



PRESIDENTIAL ADDRESS

by Nicholas L. Tilney, M. D.

The following is a transcript of the Presidential Address delivered by Doctor Nicholas Tilney, Thursday, May 30, 1996 at the annual ASTS meeting in Dallas, Texas.

It is a tremendous pleasure for me to address you as President of the American Society of Transplant Surgeons. I am well aware of the singular honor you have done me; I am delighted, humbled and appreciative.

This has been a dynamic year for our Society, for surgery, and for medicine in general. Since I have summarized much of our activities in my previous *Letters*, I won't repeat them. In addition, last year Mark Hardy told us in detail about the practical issues, problems and limitations facing our field.

This year I will indulge myself in discussing a subject of long-standing interest to me (and I hope, to others here); that of research in transplantation biology, about which this Society has much to be proud. Not only have we surgeons been the primary moving force behind the entire subject of organ transplantation, we have contributed importantly to knowledge about immunosuppression, organ storage, host allo-unresponsiveness, the multi-faceted physiology of rejection, xenografting and other related subjects.

Because of the career satisfaction in combining academic and clinical work that many of us here have experienced, I would like to mention 3 mentors who particularly influenced me in becoming an "academic surgeon." As Sir Arnold Klebs said in another context, "a scientist is not born—he has good teachers." It was my



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good fortune to enter the Peter Bent Brigham Hospital as a young resident in 1964.

During that period, I worked extensively with Joe Murray in renal transplantation, then only 3 or 4 years after the use of the first chemical immunosuppressive agent, 6-MP.

Those of us in the Transplant Unit were faced with a horrendous failure rate of both grafts and patients at 1 year. Indeed, it became clear to me that I was working in a complex clinical laboratory, the aims of which were to salvage individuals terminally ill from renal failure by the few means available, or if those means were not good enough (which they weren't), to invent new ones.

Thus, we went through a whole series of maneuvers in those days, none of which, in truth, worked particularly well. However, the occasional success (and there were some!) was striking and continued to stoke our collective enthusiasm toward subsequent ventures.

Francis D. Moore, M.D. was the Chief, very knowledgeable, very enthusiastic and very supportive. These men knew intimately both the clinical literature on the subject (such as it was) and the scientific literature, and were alert and receptive for new ideas in biology to bring directly to the bedside. In addition, there was a steady stream of notables in this new field coming through the Department to pique our imaginations, from Peter Medawar on down. And, as Frank Stuart mentioned in his Presidential Address a couple of years ago, the transplant laboratories at Harvard were populated with an astonishing array of surgical talent; all interested in this new science. Roy Calne had left, but had been replaced by Ross Sheil, Max Dubernard, Guy Alexandre, Gil Diethelm, Frank himself, Alan Birch (also a resident) and many others.

The Vietnam War was heating up and most of us residents were coming and going via the draft. Following my military service, I left for the first of 2 sessions with Professor James Gowans at the Sir William Dunn School of Pathology in Oxford, the foremost school of experimental pathology in the world at that time. My aim was to learn more about lymphocyte function, physiology and the role of these cells in allograft rejection, subjects about which I was becoming increasingly interested based on questions raised by patient problems.

Jim Gowans had received his MD in London and had returned to Oxford in 1953 after a year at the Pasteur Institute. He went to work as a young research fellow at the Dunn School, with its Di-

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rector, Howard Florey, a remarkable experimental pathologist who amongst many important studies on phagocytosis, arteriosclerosis and inflammation, had transformed penicillin from a laboratory curiosity into the most powerful agent yet available for treating bacterial infections. The laboratory in Oxford already had a background of investigations into lymphocyte activity, and as Gowans recently told me, Florey had suggested that he study this cell, introducing him to the subject with the statement that it had "blunted the wits of a number of his colleagues and he said he could see no reason why I should be spared a similar fate." A heavy challenge for a young research fellow!

However, by 1964, in a wonderful series of experiments using transferred radio-labelled thoracic duct lymphocytes, Gowans had convinced most people that an important population of long-lived small lymphocytes recirculate continuously between blood, the lymphoid organs, and lymph. These cells were shown within a few years to be thymus-derived T cells.

The 60's were an exciting time in immunology. It is worth noting that until only a few years before, the only property of the lymphocyte about which there was general agreement was that this cell was motile. An oft-quoted remark during that time came from Arnold Rich, Pathologist at Johns Hopkins, who stated rather hyperbolically "that complete ignorance of the function of this cell is one of the most humiliating and disgraceful gaps in all medical knowledge."

There was little in the literature to convince anyone that small lymphocytes had immunological function. Indeed, in his book *The Clonal Selection Theory of Acquired Immunity*, MacFarlane Burnett had written in 1959 that "an objective survey of the facts could well lead to the conclusion that there was no evidence of immunological activity in small lymphocytes".

However, ongoing work by several investigators, including Gowans himself, proved this cell to be critical in alloreactivity as well as in immunological tolerance. Recirculation was the body's means to disseminate the local antigenic message throughout the entire lymphoid system of the host, thus allowing him to marshal his entire repertoire of immunological defenses to destroy (or, depending on the circumstances, disregard) the foreign stimulus.

For a young surgeon without previous laboratory experience, working with a basic scientist like Gowans was a most instructive experience. The Dunn School was a large multi-center laboratory examining everything from macrophage physiology to cellular immunity to antibiotics; Florey and Chain's contributions to the production of penicillin had earned them the Nobel Prize in 1945; one of the other scientists, Abrams, had just discovered the antibiotic properties of the cephalosporins as I got there.

Gowans' smaller Cellular Immunology Research Unit was filled with Australians, Brits and occasional Yanks, all working on various aspects of that young science. I learned several important things from him: 1) how truly difficult creative research can be; 2) that intellectual honesty is paramount—before one presents or publishes one's findings, they must be checked and rechecked and rechecked again, often from different approaches; 3) the question one asked and attempted to answer must be clear, simple and definite. I think of this latter point not infrequently when some of the residents in our department present the fruits of their studies; these talented individuals have often worked with excellent scientists, using the most current techniques; however, when they show their highly complex data, I am sometimes not sure whether they really understand what the original question or premise was, much less the answer, or how their investigations fit into the overall picture.

My years with Gowans, coming in the middle of my residency, were intellectually my most exciting, a sentiment echoed

by many surgical residents with similar laboratory experiences I have spoken to subsequently. With this in mind, I am delighted to announce that there will now be two new "surgical scientist awards" available for our Society, one through the kindness of Roche and the intrigues of Mark Hardy; and one via a new relationship between the ASTS, the National Kidney Foundation and matching funds from Fujisawa, Ortho, and Sangstat. Particulars about these two-year, \$25,000/year scholarships, designed preferentially for residents in the midst of their surgical training, are currently in *The Chimera* and being advertized in *Transplantation*. Because they are two-year awards, they will be staggered; each will be awarded every other year. We hope that they may stimulate an interest in the science of transplantation, which may endure throughout the entire careers of those who have gained them. I would also here recognize the continuing generosity and loyalty of those companies who have supported other scholarships and efforts of our Society for so long—Sandoz, Ortho, Upjohn, Fujisawa, Sangstat, and Syntex-Hoffman LaRoche.

At this point, I would like to review the evolution of research funding in the United States and the importance of the surgeon within that system. To emphasize that adequate funding has always been a problem, one might recall a remark by Thomas Henry Huxley, given when he was President of the Royal Society of London in 1862. He called for improvement in the lot of science, but warned sharply that the pursuit of such goals could earn a man praise but not pudding. Those of us with some of our salaries on soft money and without excess pudding can certainly relate to that. Put another way, one might consider a couplet penned by the British essayist and poet, Hilaire Belloc: "I'm tired of love, I'm tired of rhyme, But money gives me pleasure, all of the time."

The scale, nature and funding of scientific laboratory efforts have changed substantially during this century. Initially, the institution itself paid for its own lab-

oratory efforts, either out of general funds or from endowments. Over the past decades, however, an increasingly large share of funding has come from the Federal Government. In 1993, for example, 63 of a total of 161 billion dollars spent on research and development in this country (c. 40%) came from this source. Of that, 25 billion went to Federal laboratories (of which there are more than 700) and 12 billion was allocated to universities. The federally-funded portion of all research performed at universities was 55%.

Early government involvement in science stemmed, in the latter half of the 19th century, from agricultural interests, initiating a relationship between government and universities which aimed to develop science for the benefit of society. Agricultural research actually remained the only sustained effort until the Second World War. Subsequently, many investigations were driven by considerations of national security; at the same time, public support for study of the natural and social sciences increased because of the promise for improving human health and comfort. Burgeoning government involvement in aeronautics, energy and space exploration created the National Science Foundation, and support for basic biologic science under the aegis of the National Institutes of Health was increased. Indeed, budgets for NIH grants grew by 500% during the 1950's. The Cold War provided even further emphasis for interactions between universities and the government. Between 1983 and 1987, for instance, the NIH budget grew at an inflation-adjusted rate of 7.1% per year. However, since the end of the Cold War and the dissolution of the Soviet Union and with downsizing of our defense priorities, increasing skepticism has not only extended to defense-related research (reasonably enough) but to other research endeavors as well.

As a result, between 1988 and 1993, the annual growth rate of the NIH budget fell to 2.4% per year (1.8% if research for AIDS is excluded). Basically, NIH budgets have remained relatively

static or declining in real dollars, although this year was, in fact, better, despite the ongoing battle of the budget. There are still some in Congress, thank goodness, who understand the importance of continued support for science.

The relationship between industry and the universities has clearly flourished over the past years, particularly as academic institutions have become such a highly-productive force in biomedical research. In fact, national growth revenues associated with products manufactured under licenses from all U.S. universities are about 9 billion dollars annually. University research, according to one estimate, has yielded 4 times as many patent applications per dollar as corporate research. As a result, corporate sponsorship of university-based research has been the fastest growing component of total research expenditures over recent years, increasing greater than 12% per year, and reaching 1.2 billion dollars in 1993. Such money, however, still cannot compensate for important Federal cutbacks. In addition, research via industrial funds is usually, by definition, product driven, unlike NIH funds which are designed for solving of basic questions in science initiated by individual investigators. And, as has been emphasized recently both by David Blumenthal and Steve Rosenberg in the NEJM, the growing relationship between universities and industries may pose great threats to the openness of scientific communication. There have been several recent examples of well-controlled data, unfavorable to a particular product, being suppressed or pulled from publication at the insistence of the sponsoring company. It is clear that profits must never interfere with truth.

A final and evolving variable in this discussion about research money is that income from practice plans, which used to be a potential source of start-up funds for young investigators or bridge money for those between grants, is now decreasing dramatically. As we are all too well aware, academic pursuits are currently being hit by a double whammy; diminished federal funding and reduced

payment from clinical practice.

That people are living longer and better than ever before (at least in developed countries) has been in no small part due to the flourishing of biomedical research. In surgery, for instance, the advances have been remarkable and have crossed the entire spectrum of the discipline. In addition, the needs of surgery have driven other sciences forward: pharmacology, immunology, cancer biology and biophysics are obvious examples. Indeed, our own specialty is a supreme example of all this, with its tradition of involved clinician-scientists investigating, defining and often creating multi-faceted treatments for organ failure.

Despite it all however, society has come to feel that it hasn't gotten its money's worth from research. Indeed, the public and elected officials seem increasingly impatient that all their ills cannot be cured, and that they can't attain eternal youth besides. The sustained public outcry that AIDS and breast cancer haven't been solved, despite huge amounts of money and effort expended, exemplify this mind set. Take the increasing funds spent on AIDS, for instance. Possibly discouraged by all these pressures, the fewer than 2% of all physicians in this country who continue to be biomedical scientists are decreasing steadily in number.

For many reasons, not the least of which are the practicalities of life (Huxley's "praise but no pudding" theme), surgeons in particular who spend so much time and effort training in and practicing their specialty must often leave their early investigative careers to go into full-time caregiving. Despite all this, however, transplant surgeons have remained pretty competitive in garnering research funds. Steve Rose of the NIH tells me that 60% of transplant-related grants are processed via the NAIAD, the remainder via diabetes and kidney disease, heart, lung and so on. The award rate is over 20%, holding relatively steady (it is up this year) and quite comparable to that of all first-time

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applicants in general. This is good and we should be reasonably pleased.

In contrast, it is distressing that when the initial awardees (overall) try for a 2nd or 3rd competing renewal, the overall success rate has fallen from c. 25% in 1973 to 11% in 1993. It is also interesting that the number of yearly applications made by MD investigators over age 46 has increased; however, those by investigators less than 36 years old has declined. Bernadette Healey summed this trend up by suggesting that "new physician scientists may have become an endangered species because they fail to compete rather than fail to succeed". Indeed, she stresses that those who fail to compete self-select themselves as unlikely to succeed. An additional corollary (and danger) to all this is that those who have been consistent and funded contributors for years may continue their productivity but without producing functional progeny. This is especially distressing when one considers that one of the strengths of the American biomedical effort (and it is virtually unique to this country) has been the emphasis on support for young people to give them the chance to test their ideas independently in the laboratory.

So here we are, the ASTS, a group of talented individuals privileged to be in a particularly intellectually demanding and rewarding specialty. The positive side remains very positive: a still relatively new and exciting subject with important continuing ramifications in other biosciences; a Nobel Prize; highly rec-

ognized, successful surgeon-scientists amongst our ranks, and fellowship-trained young people doing very well indeed. The negative side is somber, not only for our specialty, but for academic medicine in general. We all realize the problems facing every medical and surgical specialty: too much manpower, increasing micromanagement and reduced costs. The market may take care of manpower—indeed, some may have to change career plans and enter other areas. I have a feeling that the managers may decrease in number, smothering (one can't help fantasizing) on their mission and vision statements. The cost-containment issue is probably with us for some time to come; reduced clinical and research funding is adversely affecting every department of surgery in this country. Although many of the disruptive changes occurring in medicine at the present time are in the name of cost containment, one feels they are perhaps more to do with corporate greed, responsibility to stockholders and bloated executive salaries than with good patient care, teaching and research.

The ability to perform one's specialty may deteriorate in the face of primary care and capitation. Those specialists remaining may become even busier; indeed, important scientists are beginning to voice concern that the tremendous pressure for clinical services is precluding the time for scholarly reflection so necessary for the investigator. We all can relate to that. But, as Clyde Barker has suggested in a recent symposium on the impact of managed care on surgical education and research, new areas of study may well arise in our field which we cannot now easily visualize. Perhaps the critical in-

vestigations in our subject should be delegated specifically to those with a real talent for research (indeed, these may be the young individuals who gain the research fellowships that this Society and its pharmaceutical allies have provided).

It must be emphasized that surgeons as a species have been consistently able to rise to challenges and adversity. And as we see from the fruits of this and related meetings, they have continued to perform well despite often large debts incurred throughout a decade of clinical training, and increasing time constraints both in applying for funding and in performing research. Thus, it remains critical that a coterie of such individuals, many of whom are reading this, continue to assume leadership roles in research enterprises and/or close participation with colleagues in related fields. The increasing relationship between the ASTS and the ASTP, for instance, may be helpful in this regard. As surgeons, after all, we can contribute skills that other investigators cannot.

In conclusion, the evolution of organ and tissue transplantation remains an outstanding example of what Joe Murray calls the *oneness* of science; clinical problems solved in the laboratory. Pasteur noted that no category of science exists to which one could give the name of *applied science*. Science and the application of science are linked together (he said) as a fruit is to a tree that has borne it. I would predict that many of our current difficulties will eventually settle and the public will again begin to demand, expect and appreciate, as they once did, better scientific and medical solutions to their problems.



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criminal proceeding of the magnitude that we saw here, it seems to me has gone or did go beyond the bounds of common sense. . . ."

Thus ended 3 1/2 long and difficult years for Najarian and his family and the University of Minnesota surgery de-

partment. Through it all, Najarian continued to go to his office every day at the University, where he still sees patients, operates, and teaches residents and medical students. These are the things he loves, and this is where he has worked as an extraordinary surgeon for over 25 years. He says he will retire when he is tired. Who knows when that will be?

For now, Najarian looks forward to

August in Barcelona. There he will meet again with his many friends and colleagues from transplant centers around the world. Najarian's triumph only serves to distinguish him more as he goes to deliver his Presidential Address at the XVI International Congress of the Transplantation Society. Few have known such an arduous road to an honor so well deserved.

