

From genes to screens: crossing the digital-medical divide

Jeffrey M. Leiden, ASCI Presidential Address, May 6, 2000

Members, guests, and trainees, during the past year I have had the pleasure and privilege of serving as President of the American Society of Clinical Investigation, an organization with a long and rich tradition of celebrating the finest young physician scientists and supporting their roles in biomedical research. It has been a special honor for me to serve as President of the ASCI both because of the importance of its mission and because of the outstanding quality and dedication of its members. Indeed, the opportunity to work closely with my friends and colleagues on the council, the institutional representatives, and our members at large has been an immensely rewarding experience. I would especially like to thank our officers and council members who have provided me with so much support, advice, and occasionally criticism, most of which has made the job easier and more enjoyable.

The year-long term of the ASCI presidency is much like drinking a fine bottle of wine over a long evening with friends. The first part of the year is both stimulating and enjoyable — attending the mid-winter council meeting in a warm resort, making a few straightforward policy decisions about the age cutoff for ASCI membership, or debating the disposition of the ever-increasing JCI trust fund with the Editor-in-Chief. However, by mid-April, the friends are gone, you're alone, and the morning hangover sets in as one realizes that the dreaded date for the Presidential Address is approaching rapidly. The first response of most Presidents is to immediately read the addresses of their predecessors. But of course this rather humbling experience only makes matters worse as one rapidly comes to the conclusion that "it's all been said before." After all, what could I possibly add to the insightful

and inspiring comments of the many icons of academic medicine who have delivered this address in the past? Then there's the problem of trying to provide philosophical advice to one's friends and colleagues. Here I'm reminded of the story of the young school boy who was studying Socrates and the ancient Greeks. When asked to summarize what he had learned during the unit he replied, "Socrates was a very smart old man. He tried to give lots of advice to his friends. So they killed him."

In my own reading of the previous ASCI Presidential Addresses, two consistent messages came through repeatedly. First, the fantastic progress in molecular genetics, genomic sciences, and cell biology over the last 20 years has placed us on the threshold of the most exciting revolution to take place in medicine since the discovery of antibiotics and anesthetic agents at the beginning of the last century. The pace of this scientific progress has been truly breathtaking. Consider for example that the discovery of DNA as the genetic material is less than 60 years old, and yet in several months we will have in hand the fully assembled sequence of the 3×10^9 nucleotides in the human genome. Molecular cloning, the polymerase chain reaction, transgenic mice, monoclonal antibodies, and CAT scanning are all less than 30 years old. This technological explosion and its application to science has and will continue to fundamentally change the way all of us practice medicine over the next 20 years.

How ironic then that given these wonderful scientific opportunities, the second message from our past presidents is a much more sobering one: the fate of the physician scientist, particularly the young physician scientist, is seriously imperiled. Indeed over the last ten years, this theme and its causes have been discussed scientifically,

philosophically, and even facetiously by almost all of our past presidents. And as we heard so eloquently from Tim Ley last night, this problem is only getting worse. Figure 1 shows in graphic and distressing fashion that the percentage of NIH-funded M.D. and M.D./Ph.D. investigators under the age of 45 has declined linearly over the last 20 years, this despite the fact that NIH funding is now at its highest level in the last two decades and only promises to increase over the coming years.

Many logical and reasonable solutions have been proposed to address this problem. We clearly need to interest more young people in careers in science long before they enter college or medical school, we desperately need a national program of debt relief to decrease the financial burden on young M.D. investigators, and we must think seriously about shortening the training period for these M.D.-scientists so as to not lose their most productive years in training. The ASCI has taken a leadership role in lobbying for many of these changes and in the long run we may be able to convince Congress and the relevant regulatory bodies to enact at least some of them.

However, as we have discussed these issues and the more general problems facing today's academic medical centers with politicians and funding agencies over the last several years, we have all heard more and more frequently the advice, "Physician Scientists heal thyselfes." Today I'd like to consider with you whether such a self-cure is possible and to suggest to you one element of such a cure that I think until recently has been largely overlooked by many of us in academic medicine, and that is the possible role of information technology in revolutionizing biological sciences, the delivery of patient care, and the teaching of students, residents, and fellows in our academic medical centers.

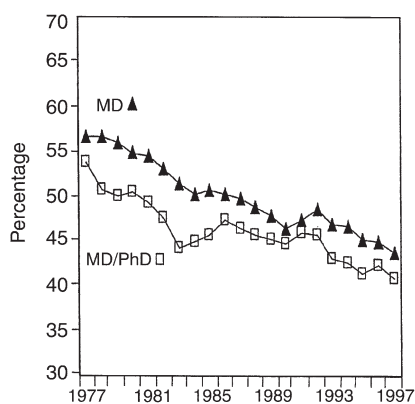


Figure 1
Percentage of M.D. and M.D./Ph.D. NIH-funded PIs 45 years old or less.

In order to be provocative I would like to take an intentionally radical and perhaps even extreme position: I would like to propose the hypothesis that despite our leadership in developing the cutting-edge technologies of the biological sciences, we physician scientists have almost ignored the parallel revolution in information technology that has taken place around us during the last twenty years. I suggest that the lack of modern bioinformatics is slowing progress in the biological sciences, contributing to cost-inefficient and sub-optimal patient care, and hindering our ability to train the next generation of physician scientists.

What is the evidence for such a radical position? I believe a few case reports will be illustrative. Last year while I was attending on the cardiology service at the University of Chicago, one of my residents presented the following case during morning rounds: JT was a 55-year-old male admitted with a three-day history of recurrent episodes of chest pain and diaphoresis. He had multiple cardiac risk factors and reported two previous admissions at an outside hospital with similar symptoms. The last of these resulted in an echocardiogram, an exercise test, and a cardiac catheterization. However, he couldn't remember the results of these studies. The resident on call had spent almost an hour the previous evening trying to obtain the records of the patient's prior admissions and test results from the outside hospital, all without success. In order to "expedite" his admission the residents had already

obtained another echocardiogram at our hospital which showed only mild LVH. Given our concerns about coronary artery disease and our inability to obtain his old records the patient underwent a stress test which revealed a question of reversible ischemia in his inferior wall. Accordingly we scheduled him for a cardiac catheterization the next day. Fortunately, that evening, the resident was able to contact an intern at the outside hospital who located the patient's previous records which he faxed to us. These showed a normal cardiac catheterization with clean coronary arteries just 4 weeks previously. The patient was discharged the next morning on antihypertensive medications. Although in the end this case had a good outcome, it is by no means atypical in our teaching hospitals — this patient had to endure a three-day hospital stay, multiple redundant tests at a cost of almost \$10,000 simply because we have no national system of medical record keeping. Consider the millions of dollars, thousands of days of lost work, and myriad complications caused each year by this lack of information technology.

Examples of a related problem are shown by in multiple newspaper articles concerning medical errors. As many of you know, a recent report by the Institute of Medicine, entitled "To err is human: building a safer health system," estimated that between 50,000 and 100,000 American patients each year die because of such medical errors. Many hundreds of thousands more suffer significant iatrogenic morbidities. The IOM estimated the costs of these errors at \$17–29 billion per year with more than half of those costs attributable to error-related medical care. Some of the most frequent mistakes documented in the IOM report involved incorrect doses or combinations of medications — a problem easily addressed with the most rudimentary computer systems (more about this later). Finally, our system of medical billing and reimbursement is horrendously complex, expensive, and inefficient. When I recently moved from Chicago to Harvard, I was asked to fill out application forms for more than 30 different insurers or HMOs, each of whom requested the same

information in different handwritten formats. Some of these forms were more than 10 pages long. CPT and ICD-9 coding books used by hospital billing offices contain thousands of different diagnosis codes, each of which can be billed at multiple levels of severity. Many of these codes are changed every couple of years. Its not surprising then that the costs of administering hospitals have risen at unprecedented rates.

What about the scientific front? What is our current state of information technology and how is it promoting or limiting scientific progress? It is obvious to all of us who try to keep up with even a single area of science that the amount of published information is exploding. Similarly, as we finish sequencing the yeast, fly, mouse, and human genomes, we are acquiring a vast goldmine of genetic information. The difficulty of course is managing, and most importantly, integrating this information. To be fair we have made an excellent start at developing computerized tools for this task. Genbank, and PubMed, Entrez, and BLAST each represent significant advances in bioinformatic technology. However in most cases these tools remain somewhat rudimentary and difficult to use. It often takes 6–9 months from submission of a scientific manuscript to its inclusion in Medline, many journals (excluding the *JCI*, of course) are still only available in paper form, to find, map, and assemble a sequenced but uncatalogued gene takes a talented postdoc several hours to days using currently available software, and computerized versions of complex and rapidly expanding intracellular signaling pathways are only beginning to be developed.

Finally, I would like to address our teaching of students residents and fellows. As financial and regulatory constraints become increasingly severe, academic physicians are being asked to spend more and more time on direct patient care related issues. Research and especially teaching are suffering terribly under this new system. The days when master clinicians could spend several hours each day teaching at the blackboard and the bedside are long gone. Students are

more and more frequently taught by residents and fellows who themselves have just 2–5 years of clinical experience. And as is true in the basic scientific and patient-care arenas, we have lagged behind many other fields in applying information technology to this problem. Most students still learn from lectures, paper textbooks, and small group bedside demonstrations of physical findings. Clinical decision-making is learned by watching older trainees and attending physicians deal with small numbers of live patients — this is both limiting in scope, idiosyncratic, and in some cases dangerous as young trainees cut their clinical decision-making teeth on real patients. This process is akin to letting new pilots learn to fly by practicing on real planes full of unsuspecting passengers, a particularly frightening analogy for many of the more senior frequent fliers in this audience!

In summary, there is tremendous opportunity for improvement in biomedical-related information technology. Such improvements would clearly both enhance the quality and reduce the cost of scientific discovery, medical care, and training. It is often easy to identify problems but difficult to understand how to fix them. In particular networked computers and informatics have been touted by both the pundits and dot-coms as the solution to all of the socioeconomic woes of Western societies. In this sense bioinformatics is reminiscent of this old joke about teenage sex:

It's on everybody's mind all of the time
Everyone is talking about it all of the time
Everyone thinks everyone else is doing it
Almost no one is really doing it
The few who are doing it are:
Doing it poorly
Sure it will be better next time
Not practicing it safely.

But joking aside, in considering the cures for the digital-medical divide it is useful to begin by asking, Are we really behind other fields in applying the advances in digital technology? And if so,

what can we learn from their experiences to facilitate the application of information technologies to science and medicine? I believe that the answer to the first question, are we behind, is clearly yes. Let us compare the information technologies used in medicine to those used in the financial world that has been quick to adapt new digital methods. In medicine we keep handwritten, non-centralized records on paper that looks like this. Sometimes we can actually find these records in our hospitals. Occasionally we can read the handwriting. However, in the world of banking if I need cash, I no longer write a paper check, I simply use a card that allows me to communicate with a centralized computer that tracks the balance in my checking account on a minute-to-minute basis. If I write a mistaken medication order for a patient, it may or may not get caught before the patient receives the medicine. Can you imagine mistakenly writing a check to your paper boy for \$1,000,000 when you meant \$10 and having the bank honor that check with only \$2,000 in your account?

When I make decisions about patient care on rounds I try to remember what I read in the *New England Journal of Medicine*, the *Lancet*, or *Circulation* several years ago and apply that memorized information to the case at hand. If I can't remember, I'm either forced to walk to the library to sort through the stacks for the relevant journal or to consult my computer, in which answers to simple queries like malignant hypertension produce results that often require sifting through thousands of articles while frequently encountering papers that “are not currently available online.” Can you imagine making decisions about investing your money in the stock market using similar processes? Instead, with the click of a button I can see all of the information about any stock, from how it performed over the last week, year, or decade, to its latest quarterly financial results as well as concise opinions from experts about its worthiness as an investment. Granted these experts are by no means perfect (as we've all learned over the last couple of months during the rollercoaster rides of the American stock markets).

Let me return to my analogy of training pilots. Long before a commercial

pilot is ever allowed to land a real plane with passengers on board, he or she has performed hundreds of simulated landings under both normal and emergency conditions — even experienced pilots are required to retrain on simulators on a regular basis. And when those pilots step into the cockpit they are aided by computerized systems that remind them in voice simulations if they forget to adjust the flaps or are descending too quickly. Would any of us suggest that the gravity and impact of our clinical decisions are less important than those of a commercial airline pilot?

Many of these same tools could and should be applied to modern medicine and science. Imagine if you will for a moment a world in which all patients carried with them a smart card that accessed a centralized and updated database with copies of all of their important medical information, problem lists, medications, allergies, and results of recent laboratory testing. Such records would be invaluable for facilitating the treatment of those patients at any hospital in the country or indeed in the world. They could also be used to standardize and automate medical billing. Perhaps most importantly such databases would be incredibly valuable resources for epidemiologic and genetic studies.

Integrated data bases containing medical textbook information on a wide range of diseases linked to relevant published scientific and clinical papers could be carried in a hand held device by all trainees and attending physicians and quickly consulted at the bedside. All orders and prescriptions could be entered on laptop or hand-held computers and automatically checked against databases of acceptable drug doses and drug interactions as well as patient-specific allergies. Such orders could even be checked for their medical appropriateness by intelligent programs containing optimized algorithms for diagnosis and treatment.

In order to widely disseminate the teaching of older master clinicians to younger trainees and to integrate the results of the latest clinical trials, students would learn from interactive software programs complete with audio and video demonstrations that

allowed them to care for simulated patients with a wide variety of disorders. Such simulators which are just beginning to be developed today might someday also be useful for updating and even assessing the medical knowledge of more senior clinicians.

Finally, from a basic scientific perspective, imagine having easy access to integrated databases that contained frequently updated information about genetic and biochemical changes in both normal and diseased cells in response to a wide variety of stimuli, that contained lists of all human disease related genes and the phenotypes of all known transgenic and knockout mice as well as the known three-dimensional structures of proteins. Such databases which again are starting to be developed in a piece meal fashion could be tightly integrated with medical and scientific journals all of which would be available entirely on line. The time from manuscript submission to publication could be shortened from months to weeks. In fact we already have a model of such a system in the OM1M database envisioned and created by one of our members, Victor McCusick. This fantastic accomplishment is a testament to the vision, creativity and determination of Dr. McCusick and his colleagues and should serve as a model for the development of additional linked genetic, clinical, and literature-derived biomedical and scientific software.

Is this vision of a digitally based science and medicine simply an unrealistic fantasy or is it achievable in the next 5-10 years? Two of the important components are already in place. First, the hardware needed to implement such a system has been available for several years and is only becoming more pow-

erful and less expensive. Secondly, the internet will clearly provide the networking backbone required for this effort. Three important components, however, are missing. First and most importantly, we need to write the integrated and standardized software that will allow us to manage this information in a user-friendly fashion. Writing such software will require not only sophisticated programmers but also a new breed of translational physician-scientists and bioinformatics experts who can help lead this effort. We must make plans to train such individuals for this exciting opportunity as soon as possible. Secondly, we need a new national consensus that supports this effort at the highest level of priority. In many ways this is the equivalent of the health-care space project. And, like the space project, it will be expensive. We need to educate our politicians and the public at large about the critical importance of this effort to the overall health care mission and to elicit public financial support for the project in such a way as to not drain resources from the support of basic science and technology efforts. Many health-care companies and insurers have already begun to develop sophisticated proprietary information systems. However, it is important that the public at large understand that leaving this task to commercial entities, as opposed to developing it in the public domain will probably not best serve the national interest.

Finally and perhaps most importantly, we as physician scientists need to lead the debate about many of the important ethical issues raised by such national medical and scientific databases. These include issues of privacy, informed consent, and potential commercialization of products developed with public health care information and funding. Safeguarding the privacy

of healthcare records is a mandatory component of any centralized data collection system. We must ensure that such records are not used by employers, insurers or others to discriminate against those with specific diseases. Although a seemingly difficult problem, this issue has been successfully dealt with by several countries including Denmark which has kept centralized health records on many of its citizens for more than 50 years without serious violations of confidentiality or privacy. Indeed it can be argued that our current system of insecure paper record keeping is far riskier than a single secure national database.

In closing, I would like to emphasize that the successful crossing of the medical-digital divide in many ways embodies the three major goals of our societies and of physician scientists more generally. As such it represents an exciting opportunity for physician scientists and academic medical centers more broadly. First, it will greatly facilitate scientific discovery and the translation of that discovery to the bedside. Secondly, it will both enhance the quality and reduce the costs of patient care, and in so doing may help rescue our academic medical centers from their current crises which are so damaging to our research and educational missions. And finally and perhaps most importantly it will transform the teaching of the next generation of physician scientists and clinicians. These are goals that we all share and value. We need to meet this challenge and opportunity with the same level of energy and creativity that we brought to the molecular revolution in medicine. Only by leading this effort can we be assured that its outcome will be consistent with the best interests of physician scientists, our patients, and the public at large.