COMMENTS

This editorial by Dr. Brewer presents a compelling analysis of the problems in clinical research and an interesting remedy, worthy of our support. We welcome replies and responses in what we hope will become a sounding board and debate on ways to improve academic medical research and education in the United States.

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Crises in Academic Medicine

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Significant attention is being paid to the decline in research involvement of physician-scientists (M.D.s primarily involved in research) in this country. For an excellent recent review, see the article on this subject in the FASEB Journal (1). In the FASEB review, which generally reports information between the 1970s and 1980s to 1997, data are provided to document the decline in all of the following: 1) Number and proportion of physicians listing research as a major professional activity with the AMA; 2) Number of M.D.s in basic science departments who are NIH grant holders; 3) Proportion of M.D.s in clinical science departments who are NIH grant holders; 4) Number of M.D.s who review grants for NIH; 5) Proportion of medical students who have strong research career interests; 6) Financial status of medical students with a great increase in debt of medical school graduates; 7) The number of younger M.D. NIH principal investigators; 8) Number of M.D. trainees in both individual and institutional training grants; and 9) The application rate of M.D.s for NIH grants, relative to the great increase in NIH funding and in Ph.D. application rates.

A little good news is mixed in with all this bad news in the FASEB report. There is the aforementioned increase in NIH funding, an increase in NIH K08 awards which offer mentored fellowships to M.D.s at a higher stipend than traditional fellowships, the continued success of the Medical Scientist Training Program (MSTP) which funds training toward concurrent M.D./Ph.D. degrees, and the information showing that M.D.s have a success rate comparable to Ph.D.s for NIH grant awards. The report points out, however, that the K08 awards do not nearly make up for the decline in M.D.s involved in training grants or individual fellowships, so that there is an overall decline in M.D.s receiving training to enter research careers. This is at a time when NIH support is increasing rapidly, and the explosion of knowledge in genetics and other fields requires more, not less, in the way of medical translational research.

The FASEB report suggests several remedies which focus on various ways of enhancing the choice of career and improving the careers of physician scientists. These latter run the gamut from better role models in medical school to debt-forgiveness programs. These are well thought out proposals and I support them. I think if they were experimented with and then adopted, they would go a long way towards mitigating the problem of not enough M.D.s involved in research.

However, I believe there are *two* crises in academic medicine (hence the plural in my title). These are: 1) The aforementioned decline in research involvement of physician-scientists; and 2) The decline in patient-oriented research (clinical research) by physicians. The remedies in the FASEB report will be very helpful to the first problem, but in my opinion they do not sufficiently address the second. For example, the report calls for expansion of the M.D./Ph.D. (MSTP) programs, but within the report, data are provided that at one major institution, 85% of MSTP graduates go into basic research while only 11% have careers with significant patient-oriented research. I think the experience elsewhere is similar. The MSTP program trains primarily "bench" scientists, not "bed" scientists or "bench-to-bed" scientists.

I'm *not* saying that M.D./Ph.D.s who do basic research are not an important component of the medical research and medical education enterprises. It is good to have researchers who have detailed knowledge of human biology and an informed perspective on the important questions in medi-

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cine doing basic research, especially if their research is related at some level to human disease. Similarly, it is very useful to have a certain number of basic science faculty with M.D.s or M.D./Ph.D.s, to provide a medical perspective in the early part of the medical school curriculum.

However, M.D./Ph.D.s who do basic science don't contribute to solving the second crisis, that of an inadequate supply of clinical investigators. For those who don't understand the difference in roles of basic scientists with an M.D. degree versus clinical investigators, think of it this way: If you are a basic scientist, would you want some doctor who sees patients all day long and has no research laboratory experience, carrying out an important enzyme purification or kinetic analysis? Or setting up a detailed gene cloning approach, even if it were a human gene important in disease causation? Or, taking it to the experience of everyone, repairing a TV set which has lost its picture? It is just as irrational to expect a basic scientist, even one with an M.D. degree, to carry out a detailed clinical investigation designed to answer important clinical questions, while protecting the rights and welfare of patients and subjects.

What are some of the clinical research projects for which the expertise of trained clinical investigators is required? Here it is important to dispel the notion that these projects are mostly handing out pills and making observations according to the protocols of pharmaceutical companies. I fear that this is the perception among most not familiar with clinical research. In research instigated by pharmaceutical companies, all the design, entrance and exclusion criteria, and what is required for efficacy and toxicity evaluations have been carefully and thoroughly thought out by the clinical research scientists at the company. The physicians at academic centers who are recruited by pharmaceutical companies to participate in this research need do little else than follow the research protocol and take care of their patients' clinical needs. Again, I'm *not* saying this isn't important work. I *am* saying it isn't the clinical research where the major new needs are arising.

These needs are great and increasing steadily. Let's begin with the needs in developing "orphan" therapies. Therapies are called orphan therapies if the population they subserve numbers less than 200,000 in the U.S. This is believed to be the cutoff point for U.S. pharmaceutical companies to justify spending research and development (R and D) funds. If the disease or disorder to be treated numbers less than that, pharmaceutical companies can't justify R&D resources to develop a therapy because the market for a successful product will not produce enough revenue to repay the investment and turn a reasonable profit. Diseases and disorders below this cutoff are called "orphans" because the pharmaceutical industry will not normally develop therapies for them.

Some might reason that if a disease is rare (less than 200,000 patients in the U.S.), maybe it isn't so important to develop a therapy for it, at least not as important as developing therapies for common diseases, which the pharmaceutical companies do work on. The problem with that reasoning is that there are a large number of orphan diseases, ranging in frequency from a few hundred patients to the 200,000 upper limit. The National Organization for Rare Diseases (NORD) estimates that there are at least 1,100 orphan diseases requiring therapy development. Looking at the current edition of Mendelian Inheritance in Man (2), which catalogues genetic diseases, 1,100 will no doubt prove to be an underestimate. If these disorders average 5,000 patients each, we're talking about 5,500,000 Americans with orphan diseases, all essentially excluded from development of therapies for their disease by pharmaceutical companies.

Development of orphan therapies requires clinical investigators trained and experienced in clinical research. If investigators at pharmaceutical companies won't do it, the only group of people capable of developing a therapy from idea to FDA approval are clinical investigators at academic and research institutions. I speak from experience. I have developed one orphan therapy through to FDA approval (3) and am in the process of developing a second (4).

The orphan therapy problem is going to become larger, not smaller. The reason is the explosion in genetic information. Disease causing genes are being identified and cloned at a rapid and increasing pace. For the most part, the genes being cloned are those that cause orphan diseases. Some of these diseases are very well known, but are nonetheless relatively rare and fit the orphan designation. They include sickle cell anemia, neurofibromatosis, Huntington's disease, amyotrophic lateral sclerosis (Lou Gehrig's disease), and one form of epilepsy, to name but a few. Each time a gene is cloned, the protein product is identified, and the biochemical function of the gene begins to be understood. This opens up the disease to new ideas for treatment, such as methods to restore function, or to inhibit negative consequences of the disease-causing mutation. The major resource for developing these ideas and acting upon them to develop a therapy (as well as improved diagnostic capability) is academic-based clinical investigators. We need an increasing supply of clinical investigators to exploit this new information. The current decline in numbers of clinical investigators, if allowed to continue, will doom patients with orphan diseases to a lack of effort in developing new therapies to help them.

Plus, the above discussion leaves out consideration of the ultimate promise of gene therapy. We all know that development of effective gene therapies has hit major road blocks. However, great efforts are being expended by the biomedical community to solve these technical problems, and there is little doubt, at least in my mind, that gene therapy technology will become a very useful way to treat many genetic diseases. Presumably basic science investigators will develop the basic technology of gene therapy. But then a host of clinical investigators will be required for the translation of this capability into meaningful treatment for each disease. Questions of efficacy, needs for retreatment,

and toxicity can only be answered by careful clinical research carried out by clinical investigators. When the log-jam breaks, and gene therapy becomes practical, the crisis in lack of an adequate number of clinical investigators will become especially obvious, and especially painful. We will have spent the resources to develop the knowledge and technology to help people with their diseases, but we haven't had the foresight to develop the clinical investigators to actually develop and establish the therapies.

So far I have emphasized therapy development, but there is much more to clinical investigation than developing new therapies. As one example, we need clinical investigators working with patients and disease processes to uncover new pathogenic mechanisms, such as environmental factors causing disease. Or to develop new procedures or approaches to mitigate disease and disease effects. These are but two examples of the multiple ways clinical investigators can move knowledge forward, and improve health care.

Clinical investigators are also important for educating medical students during their clinical years. Increasingly, clinical departments of medical schools are peopled by faculty who do little else than see patients. Such faculty can be very good teachers, but it is generally accepted that an important component of teaching medical students is the teaching carried out by those immersed in research on patients. They bring a questioning approach, a "show me the data" attitude that is very important to instill in doctors-to-be. I think both types of teachers are important, those with great clinical experience and practical know-how, and those that think about patients from a more scientific perspective. Now, however, the balance is shifting dramatically toward the former and away from the latter.

The remedies I propose include those already proposed in the FASEB report, but go beyond those to address the second crisis, that of an inadequate supply of clinical investigators. The centerpiece of my proposal is a Clinical Investigator Training Program (CITP). Modeled after the MSTP program, students would be recruited out of college who wish to make a career out of clinical investigation. The program would fund six years of training which would include medical school and two years of training in clinical research. Payback would be required if the student's plans change, and the student does not enter a career of clinical research. Space does not permit elaboration of details, but the program would be designed to recruit students who are initially motivated to do clinical research, and assist them through medical school and initial training, so that they can begin a relatively debt-free career. After a pilot period, the program should grow enough to meet the need.

Another important component of my proposal is putting clinical investigator role models in front of the CITP students (as well as other medical students). I agree with Dr. Daniel W. Foster, who said (5), while addressing the need for role models in clinical research, "Some of the best moments of my life have come from medicine, and I would not liked to have missed out on them," and "Physician scientists must become more visible (to medical students) and to convey the excitement of the discovery of new knowledge." My own experience verifies the lack of, and the need for, this kind of exposure of medical students to clinical investigator role models.

Other changes that I believe are necessary if we are to properly exploit the advances in information for the benefit of patients and medical education include new clinical investigator positions in clinical departments of medical schools. These faculty might be expected to pay a portion of their salaries from grants but they shouldn't be expected to pay more than a small component of their salaries from patient revenues, thus removing them from the current pressure to see more and more patients. Medical schools should expect these faculty to see patients as a means of generating new knowledge, not as a means of generating new income. The federal government should provide some funding for these positions, and the schools themselves should be willing to cover some of the costs. In the end, those medical centers with an excellent cadre of clinical investigators, and with a reputation for being on the cutting edge of medical care, will attract more than their share of patients.

Next, there must be grant programs to fund clinical research. It is a terrible design for NIH to mix clinical research grants in with basic science grants for review by the same study sections. Most of the current NIH study sections are appropriate only for reviewing basic science grants, period. The M.D.s who are on these study sections, and there are fewer and fewer, are generally basic scientists, and most, particularly the younger ones, have never done clinical research. We need grant programs to fund translational research—taking knowledge from the bench to the bed—where the reviewers are mostly people who have actually done this kind of work.

Finally, we must try to deal with one factor that I believe is at risk of becoming a serious disincentive to carrying out clinical research, and that is the Institutional Review Board, and the present governmental climate associated with research on human subjects. I found it an ironic juxtaposition that on one of the pages in Oncology Times (5) discussing the topic entitled, "Wanted and Needed: More Clinical Researchers with M.D. Degrees," was a sidebar entitled, "U.S. Issues New Protection for Human Subjects." Within that sidebar was the comment, "under the new rules, HHS will also pursue legislation to enable the FDA to levy civil monetary penalties for violations of informed consent and other required research practices—up to $250,000 per clinical investigator and up to $1 million per research institution." To me, those are chilling words.

Everyone agrees that over the years there have been patient abuses during clinical research (even by branches of the U.S. government!) and this occasionally happens even now, generally due to the negligence or carelessness of a clinical investigator. However, the vast majority of clinical investigators are highly ethical and want high ethical standards upheld, and appreciate the role of the IRB in protect-

ing patients and maintaining ethical standards. Therefore, we must be careful not to throw the baby out with the bath water when we go after a few miscreants. The reasons the above words are chilling is not because an experienced clinical investigator fears being fined $250,000. If one were to deliberately and seriously violate the rights of patients, that person deserves punishment. They are chilling first, because young clinical investigators may be inclined to believe that they can get into serious trouble almost by accident, perhaps by forgetting to do something, or saying the wrong thing. The climate conveyed by this crackdown and words like these can serve as serious disincentives to young clinical investigators, just at a time when the nation needs more of them. In cracking down on us old guys who should know better, the system must not frighten away young clinical investigators.

The second chilling effect this crackdown has is to make IRBs tighten up their procedures and to watch investigators more closely. This is good to the extent that it leads to better patient protection. It is bad if it creates unnecessary rigidities in the conducting of clinical research and unnecessary hassles in the lives of clinical investigators.

What is needed is a team approach. We all need each other and can benefit from each other. The government and the IRBs should take the approach that they want as many physicians to do clinical research as are competent to do so, and they will help clinical investigators make sure their research is ethical and safe for patients. This is actually the way the system works at present, but the perception is out there that it is growing more adversarial. That perception must be nipped in the bud because it can do great damage.

The programs I've outlined are not cheap nor can they be accomplished overnight. But then the tremendous success we've had in generating a mountain of biomedical information, an ever expanding mountain, hasn't been cheap, and it hasn't been accomplished overnight. It should be obvious our job is only half done. Humans, human taxpayers, paid for this wonderful mountain. We owe it to them to put our shoulders to the wheel and finish the job—translate this information into improving health care.

1. Zemlo TR, Garrison HH, Partridge NC, Ley TJ. The physician-scientist: Career issues and challenges at the year 2000. FASEB **14:**221–230, 2000.
2. McKusick VA. Mendelian inheritance in man: A catalog of human genes and genetic disorders, 12th edition. Baltimore; London: Johns Hopkins University Press, 1998.
3. Brewer GJ. Recognition, diagnosis and management of Wilson's disease. Proc Soc Exp Biol Med **223:**39–49, 2000.
4. Brewer GJ, Johnson V, Dick RD, Kluin KJ, Fink JK, Brunberg JA. Treatment of Wilson's disease with ammonium tetrathiomolybdate: II. Initial therapy in 33 neurologically affected patients and follow-up on zinc therapy. Arch Neur **53:**1017–1025, 1996.
5. Eastman PE. Wanted and needed: More clinical researchers with MD degrees. Oncology Times, pp 24–26, October, 2000.