

Clinical Investigation—On the Threshold of a Golden Era?

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Biomedical science is in an extraordinary period. The prospects for real accomplishment have rarely been so great. The future holds the promise of enormous progress and great excitement. In my own field, immunology, the introduction of three new techniques—monoclonal antibodies, gene cloning, and the cloning and long-term growth of immunocompetent cells—has had a revolutionary impact. Problems that have enticed scientists since the end of the last century, such as the genetic and molecular basis of antibody diversity, have been brought close to solution. Experiments that a few years ago we thought of as almost within the realm of science fiction, now lie within our ability to attack directly. Such revolutionary advances have occurred in virtually every one of the medical sciences. Moreover, these accomplishments have not been confined to fundamental biomedical science but have remarkably illuminated our understanding of human pathophysiology. We have every reason to believe that their impact on the treatment and prevention of human disease will be equally great.

Revolutionary periods in science, as in any field of human endeavor, often lead to changes in the organization of the field itself. Such changes affect not only our view of the shared paradigm of our field but also the human and social aspects of science. In the past biomedical science has encompassed a broad area to which individuals with very different training have made important contributions. Physicians have had a particularly important role to play, both because of their direct patient-related research and because their experience with the disordered function of disease states

has often provided the best clues to elucidating normal physiologic mechanisms. Indeed, much of the most fundamental work in many of the biomedical sciences has been carried out by individuals whose initial training was in medicine. I might again make reference to immunology where many of the United States investigators who have been leaders in the new technologies I referred to before have been M.D.'s. Of 28 immunologists who are members of the National Academy of Sciences, 18 are individuals whose initial degree was an M.D. from a United States medical school and three received M.D.'s from foreign schools. Two of three United States Nobel laureates in the field of immunology during the past decade have been trained in medicine—Gerald Edelman and Baruj Benacerraf.

Unfortunately, many of us have reason to be concerned that the degree of physician representation in science is changing. It is not so much that physician-scientists cannot adapt to the revolutionary new technologies of modern science; indeed, many of them have been involved in the development of these techniques as is clearly revealed by the statistics I have already cited and by the exciting papers presented at this meeting. Rather, the problem appears to lie, as most of you will certainly appreciate, in diminishing opportunities for young physicians to undertake the increasingly rigorous training necessary for a serious scientific career and, perhaps more importantly, in a change in their interest in doing so.

Of course, it can be argued that any decline in the number of physicians entering research careers might

have only limited effects on scientific progress and that the concerns I have expressed simply reflect the parochial distress of any group anxious to protect its position in the face of changing circumstance. I am certain that you will agree that we cannot accept that argument. Obviously, the process of clinical investigation, notwithstanding the remarkable contributions of our Ph.D. colleagues, will largely remain a field led by physicians. The entry of fewer physicians into research involving direct interaction with patients could disrupt the entire process through which progress in biomedical science is translated into new means of preventing and treating disease. Furthermore, a lack of the insights gained from the clinical investigator's experience with "experiments of nature" will slow or, at the very least, change the course of fundamental medical research. Thus, we have the paradoxical situation that at a time when the accomplishments and prospects for biomedical science are almost unprecedented, a potential shortage of physician-investigators may impose serious limitations on our ability to realize the full potential of these advances.

My concern with this problem is by no means unique. Presidents of the American Society for Clinical Investigation, the American Federation for Clinical Research, and the Association of American Physicians have considered the future of clinical research in presidential addresses with increasing frequency. However, the issue is of such critical importance that a re-examination of the problem is warranted. Indeed, the attitudes of the new administration toward the support of research and particularly research training give our concern on this point a special urgency.

Changing interests in career goals are always difficult to document but a variety of surveys have indicated that there has been a precipitous fall in the number of young physicians expressing a serious interest in careers in clinical and related sciences. Indeed, some have suggested that the number of young physicians who enter science may now be too low to maintain our current level of effort much less allow the exploitation of the striking new opportunities presented by progress in fundamental science. Although the accuracy of these estimates is open to question, virtually every physician-scientist with whom I have spoken would agree that medical students and house officers today are much less likely to have done serious research or to be contemplating a research career than those of us who trained 15 years ago.

The reasons given for this apparent change of interest are of three general types: first, a perception that today's students have fundamentally different goals and aspirations from those of the previous generation; second, a concern about the uncertainties of the academic life, with particular emphasis on instability of funding in research versus the substantial financial rewards avail-

able to practitioners of medicine; and, finally, the problem of the structure of medical curricula and training programs, and the rigidity of board requirements for certification which often influences a research-oriented individual to postpone scientific training until quite late in his career.

Our potential influence on each of these areas is, of course, very different. We as members of the clinical research community can do little to affect the overall goals of society or to change fundamental attitudes of medical students. It is possible that we could increase the potential interest of new groups of medical students in research careers by urging our colleagues on admission committees to make a special effort to see that research-oriented students make up a certain fraction of this class.

The differences in financial rewards of an academic, research-oriented career versus one totally or principally devoted to practice are determined by forces unlikely to change until a true excess in numbers of physicians is realized or until direct governmental action places limits upon them. In either case, our Society's actions are unlikely to lead to any major changes in this difference in remuneration nor is it clear that any action on our part would be appropriate.

The alternative possibility, that of making academic careers more attractive to students by making such careers more secure, also has serious difficulties. True security in a research career depends upon a tenured position carrying a "hard" salary, upon the virtual certainty of funding at a level that can support a reasonable research program, and upon relatively limited institutional responsibilities. The issue of tenured hard salaries is fundamentally associated with the finances of medical schools; in many instances, substantial income is derived from practice plans and, often, there is pressure upon a faculty member to contribute more time to this activity. In addition, grants are an increasingly important source of salary support. Thus, even for tenured faculty, salary support is by no means a simple matter. For nontenured faculty, these pressures are often considerably more acute. The recent cuts in training funds and the decisions of several NIH institutes to phase out research career development awards will have far reaching consequences.

Nonetheless, we must ask whether the nature of the current granting system is basically responsible for this instability. In particular, do physicians compete poorly in this system? Are study sections less willing to fund clinically related studies? Are physician-scientists at a disadvantage in comparison to their Ph.D. counterparts either because of a less rigorous preparation for science or because their clinical responsibilities make it more difficult for them to remain competitive? Although we cannot fully discount any of these possibilities, current figures indicate that new grant ap-

plications from M.D.'s and from Ph.D.'s are equally likely to be funded. Whether a legitimate case could be made for some advantage being given in the consideration for funding of clinical research projects submitted by physicians is far from clear.

The uncertainty of the funding of physician-scientists is mainly dictated by the uncertainty of all NIH funding. Indeed, the competitiveness of the grant system has been instrumental in the maintenance of the quality of NIH-supported research. Strong arguments can be made for helping the young investigator and for providing some type of assured support for truly distinguished scientists. However, as long as money is limited, and we can be quite certain that it will be limited for the foreseeable future, competitiveness and lack of financial security in scientific pursuits are facts of life. Yet, it is not only in clinical research but in all creative endeavors that such risk must be accepted. Indeed, it can be argued that the medical researcher and particularly the physician-scientist is among the most secure of those engaged in any type of research or scholarly activity.

Thus, I would conclude that attempting to reduce the degree of uncertainty for physician-scientists could only be accomplished by an increase in the overall level of funding of biomedical research in the United States. There is no doubt, however, that the current administration's goal of cuts in real dollar budgets for NIH-sponsored research will worsen, not improve, this problem. We need to make the point to our leaders that sensible investments of reasonable sums of money can make careers in clinical science more attractive to the current generation of students and house officers.

Even more serious than possible cuts in the research budget is the continuing assault on the training process by governmental groups either do not fully appreciate the nature and importance of training for clinical research or who have a fundamental philosophical objection to the use of federal funds for training of any type.

Each of us has a responsibility to make clear to our senators and representatives the special nature of training for clinical research and the great importance this training subserves. I am confident that emphasizing the unusual range of talents needed for a career in clinical research, the importance to the national goal of better health care in the future, and the fact that no private organization could undertake this critical responsibility will form the basis of a persuasive argument for expanding rather than cutting programs for the training of physicians involved in science. We need to stress that programs which provide continuing support during postdoctoral and early postfellowship years are particularly important.

There is one area of the complex problem of the

entry of young physicians into investigative careers in which we can have major influence. We must be certain that the training offered is excellent and, in particular, that it will prepare them for the research of the future, not that of the past. The issue of the quality of medical research training is ultimately related to the entire question of the structure of medical education and of board requirements.

When interviewing individuals for research associate positions at the National Institutes of Health, I commonly discover that the candidates have excellent undergraduate and medical school academic records, that they have superb letters of recommendation from the people who supervise their house staff work, and that they present their interest in a research career in a serious, apparently well thought-out and cogent manner. However, these same individuals, most of whom have completed three years of postmedical school training and are already 29 years old, lack any major scientific experience. One is concerned that someone who has not picked up a pipette until he is almost thirty is most likely to break it.

Furthermore, applicants for NIH associateships often represent a group that is willing to break out of the increasingly rigid tracking which normally leads residents to go directly into subspecialty programs, with the expectation that they can obtain the training necessary for subspecialty certification and can begin research training at the same time. In many instances, perhaps in a majority of cases, this reasonable desire on the part of the individual often leads to a choice that seriously compromises either his clinical or research training, most usually the latter. I cannot emphasize too strongly that training for research today is a rigorous and time-consuming task. Most fields of biomedical research require sophisticated technical skills. It is unlikely that a part-time experience of one or two years in a setting where fundamental research may not be the primary goal can provide the preparation needed for those who will be the future leaders of clinical investigation.

We, as advisors and mentors of the students and trainees who are oriented to research careers, must take the responsible and sometimes difficult position that training for research should be done in places where research and training are primary goals and which have demonstrated excellence in both these areas. Furthermore, such training is a lengthy process. Generally, a minimum of three years is required to equip an individual to undertake meaningful independent work of an important nature. I spent six years in postdoctoral training before establishing an independent laboratory. I suspect that many of you here today also had very extensive training.

As I have already noted, most medical students of today are less likely to do research during their student

days than was true in the past. There is, however, one highly selected group that does receive strong research experience in medical school. These are students enrolled in combined M.D., Ph.D. programs. The medical scientist training program, or MSTP, supports students to undertake both degrees, generally in seven years, with the Ph.D. work usually done during the middle of this period. Currently, there are more than 600 students enrolled in this program, supported by the National Institute of General Medical Sciences (NIGMS), and approximately 100 students will graduate per year if the program is maintained at its current level. Initial analysis by NIGMS, made available to me through the kindness of Dr. Vincent Price, suggests that these programs can be very effective in developing physician-investigators. A study of graduates who received M.D./Ph.D. degrees before 1974 from programs at Duke, Albert Einstein, and New York University reveals that 60–70% have established successful research careers. It is striking that even for this highly motivated group a return to a major research activity within three years of graduation from medical school was critical. Virtually all successful M.D./Ph.D. graduates who successfully established themselves in an investigative career had returned to serious research within that time.

Whether the M.D./Ph.D. program is the only or even the preferred route for future entrants into clinical research is far from certain. However, the message is loud and clear that research experience in medical school and serious research undertaken within three years of graduation, and sooner if possible, will be required to produce the young investigators our nation needs. Practically speaking, then, we need to make a research career interesting and exciting to students by involving them early and by maintaining the continued encouragement and counsel needed to keep their interest up and help them make difficult career decisions. We must do our utmost to see that they are not discouraged by rigid board certification requirements from seeking clinical or basic research opportunities. The current eligibility requirement of the American Board of Internal Medicine of three years of medical house staff experience should be modified for those who intend to undertake serious research training. Such individuals should be allowed great flexibility in choosing their third year, and a program that is largely or even completely research in nature should be acceptable for board eligibility requirements. I propose this because I believe we need to encourage physicians to undertake research training in the best possible setting. Limiting choices to institutions which may provide a modicum of clinical experience in addition to a research experience pro-

vides no real advantage and often excludes some of the very best training opportunities. Furthermore, I think it not unreasonable to suggest that for many young physician-scientists, subspecialty training could be done after completion of research training, in an on-the-job mode in which the individual has a junior faculty appointment.

Our actions then should be concentrated in those areas in which we have a reasonable likelihood of succeeding. These include strong personal support of interested students and house officers by faculty scientists, strong representation to certifying boards to recognize the need for flexibility in considering individuals who plan research careers, and, above all, concerted efforts to convince our legislators and our administration that governmental programs aimed at training physician-scientists need to be strengthened and extended rather than cut.

In the past, the American Society for Clinical Investigation has not regarded political action as one of its major concerns. Since we have an active membership of only 500, this is not surprising. The Society's current activities—holding an annual meeting, publishing *The Journal of Clinical Investigation*, and electing new members—fully consume its slender resources. Yet, we and our emeritus members, together with our colleagues in the AFCR and the AAP, constitute the group with the greatest appreciation of the importance of the clinical research process. It is clear that many of the problems that limit the entry of young physicians into clinical investigation can only be solved in political arenas. Although the resources of the ASCI alone may be insufficient to mount the type of effort needed to adequately represent us in the legislative process, the three societies acting together, as they do to hold these meetings, could provide a mechanism for a continuing involvement by a stable public affairs group representing the overall goals of clinical investigation. I believe the time has come for the societies to use the political process and to marshal their considerable prestige in such a joint venture. I believe that Anthony Fauci will consider approaches to influencing the political process in his AFCR Presidential Address tomorrow.

Modern biomedical research is in the midst of a golden era. Whether clinical investigation in the United States will continue to be included in this extraordinary progress will largely depend on whether our junior colleagues choose to enter research careers. If we do not recognize this and act to ensure it, who will? If we, individually and collectively, make a strong and compelling case, we can have every expectation that clinical research in America will continue to flourish.