



2007 American Society for Clinical Investigation Presidential Address

In the palace of the sultan

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It is a rare privilege to stand in front of this group of distinguished physician-scientists today. I admit to feeling more than a little awed by this privilege for several reasons. First, as has been noted by many previous Presidents quaking in their boots up here, this podium has been host to legends – including some of my own personal heroes. I am deeply humbled to stand in the place of people like John Merrill, Eugene Braunwald, Stu Orkin, Rick Klausner, David Ginsburg, Ed Benz, Joe Goldstein, Bill Kelley, and many others who have been true leaders of American medicine. Secondly, I believe this privilege confers on me a responsibility to use this time to say something original, meaningful, and hopeful. Finally, who am I to be here at all? When I was elected, I was a Professor of Medicine at the University of Pennsylvania, an academic clinical investigator. But now, I work for a drug company. Not wanting to rehash the rancor around this topic that erupted at last year's Joint Meeting, I will only say that wherever my paycheck comes from, I am physician-scientist to the core. I am single-mindedly committed to doing clinical research with the potential for clear and immediate impact on patients and their families, guided only by the needs of those people. This is what I did when I was at Penn, and this is what I do now at GlaxoSmithKline. My laboratory group at GSK works to identify the patients most likely to benefit from new targeted cancer therapies in development, and my clinical group designs and executes the clinical trials to evaluate those drugs. It's one of the coolest clinical investigation jobs in the world.

To point two, the topic of my presidential address, I found to my dismay that many of the themes I had in mind had not only been raised before, but in fact had been discussed

so many times that I began to wonder what happened to the imaginative spirit of some of the world's greatest clinician scientists when they became Presidents of the ASCI. In fact, David Ginsburg, on the occasion of his ASCI Presidential Address (1), graphed the topics covered, and, not unexpectedly, the "Big Five" are 1) The Future of the Physician Scientist (said to be in dire need of rescue to avoid immediate extinction in most Addresses since the society was chartered in 1908), 2) Defining Clinical Science (hotly debated annually by every ASCI Council in the history of the society during review of membership nominations), 3) The State of the ASCI (said to be on the verge of collapse since just shortly after its formation ninety-nine years ago), 4) Education and Mentoring, and 5) Research Funding (an unavoidable topic when two or more physician-scientists are in the same room for more than five minutes). So I gave up on original, and I strive only for meaningful and hopeful.

Today I would like to discuss three issues in academic medicine that I believe are having a serious negative effect on the pace and quality of academic clinical investigation. Some may seem minor on the surface, some are more obviously substantial, but all three are things that I believe ASCI members can help to change, individually and collectively, and in so doing can make a real difference in our ability to do what we do: find new ways to help patients through our research. These three issues are 1) the cost to creative time of "feeding the beast" of the academic bureaucracy; 2) the innovation-squelching nature of the current peer-review system, and 3) the loss of physicians with a passion for clinical investigation as the leaders of academic medical centers. The tasks and energy required for investigators to survive, to say nothing of flourish, in the face of these problems leave everyone spending far too much time doing things that contribute very little to important, clinically relevant research.

Problem one: feeding the beast

To put this in a personal context, let me take you back to a spring morning four years ago. I was sitting in my office at

Penn, the sun glinting off the oil refineries in southwest Philly, feeling crushed by the ever-growing pile of looming grant deadlines (often resubmissions that were ultimately funded without a substantive change in the research plan, and certainly no change at all in what we actually did), a huge box from the Executive Secretary of my study section (now replaced with a deceptively tiny CD), manuscript reviews that were overdue, support letters to write for promotions and other people's piles of grants, the always irritating reviews of my own work by reviewers who "didn't get it" which needed more work and rebuttals, the more important piles of unread papers, and, most importantly, but often at the bottom of the list, all the people in my group who needed my attention but were not getting enough of it because of the aforementioned pile of work. Of course what I was doing was my e-mail – it's a convenient excuse for not doing all the rest of it (e-mail does present a series of manageable tasks that provide a measure of satisfaction when it's the only thing one can hope to start and finish that day) – when David Ginsburg called. I love David Ginsburg and am always thrilled to hear from him, but I admit to a twinge of trepidation on picking up the phone, as it was unlikely, given that he is just as busy as the rest of us, that he was just calling to chat. What did he want me to do enough that he wasn't going to let me out of it in an e-mail?

You may have guessed that he was calling to ask me to run for ASCI President, clearly a carefully orchestrated request. David is someone I hugely admire and a long-time friend – someone to whom I would not say no. But I did – I said no. I was honored almost beyond speech to be asked but I was so overwhelmed with the sheer volume of my existing responsibilities that the thought of taking on anything else practically brought me to tears – the Bionic Woman was now Woman on the Verge of a Nervous Breakdown. I am an efficient, disciplined, embarrassingly organized person – a first-intern-out-of-the-hospital, alphabetized-spice-rack kind of person – and I was drowning. I went home every day for dinner with my family, but I was working

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late every night, and many weekends, just to keep afloat in the sea of manuscripts and grants, mine and other people's, that had to be submitted, and resubmitted, and resubmitted again. And the more senior I became, the bigger the applications got — my last one was a program project application well over a thousand pages. I could barely make time to go to the bathroom most days until it was practically a medical emergency. How could I possibly take on one more responsibility? Reluctantly, unbelievably, I said no; I couldn't do it. David sympathized, cajoled, and tried to lure me with the prospect of mid-winter Council meetings in sunny locations with good food and lots of wine. But I held firm and put the phone down, feeling mortified at having turned down such an honor, guilty for saying no to my friend, angry at my pile of mostly busywork for keeping me from being able to say yes, and frustrated that I, Dr. Organized, could not seem to manage it all more efficiently. But I did need to say no to something, or I was going to lose my mind.

Of course, that was not the end of the story. About twenty minutes later, proudly having dispatched seven or eight more emails, there was a booming knock on my door that could be only one of two things — either the Sasquatch or Craig Thompson, the academic equivalent of Tony Soprano, was coming in to make me an offer I couldn't refuse. So, faced with two broken knees or being on the ASCI ballot, here I am.

Truthfully, I will always be grateful to David and Craig for talking me into this — it has been a true honor and fantastic experience to serve as ASCI President. Let me digress for just a minute to say what a pleasure it has been to work with the Past Presidents Len Zon and Eric Fearon, the President-Elect Charles Sawyers, and all the Council members who have given so generously of their own time over the past four years, and to thank them for their hard work and dedication to the ASCI. There is no adequate way to thank John Hawley, the Executive Director, Karen Kosht, the Managing Director, and the entire ASCI staff for their guidance and support, particularly this year. In addition to making all the working parts move properly and on time and all the work he does for the *JCI*, John responded enthusiastically to the demands of instituting several new programs and procedures this year, always a voice of reason and calm, to be counted on to step in just when I was about to melt

down. The ASCI would not and could not exist without him.

But back to the question: why in the world would I be reluctant to accept such an honor? And not just an honor, but the chance to lead the society of the most accomplished academic investigators in the world, a position from which one could really make a difference? This, for me, was the cost of "feeding the beast": The weight of academic "activities of daily living" were taking so much time away from the important things that I had practically forgotten what they were. Thinking creatively, reading thoughtfully, and having a personal investment in fostering and transforming clinical investigation, including working through the ASCI, is to me the real work of being a clinical investigator. How often did I sit down at my desk in the morning and open my e-mail, and how often did I block off the morning to read papers that might take our work in a promising new direction, and really think? How much of what I did every day really had the potential to make a difference, and how much of it was just feeding the beast? No one person can disassemble this Goliath single-handedly, stripping it back to its essential parts, but all of us can make a difference if we pay attention.

Reflecting on these issues for myself, I did make some changes, and for the most part I have stuck with them. I stopped opening my e-mail first thing in the morning, and I left it alone all day. Issues that would have distracted me during the day were sometimes resolved by the time I got to them, the rest of them were still there, and the volume of my e-mail dropped noticeably when people began to realize that they were unlikely to get an immediate response. Nothing bad happened. E-mail is not important.

I vowed to change my reviewing style. Why is it that not a single paper is accepted without revisions any more? My personal record (for a solicited manuscript!) was eighteen pages of reviews from six different reviewers — and the resulting rebuttal, which did not substantially alter the paper, was almost twice that long. This issue may seem trivial, but consider the annual collective effort of manuscript writing, submitting, and reviewing that exists just among the people in this room, and think what you could do with the time generated by streamlining this process. So I try to focus my reviews on the big picture: whether the question being asked is an important one and whether the data support the conclu-

sions. I make my reviews short, to the point, and even complimentary and encouraging when warranted. I work hard to resist the temptation to describe what I would have done, or merely expound on the topic, and I carefully consider whether my requests for any additional experiments are really necessary, or just what I would do next. Primarily, I try to decide if the data are worth putting into the scientific literature for others to consider and evaluate. This does shorten the time it takes to write a review, but more importantly what I hope it does is to allow the authors to work on their project, not on their manuscript. While addressing a subtly different problem, the sentiment was succinctly expressed by Nobelist Max Delbruck in a letter to the wife of his friend, Seymour Benzer: "Dear Dotty, please tell Seymour to stop writing so many papers. If I gave them the attention his papers used to deserve, they would take all my time. If he must continue, tell him to do what Ernst Mayr asked his mother to do in her long daily letters, namely underline what is important."

Problem two: the peer-review system

The third thing I promised myself was to change the way I was approaching grant reviews and to encourage my study section to do the same. Here, too, I tried hard to focus on the big picture, and not to worry too much about the details. To ask, "Is this an important question, with plausible hypotheses?" and never to say things like "overly ambitious" or "it may not work." What in the world is the benefit of discouraging scientific ambition? And to the latter point, Terri Strom, known for his ability and willingness to cut to the core of any issue, said it best in response to such a criticism: "If we knew it would work it wouldn't be research." I tried hard to champion innovation and imagination, even when it seemed weird. Both Eric Fearon and Jeff Trent, as study-section chairs, have commented that I have "really odd taste in grants" — but I am proud of that. Consider the central tenet of Sir Peter Medawar's *Advice to a Young Scientist*: Ask important questions (2). Important questions are hard to answer and are unlikely to be answered with the work we generally consider prudent to put in a K08 or R01 application.

We complain endlessly about the review system, how we all know most of the work is done before the proposal is submitted, how timid we all are about submitting something really different — but we *are* the system and we are the only ones who can



change it. Some of you heard last night from Brett Giroir about true innovation, and you saw what can be accomplished when smart people are free to think about, and to work on, really hard problems with transforming solutions. Chances are that you are not seeing that in your study section, and if you are, it's not getting funded. We can change that! If we don't, who will? In fact, that is the very spirit of the ASCI.

As you will hear much more about next year, our one hundredth anniversary, the ASCI was started in 1908 by a small group of clinical investigators who, having no place to present and discuss their clinical research because they had not gained admission to the Association of American Physicians, declared the AAP unworthy and started a new society. The ASCI was started with the avowed purpose of encouraging medical research by physicians engaged in medical practice, which was not supported by established medical schools at the time. It was a rebellious attempt to create something new, to challenge the status quo, to be innovative, and thereby to make a difference to patients.

The initial discussion took place on the Atlantic City boardwalk after an AMA meeting and was led by Samuel J. Meltzer who, born in Russia in 1851, was to become the ASCI's first President (3). Dr. Meltzer had a clinical practice in Harlem and did pharmacology on the side. He listed his research interests as anesthesia, the clinical effects of epinephrine, and the role of Mg^{++} in human health. He also studied swallowing by passing tubes into his own stomach (no R01 for him with such unfocused research interests and inadequate protected time). He and his colleagues described the AAP as having become a "conservative and somewhat dull society, unaware of the tremendous advances being made in medicine," its members "somewhat set in their ways, and not very scientific," and they formed the ASCI as a protest against these "distinguished stiff shirts." The newly formed Society consisted of "rebels and roughnecks" who were not constrained by the status quo, not distracted by the things that did not really make a difference, and they called themselves "Young Turks" to express this spirit.

The original Young Turks were an actually Turkish group of intellectuals who formed their society in 1865 to advocate change from the repressive, authoritarian government of the Ottoman Empire to a constitutional parliamentary system. By the summer

of 1908, the Young Turks were a coalition of reform-minded groups who rebelled against the last Sultan of the Ottoman Empire. The Sultan, upon learning that the determined and energetic Young Turks were marching on Istanbul, capitulated without a fight, and the Ottoman Empire fell.

My analogy is an obvious one: the spirit of the ASCI is one of rebellion against a status quo that is not serving its purpose and collapsing under its own weight, of finding a way to do what really matters in an environment not conducive to the goals of its members. Like the original Young Turks, the ASCI was, and remains, a nidus of intellectual force and scientific excellence whose members have espoused, as a primary goal, doing research that makes a difference to patients. If the environment for doing that work has become less than optimal, who but we are best suited to change it?

Unfortunately, as the real Young Turks became the established status quo, they lost their way. By 1912, the leadership of the Young Turks had split into two factions. One faction was still committed to liberalizing the country, but the second, headed by a triumvirate called the Three Pashas, rejected the more idealist faction and assumed full leadership of the country after assassinating the idealistic minister of war. The Three Pashas, now content to be living in the palace of the sultan themselves, ruled until the end of World War I, and, as a tragic historical aside, were responsible for the Armenian Genocide.

Certainly I am not espousing armed rebellion against journal editors and program officers. My point is that we must look to ourselves as the solution to academic bureaucracy and unimaginative research funding. We maintain what I believe is an environment that is too overburdened with its own workings to optimally support innovation and imagination. We are being slowly crushed by a system that, like most systems, only acquires process over time and never loses it.

Problem three: academic leadership

You may well and rightly argue that how often you check your e-mail, or changing the way you review manuscripts, or even risking the scorn of your colleagues by taking up the cause of a grant proposal that does not fit the mold will not change the world. So for my last point: something a little bigger. In the membership of the ASCI, many sitting in this room today, are the undisputed scientific leaders of clinical

investigation in this country. But how many of you are division chiefs, or department chairs, or deans? How many of you aspire to those jobs any more? And how many would even accept one if offered? Some of this shift away from academic leaders being the leaders of academic medical centers comes from the time drain of feeding the beast — the acknowledged impossibility of maintaining an active, cutting-edge lab while doing one of these jobs. But I believe there is a much more destructive issue at play, and that is the premium now put on the financial bottom line. It seems that clinical investigation and the benefits it brings to human health and well-being are slipping out of the mission statements of academic medical centers, and leadership positions are increasingly being held not by our biggest idols, the likes of Robert Petersdorf, Bill Kelley, and Sam Thier — to name three legends I have had the great privilege of working for — but by people who, instead of acting as scientific leaders and role models, end up as adversaries to many faculty because of the business models under which they are required to operate. In his 2001 ASCI Presidential Address, Gary Koretsky said, "It now seems that MD/MBAs may be more valued than MD/PhDs . . . and the most successful physician-scientists, who a decade ago would have been natural candidates for positions as division heads or department chairs, now often recoil at the notion that they be considered for these jobs" (4). I argue that the situation has worsened over the intervening six years.

The loss of our heroes as our leaders is having devastating effects on morale, and it ultimately leads to a dangerous research strategy — that of investing institutional research resources primarily in those individuals and departments that generate the most revenue, often as a reactionary strategy to retain the people who generate the most clinical income. As a by-product, this shift in academic leadership has had a deleterious affect on the ASCI — as the number of deans and department chairs who are ASCI members continually drops, so does the visibility, the relevance, and the influence of the members of this Society. So, it is a far greater personal investment than changing how you approach e-mail, review manuscripts, or triage grants, and I confess that I could not muster the energy myself to do it, but consider the impact of idealist Young Turks taking back a meaningful role in academic leadership.



What can the ASCI do?

The year of my Presidency started with a bang, just days after the now-infamous editorial in the *JCI* by Andy Marks about the dismal state of federal research funding (5). Whether or not you agreed with Andy's approach to bringing attention to this truly disastrous situation, there was uniform agreement that one of the most damaging aspects of very low paylines is the effect that it has on an entire cadre of talented young investigators, who are demoralized and discouraged by repeated unsuccessful attempts to secure their first grants.

Continuing on my quest to improve the state of clinical investigation, I felt it was time for the ASCI to take on a role that it has not taken on before, and to play our part in helping the most promising young investigators through these difficult times in a tangible, meaningful way. With the support of the Council and the ASCI staff, we started what I hope will be an ongoing ASCI Young Investigator Award program. We committed funds to provide up to five K08 or first-time R01 applicants whose applications were near, but above, the payline with a one-year grant of \$70,000 to support them during the resubmission cycle. Applicants were required to have an ASCI member mentor, and, in keeping with my personal paperwork reduction program, we made the application process as simple as we could. We received twenty-five applications, and I am very proud to announce today the recipients of the 2007 ASCI Young Investigator Awards:

Clemens Bergwitz from Harald Jueppner's lab at the Massachusetts General Hospital

Rosemary Sampogna from Qais Al-Aqwati's lab at Columbia University

Christopher Huston, who trained in Bill Petri's lab and who is now at the University of Vermont

Antonios Aliprantis from Laurie Glimcher's lab at Harvard School of Public Health

I also would like to congratulate five other investigators who scored well enough to be funded by the ASCI but received word in March that their K08 applications were below the new paylines set after the federal budget was passed, thus declined their awards: Robert Schwabe from David



Figure 1

Brenner's lab at Columbia, Sridhar Rao from Stu Orkin's lab at Boston Children's Hospital, Adam Cohen from Alan Houghton's lab at Memorial Sloan-Kettering Cancer Center, Nancy Kim from Alan Luster's lab at the MGH, and Barbara Balestrieri from Frank Austen's lab at the Brigham and Women's Hospital.

Thus nine young investigators from ASCI mentor labs heard that we believed in them enough to support them while their first grants were being resubmitted. I believe the interim support the ASCI provided for these four people is important far beyond the money – we hope it also provides them with the encouragement and confidence to keep trying in a difficult system. The ASCI is a relatively small society, but we do have substantial assets that come from the success of the *JCI*. And while we must be prudent with those funds in this time of uncertainty around subscription and advertising income in a world of electronic access, I believe this allows us the luxury of using some of those funds to invest in the future of clinical investigation through these awards, and I am proud to announce that yesterday the ASCI Council voted unanimously to continue this important initiative next year.

I believe that the ASCI can, as a society, do some of the things that will make a difference for clinical investigators now and for the future, and the Young Investigator

Awards program is one example. However, I believe the even greater strength of the ASCI lies in the energy, individual talents, and leadership of its auspicious membership. I believe that each of us can, and must, help bring the focus back to what really matters, to what really makes a difference to patients, if we constantly remind ourselves why we wanted to be doctors and scientists in the first place and make the time and take the risks needed to do innovative work on difficult, clinically relevant problems.

The ASCI is an amazing society. Among our membership are 148 members of the National Academy, 29 Lasker Award winners, and 15 Nobel laureates. The accomplishments of the members of this society throughout its history have transformed the lives of millions of people. To list just a few examples as a reminder of what we can do, what is yet to be done, and how much what we can do matters, consider Mike Brown and Joe Goldstein's work on cholesterol metabolism and the number of lives saved this year alone from the widespread use of statins. Consider Bob Schwartz's groundbreaking discovery of the immunosuppressive properties of 6-mercaptopurine, which allowed the first renal transplant to be performed. This discovery informed Tony Fauci and Sheldon Wolff's work on steroids and low-dose cytoxan for vasculitis, the first immunomodulatory therapy for rheumatic disease, which was followed



by Bruce Beutler and Tony Cerami's discovery of TNF, and the resultant development of anti-TNF antibodies for patients with rheumatoid arthritis. You only have to see one person crippled by this devastating disease who gets better – really better – with this treatment to viscerally understand the impact of this work. Consider the leaps made by Brian Druker and Charles Sawyers, which not only led to Gleevec, a drug that transforms the lives of people with chronic myelogenous leukemia, but perhaps more importantly convinced the entire pharmaceutical industry that targeted therapy is the future. But consider also advances so fundamental to modern medical practice that we don't even think about them – like combination chemotherapy, pioneered by Tom Frei, Emil Freireich, and Jim Holland on the basis of the success of combination drug therapy for tuberculosis. Following on glimmers of success with leukemia, George Canellos and Vince DeVita figured out how to cure Hodgkin's Disease. George was already a legend when I was an oncology fellow at Dana-Farber, but I admit

I didn't think much about Hodgkin's Disease – even then, it seemed so easy to cure. Like most of you, I never knew the time when everyone died from Hodgkin's Disease. But suddenly, one day five years ago, it became the only thing I thought about, when my fifteen-year-old son Josh was diagnosed with Hodgkin's Disease. Some of you know Josh, some of you met him at dinner last night, but all of you can see that George and Vince's pioneering clinical investigation saved Josh's life (Figure 1). Thanks to them, to countless other clinical investigators who came after them, and to his doctor, John Maris (a new ASCI member sitting in the room right now, who spoke this morning about his own efforts to make neuroblastoma as easy to cure as Hodgkin's Disease), Josh is a healthy, happy junior in college whose only medical problem at the moment is probably hypothermia from going to the Cubs game today.

These are just a few of the many transforming clinical advances by ASCI members in recent years. We can do amazing things, things we cannot yet even imagine.

But we need to make time to be creative, to work in a funding environment that supports innovation and takes risks, and to be willing to exert the leadership to make that happen. The ASCI, the Young Turks, was formed in the spirit of rebellion against a mindset the original society members felt was stifling research that could really make a difference to patients. The sultan has crept back into the palace, but we can chase him out again. Each one of us can make a difference, individually and collectively, and we have to, because what is at stake is the lives of all those people still to benefit from the work that each of us does.

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