries, which will hopefully shorten the disease-gene discovery process for multigenic disorders.

Human genetics has been an ideal career choice for Drs. Altshuler and Hirschhorn because it has allowed them to directly relate their research interests to their clinical work, studying the molecular bases of endocrinologic disorders. Furthermore, human genetics research itself directly calls upon their clinical expertise to ensure correct diagnoses. Dr. Hirschhorn remarks, “Not a day goes by without drawing upon skills from both my clinical and scientific training.”

-Andy Elia (HST-BBS) is a 5th year M.D.-Ph.D. student.
I got up with the rest of my class. “Hey, what are you doing here?” one of them asked. “Aren’t you supposed to be in lab?”

“Maybe,” I joked. “Hi, I’m the medical student that’s supposed to work with you,” I said.

The intern looked up and studied me carefully.

“I didn’t know that Team 3 had medical students,” one of the nurses said helpfully. The intern was still looking surprised. My stethoscope felt very heavy, hanging around my neck.

“Hey, no problem, no problem,” he finally said. He smiled. “When do you start? Tomorrow? Great, no problem. Um, just come in, we round at 8:00 am, you can pre-round on a patient. Hey, if you want, you can order the labs and meds.”

I thought back to my Patient-Doctor 2 knowledge, none of which had prepared me to do any of what he had just suggested. In fact, I had no idea what he had just said. I was about to tell him this when his pager went off and he disappeared down the hallway, white coat flapping behind him. I stood there with my backpack, trying to absorb the huge trail of paperwork, the fly-bys of nurse assistants, the beeping telemetry units, the phones ringing, the bright lights. It was like Broadway, and I felt like a green-bean actor looking for a small role somewhere. Anywhere.

A visitor stopped by the nurses’ station. “I’m sorry,” he said. “I’m trying to get home. Do you know where the nearest bus stop is?”

“I know where it is,” I said. “I’ll show you.”

Somewhere along the way, things got into some kind of rhythm, although I can’t pinpoint exactly when. I got my first patient. Drew my first arterial blood gas. Got up before the sunrise. Wrote my first note. Had my pager go off in the subway.

“How come you decided to do the medicine rotation before starting graduate school?” someone would ask.

I explained the theory of Med School Momentum, the theory of Wanting to Stay with my Med School Class. “Oh,” they said.

Somewhere along the way, the slash between M.D. and Ph.D. began to blur. More often than I expected, medicine and molecular science would intersect. Our medical team would discuss pathophysiology on the cellular or subcellular level. The newest therapeutic treatments seemed to aim at smaller and more specific targets, and being able to understand the body on that scale was increasingly important. I found that having some laboratory experience in molecular biology and genetics made it easier to explain to patients and their families some of the medical tests that we use, as well as the way that drugs work.

Flipping through the BBS rotation manual one summer evening, I also realized that everything seemed to make more sense. It was like in The Usual Suspects when you find out that Kevin Spacey was Keyser Soze all along, which makes you want to go watch the movie all over again. In a similar way, with even the smallest of hospital experience behind me, I was more able to understand why anyone might be interested in studying such a specific part of a specific protein, or in examining a particular subtlety of an immunologic mechanism. A lot of things I didn’t understand suddenly seemed logical.

“But aren’t you going to forget everything by the time you get back?” someone would ask.

This may be true to some extent. But if practicing medicine is anything like riding a bicycle, it’ll all come back faster, I reasoned. After a few weeks on the wards, it seemed more apparent that practicing medicine involved many intangible skills and practices in addition to knowing a lot of facts. It was difficult to quantify what you would forget. Or, what you would remember.

The summer passed quickly. Two inpatient months came and went, and suddenly it was almost September.

The bus driver pulled up to the curb, and the door opened. No one moved. Then, I realized it was for me.

“Well, someone requested a stop,” the driver said.

I got up, gathered my stethoscope, tongue depressors, medical vocabulary, and sleep deprivation, and headed to the door.

“Thanks for the ride,” I said. “When does the next bus come by?”

He looked at me, then at his watch. “About four years,” he said. “See you there,” I said.

The doors closed, and I waved as the bus disappeared down the street.

- Bryan Sun (Holmes-BBS) is a 3rd year M.D.-Ph.D. student.
students in a variety of venues, and my most current time as one of the deans at what many consider a reasonably good institution of higher learning, I must say that, of all the experiences so far, few have been as challenging, absorbing and fulfilling as the attempts to understand our world through scientific inquiry. I have the deepest respect for those individuals, both pure scientists and physician-scientists, who choose to devote their careers to research. This viewpoint is not meant to eclipse in any way the great contributions provided by others in medicine. The many roles we can have – as clinicians, teachers, policy-makers, and so forth – are all equally valuable and important. However, the path of science – good science - demands a distinctive amalgam of intellectual rigor, personal sacrifice, and courage. Those of you who choose this path do so knowing that your work will - possibly, hopefully, someday - translate into something that will make the world a much better place. I admire you greatly.

Having revealed my inclinations at the outset of my talk, I then offered the following pieces of advice regarding the pursuit of a career in biomedical science...

1. Respect your mentors...

Learning the approaches and methods of science takes a long time and is, ultimately, a rather lonely process. However, it is vital to seek out the great teachers who will help mentor and guide you through the various segments of your career. Maintain a sense of respect for their wisdom and experience. Over time, there is too often a tendency to focus more on the flaws and shortcomings of one’s mentor rather than their unique and valuable insights. Keep in mind that successful scientists are typically drawn into an ever-expanding sphere of influence that will take them away from a singular focus on your needs. Manuscript reviews, study sections, fund-raising, advocacy for science – are all part of a scientific career. Learn as much as you possibly can from your teachers, but don’t be too disappointed by their involvement with issues that go beyond your next experiment.

...but do not worship them.

Of course, your great teachers (like all of us) are not immune from flaws and shortcomings. They will likely offer you the occasional bad advice. They may not give you all the attention you deserve. And, astonishingly, they may occasionally place their own needs in front of yours! You should glean from them what you can, but be respectfully relentless in your questions and challenges, and, above all, do not aspire to be in their image. In fact, the very best mentors, like good parents, will do whatever they can to make sure that their students become even more successful than themselves.

2. Creativity is the currency of academia...

The steps that lead to success in academia often seem shrouded in mystery, and it is very difficult to gain a sense of certainty in an environment in which there are no clear, singular benchmarks for achievement. I remember well the rather plain feeling of insecurity as I entered into my first year as an assistant professor. How does “the system” decide whether you should be promoted? What is sufficient in terms of publishing and obtaining grants? Is it necessary or sufficient to be a team player and an overall nice person? Based on my experience with decisions about recruitments, promotions, and the awarding of research grants, I now realize the process is not mysterious at all. Academia prizes and rewards creativity. All of us are expected to contribute to the many collective efforts of the academic enterprise, and we should aspire to be kind and selfless members of the community. However, your contributions, whether in research, teaching, or service, will be evaluated primarily on the basis of their creativity.

...as long as it sees the light of day.

Despite the primacy of creativity in academia, however, it is essential to note that pure creativity, per se, is not sufficient for advancement. Discovering a brilliant solution to a vexing problem may be gratifying, but academia requires that your contribution be judged by the scientific community at large. This means that you must communicate your creative accomplishments to others – i.e. through publications, lectures and other means of conveying discovery. Furthermore, academia pays attention to the quality of those who judge your work – hence the emphasis on publications that gain the prestige associated with the most respected journals. The adage “publish or perish” is not as malevolent as you might think – it is a straight-forward way of saying that your creative work must be available for others to judge.

3. Feel nervous when not exploring at the boundaries...

Finally, a comment about how to choose from among the seemingly endless set of questions for study. Your intuition and natural proclivities will point you in certain directions, and advice from your mentors should be used judiciously. However, above all, try as hard as you can to pursue questions that are bold and at the boundaries of what we do and do not know. The cautious study of problems that have essentially been solved, or that are pedestrian or unexciting, may yield a sense of calm and safety that will have a short half-life in academia. If you are having trouble sensing a close proximity of your work with the boundaries of your field, remain uneasy until you are once again standing at the edge.

...enjoy the fall when you do.

Of course, exploring boundaries carries the risk of falling – and, depending on your perspective, this can be frightening, exhilarating, or both. In fact, slipping and falling and grasping for handholds are a regular part of the experience of science. These struggles come in the form of ruined experiments (if not entire projects), rejected manuscripts, failed grant applications, scientific feuds and the seeming ignominy of being scooped. Accept leaping as an integral part of the adventure. Even more, embrace the fall, and see it as a worthwhile price for the joy of dancing about at the cutting edge.
For the Record

Recent Publications


For the Record

Recent Publications


Tavazoie SF, Reid RC. Fine-scale analysis of receptive-field maturation in the developing ferret lateral geniculate nucleus. *Soc. For Neuroscience abst.* 1999 506.3.

Ware ML, Tavazoie SF, Reid CB, Walsh CA. Coexistence of widespread clones and large radial clones in early embryonic ferret cortex. *Cerebral Cortex.* 1999 Sep;9(6):636-45.


* the authors contributed equally to the work
**Ph.D.s Completed**

**Vincent Aguirre**, Biological Chemistry and Molecular Pharmacology—(DMS) [Morris White, Ph.D.] Identification of Serine Phosphorylation Sites in IRS1 that Inhibit Insulin Action (8/00)

**Tammy T. Chang**, Immunology—(DMS) [Arlene Sharpe, M.D., Ph.D., Vijay Kuchroo, Ph.D.] The Role of B7 Costimulation in the Development of Experimental Autoimmune Encephalomyelitis (7/00)

**Eugene Y. Koh**, Biology—(MIT) [Robert A. Weinberg, Ph.D.] Going Retro in the Hunt for Gene X (11/00)

**Chieuwei Eric Liao**, Genetics—(DMS) [Leonard Zon, M.D.] Genetic Analysis of Hematopoiesis in Zebrafish: Hemangiblast, Stem Cell, and Erythroid Differentiation in the cloche, bloodless and riesling Mutants (8/00)

**Scott Raymon Naisbitt**, Neuroscience—(DMS) [Morgan Sheng, Ph.D.] The Molecular Organization of the Postsynaptic Density by GRAP and Shank (9/00)

**Jaquin C. Niles**, Toxicology—(MIT) [Steven Tannebaum, Ph.D.] Chemical Characterization of Peroxynitrite-Induced Guanine and 8-Oxoguanine Reaction Products (9/00)

**John Basil Reppas**, Neuroscience—(DMS) [R. Clay Reid, M.D., Ph.D.] Saccadic Eye Movements and Early Vision (9/00)

**Rajat Rohatgi**, Cell Biology—(DMS) [Marc Kirschner, Ph.D.] Biochemical Dissection of a Signaling Pathway that Controls Actin Assembly (8/00)

**Adam Jeremy Shaywitz**, Biological Chemistry and Molecular Pharmacology—(DMS) [Michael Greenberg, Ph.D.] Role of the Phosphorylation-Dependent CREB/CBP Interaction in Transcriptional Activation by CREB (9/00)

**Elizabeth K. Speliotes**, Biology—(MIT) [Robert Horvitz, Ph.D.] The survivin-like C. elegans protein BIR-1 acts with the Aurora-like kinase AIR-2 to affect chromosomes and the spindle midzone (10/00)

**Clifford Yoon**, Biological Chemistry and Molecular Pharmacology—(DMS) [Bruce Spiegelman, Ph.D.] Transcriptional Regulation of Metabolism by PPARγ and PPARγ coactivator-1 (01/01)

*DMS = Division of Medical Sciences, Harvard Graduate School of Arts and Sciences*

For the Record

**Annual M.D.-Ph.D. Women’s Dinner** held at the home of Dr. Nancy Andrews: L-R: Anna Farago, Gisela Sandoval, Rebecca Spencer, Shannon MacDonald, Zarine Balsara and Christina Mills.

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**Clifford Yoon**, Biological Chemistry and Molecular Pharmacology—(DMS) [Bruce Spiegelman, Ph.D.] Transcriptional Regulation of Metabolism by PPARγ and PPARγ coactivator-1 (01/01)

*DMS = Division of Medical Sciences, Harvard Graduate School of Arts and Sciences*
Michael Peter Shepley (1954-2000)
Harvard M.D.-Ph.D. Class of 1992

Michael Peter Shepley, M.D., Ph.D. Assistant Professor in Research Medicine at SUNY Stony Brook, New York died on October 15, 2000 at the age of 45. Michael began his M.D.-Ph.D. program at Harvard Medical School in 1980 to pursue a career in academic medicine and clinical research in neuroscience. Initially, he was interested in studying the biophysics of conduction block and “remission” in demyelinating plaques associated with such diseases as multiple sclerosis. We asked Dr. Edward A. Kravitz, George Packer Berry Professor of Neurobiology and Dr. Morris J. Karnovsky, Shattuck Professor of Pathological Anatomy to share their thoughts about Michael.

Dr. Kravitz: I was the Director of the Program in Neuroscience in 1982, at the time that Michael first applied to our Ph.D. program, and I got to know him quite well. The neuroscience graduate program was in its infancy when Michael joined us in 1984, and from the start, he was not shy in offering his ideas as the program was evolving. He often came by my office to chat, to have a cup of tea, and to offer some thoughtful advice on how to improve the program. While he was outspoken about our activities, he had a sincere interest in making a positive contribution. With a big smile on his face, Michael once gave me a photograph of a baby tiger being spoon fed some medicine that he obviously did not like the taste of. I never was quite sure whether Michael or I was supposed to be the one holding the spoon, but the point was well taken.

Dr. Karnovsky: Michael’s research was first class. He did his thesis research in Howard Weiner’s laboratory on the mechanisms underlying the neurotropic activity of polio virus. Michael found that a 100-kDa glycoprotein was involved in the attachment of the virus to cells of the nervous system. His thesis title was “Monoclonal antibody identification of a 100-kDa membrane protein in HeLa cells and human spinal cord involved in polio virus attachment.” Thereafter, he showed that this molecule was, interestingly, CD44, the lymphocyte homing receptor and a receptor for hyaluronate. Michael continued these studies as a postdoctoral fellow in the Racaniello laboratory at Columbia University. He found that CD44 interacted with the polio virus receptor. In his recent research as an Assistant Professor at Stony Brook, Michael was in the midst of studying this association and what it means. This is an important line of investigation in which Michael made fundamental discoveries and it is a loss to the field that he will not be continuing his research.

I knew Michael from his student days and throughout his subsequent career. Besides his scientific interests, Michael’s other passion was fly fishing and fly tying. He was a master of the latter despite his physical disability, and he was proud that some of the patterns he invented were successfully sold commercially. It was great fun to fish with him: his enthusiasm and energy were infectious if not exhausting.

Michael’s achievements were obtained courageously in the face of daunting physical problems. His devotion to, and persistence in, scientific research, were obvious from his first days as a graduate student and were undiminished until the time of his death.

Donations in memory of Dr. Michael P. Shepley may be made to the March of Dimes Birth Defects Foundation, 1275 Mamaroneck Avenue, White Plains, New York 10605.
M.D.-Ph.D. Students Gather in Aspen

by Michelle Lee

Last summer I attended the 15th Annual National M.D.-Ph.D. Student Conference in Aspen, Colorado. The conference brought together about 100 M.D.-Ph.D. students from around the country. Featured speakers included: Phillip Sharp, Ph.D.; Richard Tsien, Ph.D.; Susan Taylor, Ph.D.; Diane Mathis, Ph.D.; and Jennifer Lippincott-Schwartz, Ph.D. Brian Druker, M.D., the closing speaker for the conference, spoke about his impressive bench to bedside work on the tyrosine kinase inhibitor ST1571, which is currently in clinical trials as a specific therapy for chronic myelogenous leukemia.

Student speakers, including myself, presented work in such fields as immunology, physiology, and developmental biology; student posters were similarly from diverse fields. A career panel discussion demonstrated that many M.D.-Ph.D. students have similar concerns about balancing medicine, research, and personal lives.

Opportunities for physician-scientists at the NIH were discussed (see www.training.nih.gov and www.abim.org), as were new roles for M.D.-Ph.D.s in the biotechnology industry - helping companies set achievable priorities. Dr. Leon Rosenberg encouraged students to read a recent article about the challenge of training physician-scientists (Annals of Internal Medicine. 2000. 133(10):831-832; in the same issue, see also 800-807).

By attending the M.D.-Ph.D. Student Conference, I had the opportunity to speak with many other students who have similar and different insights on making career decisions similar to those each of us will make; furthermore, Aspen is a beautiful place to visit. Therefore, I encourage other students to consider attending the M.D.-Ph.D. Student conference in Aspen this summer (check out the website, www.uchsc.edu/sm/mstp/aspen01/index.html).

-Michelle Lee (Holmes-BBS) is a 8th year M.D.-Ph.D. student.
For the Record

Incoming M.D.-Ph.D. Students, 2000-2001

Andrew J. Aguirre of Standish, MI, graduated from the University of Michigan with a B.S. in Biology in 2000.

Allen W. Bryan, Jr. of Columbus, MS, graduated from Mississippi State University with a B.S. in Physics in 2000.

Savita V. Dandapani of Colorado Springs, CO, received a B.S. in Biology/Literature in 2000 from the Massachusetts Institute of Technology.

Anna F. Farago of Newton, MA, graduated from Haverford College in 2000 with a B.S. in Biology.

A. Paiman Ghafoori of Northglenn, CO, received a B.A. in Biology from the University of Colorado at Boulder in 2000.

Raj Gopalakrishnan of Honolulu, HI, graduated from the University of California at Irvine in 2000 with a B.S. in Biology.

Todd M. Herrington of Irvine, CA, received a B.S. in Biology from Stanford University in 1999.

Robert S. Ohgami of Redwood City, CA, graduated from Princeton University and received a B.A. in Molecular Biology in 2000.

Cullen M. Taniguchi of Mililani, HI, completed a B.A. in Chemistry from Occidental College in 1998 and a M. Phil. in the History of Medicine from the University of Oxford, England as a Rhodes Scholar in 2000.

Leo L. Tsai of Forest Hills, NY, received his B.A. from Williams College in Physics/Economics/Chemistry in 1998 and a M.Sc. in Medical Physics in 2000 from Cambridge University, England.


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