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ASCI Presidential Address *Mentoring and teaching clinical investigation*

Kenneth Kaushansky

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ASCI Presidential Address | Supplement

A man walking along a road comes across three bricklayers. When asked what he is doing, the first bricklayer replies, “I am laying bricks.” When asked the same question, the second bricklayer answers, “I am making my living.” When asked what he is doing, the third bricklayer steps back, looks around, and responds, “I am building a cathedral.” It is my great privilege and pleasure to address the ninety-sixth annual meeting of the American Society for Clinical Investigation. I will begin with many thanks: to the council members who provide sage advice and a critical eye; to our staff, who provide dedicated direction and a keen sense of corporate memory; to the members of the ASCI in 2001, who felt it appropriate that I serve on the ASCI Council; and to the Presidents who have come before for providing the insights and precepts that have helped shape our Society into an organization of extremely dedicated men and women that continues as the leading advocate for scholarship in medicine. I will also try to follow the advice of the seventeenth-century Catalan philosopher Baltasar Gracian, who stated, “What is good, is doubly so if it be short; and in like manner, what is bad, is less so if there be little of it.” Most recent Presidential Addresses have begun with a palpable […]

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Mentoring and teaching clinical investigation

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Most recent Presidential Addresses have begun with a palpable angst, prompted by one of the major challenges of ASCI leadership — preparation of the Address itself. Although I cannot speak for others, my apprehension was due to the sense of awe that developed while carrying out the unwritten oath of office requiring each President to read the prior Addresses in the months prior to the annual meeting. The angst of writing the Address comes from considering the accomplishments and panache of the individuals who have previously held the ASCI gavel and used this pulpit to espouse acute wisdom and uncommon insight and to create new professional diagnoses and level outstanding wit — the Clem Finches, Joe Goldsteins, Holly Smiths, Gene Braunwalds, and Don Seldins. We have a distinguished history and an outstanding cause, and I applaud the members of the ASCI.

In reading over prior Addresses, I was struck by the many recurring themes that our past presidents chose to highlight: the spirit of science, the imbalance between MD and PhD biomedical researchers, financial support for clinical investigation and the favorable economics of investing in biomedical research, and diversity in the ranks of American academic medicine. But of all the challenges facing us as a Society within our broader society, I am most concerned about our ability to mentor and teach our learners, and am frequently reminded of the pure joy that endeavor can bring to the physician-scientist.

Rather than being intimidated by the prospect of having my remarks compared to those of Presidents past — such as Joe Goldstein's insightful 1986 talk formulating the malady of insufficient technical training and consequent lack of courage in junior faculty which I paraphrased to a group of junior faculty members just last week, or Tom Stossel's witty and wise apocalyptic fable in 1987's Brave New Medicine, or Ed Benz's 1992 celebratory Presidential remarks — I relish the chance to convince you that perhaps our greatest challenge as advocates for the physician-scientist is the issue of teaching.

We must teach, teach often, and teach widely. We must teach medical students the rewards of marrying scientific inquiry and clinical medicine; we must teach residents that the singular discovery of new knowledge can sometimes impact tens of thousands of patients; we must nurture our fellows and junior faculty members, providing them the tools of the trade and instilling in them the tremendous excitement that comes from solving the mystery of an idiopathic disorder or bringing effective therapy to patients. And because teaching can impact these constituencies, we must teach the public about the values and processes and power of biomedical science, replacing the fear of things unknown with a renewed enthusiasm for the reward and potential made possible by strong support for clinical investigation. To reiterate: it is clear that we must teach, teach often, and teach widely. And we must teach the grand landscape — the larger context of clinical investigation — to demonstrate to each of these groups how the act of asking scientific questions with a clinician's intuition can build "cathedrals."

Teaching medical students and residents the power of clinical investigation

The US Public Health Service initiative *Healthy People 2010* lists the major national health concerns: tobacco use, substance abuse, cancer, osteoporosis, diabetes, cardiovascular disease, immunization and infections, blood pressure, nutrition, sexually transmitted diseases and many others (1). The theme of the program argues that all citizens should have a better understanding of those factors that affect personal health. I would argue that to achieve this goal we need both a citizenry that understands the processes of science and medicine, as well as high-quality students selecting a career in the science of medicine to do today's work.

Of the plethora of enjoyable tasks of being a Chair of a Department of Medicine, one of the most enjoyable is speaking with fourth-year students while preparing their letters of recommendation. While basking in their enthusiasm for the upcoming years of residency, I always manage to inquire whether they appreciate the connections between their first two years of basic science curriculum and their third and fourth years of clinical rotations. Although an occasional student sees the relationship, most do not. Rather, they usually express great joy in shedding the shackles of classroom work for "real medicine" — interviewing and examining patients, formulating a differential diagnosis, doing scut work, and watching their patient rise from the near dead and walk out of the hospital. They often miss, for example, the integral significance of the immunology they studied in their second year to the survival of their patients' renal allografts, or how the molecular biology they labored over makes the diagnosis of tuberculosis or AIDS so much quicker and easier, or how the signal transduction studies they slept through

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in cell biology yielded the development of a remarkable new drug for patients with chronic myelogenous leukemia. Many just don't get the connection — they do not see the cathedral — and we must fix this situation. We must offer bench-to-bedside opportunities to illustrate — some might say indoctrinate — the power of translational medicine throughout the four-year medical school curriculum.

Academic medicine is just beginning to pay attention to this issue. Three years ago, the Mount Sinai School of Medicine introduced a full-time three-week course for first-year students that emphasizes the link between basic science concepts introduced at the bench and the clinical care of patients. The goal of the course was to reenergize students' career choices by allowing them to experience an in-depth, bench-to-bedside look at a particular topic in medicine. At the completion of the first such offering, most students commented that the program successfully helped them to overcome their end-of-first-year blues and that the course should be continued. Additionally, many recommended additional topics for future study. The creators of this approach, Herold, McArdle, and Stagnaro-Green, believe the program promotes the development of physicians with an appreciation of the scientific basis of disease (2).

Another avenue to instill in students a strong appreciation for the science of medicine is an independent study project (ISP) designed to develop the self-directed thought and problem-solving abilities necessary to optimize a career in medicine. But we must go beyond merely providing the opportunity; we must be certain the projects are rigorous, carefully mentored, and that they utilize scholarly methods to investigate and generate new information. Examples of recent ISPs at our institution include Protein Kinase A Gene Therapy, Angiogenesis in Tumor Metastasis, and B-type Naturetic Peptide for Early Detection of LPS-Induced Cardiac Dysfunction. There is now evidence that such research projects are viewed favorably by students. For example, William Frishman has shown that an intensive six-month mentored research project, replacing traditional clinical electives and carried out in the fourth year at the Albert Einstein School of Medicine, was very favorably reviewed. An overwhelming number of the responding students reported that the research increased their ability to formulate a hypothesis, furthered their knowledge of research techniques, and enhanced their ability to critically evaluate a medical or scientific manuscript. Perhaps most importantly, 85% responded that the project impacted their careers in medicine. (3).

Table 1
Examples of resident research blocks, 2002–2003, University of California San Diego

N-glycolylneuramic acid, a common mammalian sialic acid no longer endogenously produced by man
p38 MAPK activation in human tissues: Modulation by insulin, obesity and type II diabetes mellitus
Cardiomyopathy associated with methamphetamine abuse
Assessment of coronary flow reserve using myocardial contrast echo
Purification of surfactant protein D and development of an ELISA for measuring levels in BAL fluid

In addition to medical students, I believe resident physicians are equally critical to the mission of repopulating academic medicine. Many of my predecessors have spoken of the "pipeline" problem and how MD/PhD or medical scientist training programs (MSTP) are ideal means of providing well-trained individuals ready to assume the ranks as productive physician-scientists and leaders of academic medicine. Although MSTP programs are clearly an outstanding source of future members for the ASCI and AAP, the level of support for these and other such programs is not keeping pace with the demand, despite intense and persuasive lobbying efforts. Moreover, we are not keeping some MSTP students "on task." As a department chair at a research-intensive school with a vigorous MSTP program, each year I still come across several MD/PhD graduates who are more interested in a career that allows "civilized" work hours, high salaries, and ready access to recreational facilities than they are in the pursuit of academic medicine.

A second important source of nascent physician-scientists is a much larger group of "late bloomers," a term used by Ajit Varki in his 1999 Presidential Address to describe physician-scientists like himself and me, whose scientific spirit was kindled during medical school, residency or fellowship. Unfortunately, the number of late-bloomer physician-scientists has declined impressively during the past two decades. We must correct this trend by cultivating science in our residents and fellows, help them to see the cathedral in the bricks, and thus provide the large number of late-blooming physician-scientists needed to repopulate our species.

One strategy our residency program and others have used to address this trend has been to implement a research elective block. It appears such programs are quite popular with residents and impact their career decisions. In our first year of offering research blocks, nine residents spent two to three months in the laboratory of a faculty mentor and then presented their work at a wonderful research symposium late in the year where we brought in good San Diego Mexican food and enjoyed a night of science, camaraderie, and mentoring. And because of this effort, I believe we witnessed many residents seeing the cathedral for the first time. The last two years have seen seventeen and nineteen of our residents enlist in scientific electives; some of the titles of their projects are shown in Table 1, demonstrating that their work is not trivial in scope or level of sophistication.

I doubt many in this audience will disagree that these two groups, medical students and residents, are our best substrate — the most likely population on whom we can draw the next generation of talented clinical investigators and physician-scientists. However, it is also clear that this substrate is very volatile, one sensitive to the discouraging word. While on my first interview for my present day job I asked to speak with the chief medical residents. Although my employer — a late-bloomer physician-scientist with impeccable credentials himself — found the request a little odd, I learned a great deal from my interaction with these bright and energetic mirrors. I soon learned from them that many in the faculty were dissatisfied, angry over compensation and a perceived lack of support for scholarly activities. This perception was held by a small but vocal minority of individuals who had frequent contact with the house staff, and although this was clearly an extremely talented group of young physicians, all four chief residents have since left or plan to leave academics for practice.

Thus, it is clear that the messages we send to our charges can be devastating or inspiring; the choice is ours.

In addition to showing lack of support, some academic faculty send a perhaps even more pernicious message: teaching and mentoring students and residents can be left to others. Many of our most successful physician-scientists are playing far less of a role in academic departments so they may concentrate their efforts solely on scientific pursuits. I couldn't more strongly disapprove of this abandonment of students and residents. If we are to do more than pay lip-service to the career pathway of clinical investigation, the most successful physician-scientists must become highly accessible to these learners. This accessibility could take the form of participation in morning report, the giving of professors rounds or grand rounds, or even attending on a general medicine service, where individuals could use their experience as both physicians and scientists to encourage their fellows and students to make the vital connections between the art and science of medicine — to paint a picture of the cathedral. Taking on a service responsibility provides an added dividend: not only will successful physician-scientists and clinical investigators serve as outstanding role models to many, they will free up junior faculty from some of their clinical responsibilities, allowing the latter the time necessary to develop their investigational skills. Moreover, although I might be a chorus of one, I would even counsel successful physician-scientists to take the further step of "going over to the dark side" to assume the chairmanship of a medicine, pediatrics, or pathology department. Here, too, late bloomers are vital: of the many physician-scientists who presently serve as chairs of departments of medicine in the US, only two have been trained in traditional MSTP programs.

Provide fellows and junior faculty members the training and environment they need to be successful

It is clear that no matter how impressive the molecular discoveries made at the laboratory bench, they can only be translated into remedies for human disease by physicians who engage in clinical investigation. As I mentioned earlier, in 1986, Joe Goldstein spoke of a syndrome of insufficient training, which he called Paralyzed Academic Investigator Disease, or PAIDS. This syndrome is epitomized by the young investigator whose career is stuck for the lack of technical training needed to follow a path of laboratory-based investigation wherever it may lead. However, in this age of translational medicine, the basic or disease-oriented researcher is not the lone sufferer of PAIDS; it can strike burgeoning clinical investigators. Concern for the health of this group of investigators is easily illustrated; for example, the proportion of physician researchers applying for clinically oriented NIH grants declined from 40% of total applicants in 1972 to 25% in 1997 (4). In response, several new initiatives have been forthcoming. The NIH has launched the K23 program, a mentored clinical investigator award, and funded 152 such awards in 2001. Moreover, private foundations, such as the Doris Duke Charitable Foundation, the Burroughs Wellcome Fund, and the Howard Hughes Medical Institute, have also established programs to support young clinical researchers and their mentors. But now that financial support for clinical investigation has rebounded, the next weakest brick in the cathedral is teaching and mentoring. All too often, although grant or departmental dollars provide junior faculty time protected from high-throughput clinical care, many leaders in academic medical centers expect nascent clinical investigators to form by spontaneous generation. Although our emerging clinical investigators are excellent clinicians, they are not yet excellent investigators. I would argue that contemporary clinical research requires a new model for training investigators, one that leads to the design and execution of clinical trials that answer more questions than they raise. We must continue to participate in and support the development of innovative teaching and mentoring programs as they are our incubators for the clinical researchers of the twenty-first century. Such programs should combine seminars in which senior clinical investigators describe their own work with didactic training in clinical research methods, including courses in clinical trial design, biostatistics, bioethics, and clinical research methods, and include faculty-mentored research projects. Our particular version at the University of California, San Diego, is termed Clinical Research Enhancement through Supplemental Training, or CREST. The program is funded by one of the fifty-seven K30 awards from the NIH. Although David Nathan and Jean Wilson concluded that the net result of efforts such as K23 and K30 awards has been "to diminish the aura of discouragement and crisis surrounding clinical investigation," they also argue that continued, careful attention to the support of clinical research remains crucial (5). I would add that funding is not enough: teaching and mentoring are vital complements to financial support.

Despite all of the recent attention focused on clinical research as a means for translating basic discovery into patient care, for translational research to flourish, the basic biomedical science and disease-oriented research communities must remain innovative and strong. It is a common observation that biomedical science is changing radically; perhaps the most obvious pillar of the previous era of medicine to crumble is the organization of research around clinically defined disciplines of medicine. Although I am a card-carrying hematologist, my laboratory studies the molecular mechanisms by which cytokines influence blood cell development. In the present era of biomedicine it makes as much sense for my laboratory to be located adjacent to a rheumatologist studying the effects of TNF on rheumatoid synoviocytes, or adjoining an endocrinologist who studies the signals generated when insulin binds to its receptor on a myocyte, as it is to be contiguous with another hematologist who studies the structure of globin. It is critical to place basic biomedical and disease-oriented physician-scientists — especially new investigators — amidst neighbors who can provide critical and enthusiastic mentoring. Such influence has the potential to both enhance investigators' skills as well as instill in them the excitement that is academics, the spirit of science.

I spoke earlier of the impact of negative comments from senior faculty; in my view a second source of negativism is the editorializing that abounds in times of perceived fiscal hardship. Junior faculty members and transitioning fellows are too often discouraged when they read editorials stating that the physician-scientist is a dinosaur, that physician-scientists are neither physicians nor scientists, or that funding is impossible. We were recently attempting to recruit a junior faculty member, an MD/PhD-trained medical subspecialist, who, despite having penned twelve strong publications, having been allotted 80% time for research, and having been successful in obtaining a K08 award, was convinced that his upcoming R01 application was doomed. One approach to address this crisis in confidence is to create a nurturing environment with strong mentors. As Ed Benz suggested in his 1992 Presidential Address, in each of our pasts someone motivated us to give research a try, made us feel good about our chances for success, and served as a role model for how

the life of a physician-scientist can be highly rewarding. The quality of our contacts with these people — our mentors — probably had a greater impact on our career decision choices than any other single factor.

Teaching the public that scientists are creative and caring, and that science can be harnessed to improve the state of human health

If we are successful in the efforts I've described thus far, our students, residents, fellows, and junior faculty will understand that biomedical science must be robust and based on the logical application of rigorous methods and objective analyses, with conclusions coming only from a careful assessment of all the evidence. Unfortunately, if that is all we do, we may still fall short of improving the state of clinical investigation. When our Society was founded in 1908, the gap between the biomedical knowledge base of the seventeen charter members and society at large was wide, but this gap has grown substantially wider with each passing decade. As it widens, so too does public distrust in our profession. Many recent polls point to large numbers of the public who believe the sun rotates around the earth, in extrasensory perception, and that evolution is only a theory. I would argue that we must close this gap between science and the public if we are to improve the state of clinical investigation. We must teach that scientific innovation is the key to improved health and must be expanded, not, as some cynics proclaim, bridled because of adverse effects on health care economics. We must encourage public understanding of the necessity of revision to scientific theories and explain that re-examination of past conclusions is axiomatic to rigorous science. For example, when new studies reverse the existing recommendations for estrogen therapy of post-menopausal women, it's because the study was finally done the proper way. We must teach the fundamental importance of biomedicine to society and respond to the challenges of anti-scientific attitudes. Imagine what the state of biomedical investigation would be if we had a scientifically literate electorate or the willingness of patients to participate in clinical investigation. But we must be careful not to step over the line of ethical science or to offer expectations that cannot possibly be fulfilled. Claims such as those made in 1982 that an AIDS vaccine was only a year or two away, or those in 1985 that gene therapy is just around the corner, or those last year that death and suffering from cancer will be eliminated in ten years, are toxic to the public trust and can have a chilling effect on scientific credibility.

From what I have seen and read on the subject, we in biomedicine are very much in need of more Carl Sagans. Sagan played a leading role in the American space program from its inception. As a consultant to NASA, he briefed the Apollo astronauts before their flights to the Moon and designed many of the scientific experiments carried on the unmanned Mariner, Viking, Voyager, and Galileo expeditions to the planets. He contributed to our understanding of the high temperature on Venus (a massive greenhouse effect), the seasonal changes on Mars (due to windblown dust), and the reddish haze of Saturn's moon Titan (composed of complex organic molecules). For twelve years Carl Sagan was editor-in-chief of the journal *Icarus*, the leading professional publication devoted to research in the planetary sciences. He was the co-founder and first president of The Planetary Society, and a Distinguished Visiting Scientist at the California Institute of Technology. In short, Sagan was a scientific nerd and an accomplished leader in his field, much like many of the members of our Society. But few outside of scientific circles remember Carl Sagan for these contributions; rather, Sagan is remembered for bringing science to the public. His Pulitzer Prize-winning book *Cosmos* remains the best-selling science book published in the English language. The Emmy and Peabody Award-winning television series based on his book has been seen by 500 million people in 60 countries. As a result, Carl Sagan received the 1994 Public Welfare Medal, the highest award of the National Academy of Sciences, for distinguished contributions in the application of science to the public welfare. The award reads "[H]is ability to capture the imagination of millions and to explain difficult concepts in understandable terms is a magnificent achievement . . ." I would argue the study of science in medicine is just as moving as that of the planets, and just as relevant, if not more so, to the public welfare. Like astronomy, medicine needs its Carl Sagans to improve public understanding and perception.

Many of you have heard me state my belief that the pursuit of a career in academic medicine is a genetic disorder, displaying autosomal recessive inheritance: you need two mutant alleles to be so afflicted. I would argue that one of the phenotypes of this genotype is the need to teach. The need is fulfilled by the great sense of satisfaction derived from the smile that punctuates a successful Socratic discussion with students and residents, acknowledging they finally got it, by the contentment that comes with the first publication or first grant obtained by your fellow, or by the pride in seeing someone you mentored promoted to professor or elected to the ASCI. I would submit the following question to you: can we really afford not to teach? Teaching is what we are all about. It is good for the soul, and without it our Society and all it stands for will become a footnote in the ancient history that was clinical investigation. I encourage all of you to teach and mentor more bricklayers who will in turn build more cathedrals.

Acknowledgments

Given these comments on mentors and mentoring, I wish to express my great thanks to many individuals who mentored me and in so doing taught me the value of mentoring: Clem Finch, a former ASCI President who convinced me that hematology holds many biochemical and molecular biological rewards; Earl Davie, for bringing humor to the laboratory and teaching me to remain focused on good projects; ASCI members Barry Coller, Andy Shaffer, and Ed Benz, the latter of whom is also a former ASCI President who counseled me that being a Chair of Medicine can be gratifying, fulfilling, and important; and John Adamson, who taught me the value of scientific excitement, integrity, and of always asking the next question — not to mention for investing much red ink in my first few manuscripts. Lastly, and most importantly, my wife Lauren and our children, Alexis and Joshua, whose patience, understanding and literary, scientific, and political discussions are awe-inspiring.

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