The Conundrum of Clinical Research: Bridges, Linchpins, and Keystones

Gordon H. Williams, MD

Before the middle of this century, most advances in medical research were based on the principles of physiology. However, a presumed deficiency of this approach was the inability to answer fundamental questions as to how processes work at a cellular level. By the 1950s biochemistry, enzymology, and protein chemistry had developed to the extent that leading academic physicians believed that the future of medical research lay in using these disciplines and a reductionist approach to answer fundamental questions. Thus, the physician-scientist was reformulated as a physician who also was an expert in the reductionist sciences, such as biochemistry, protein chemistry, and enzymology (1,2). It was anticipated that a medical background and the knowledge gained from training in the basic sciences would lead to a more rapid progress in understanding fundamental processes of medicine. The National Institutes of Health (NIH) supported this approach with the development of the Medical Scientist Training Program (MSTP) in the mid 1960s to foster the simultaneous training of a physician and a scientist (the MD, PhD program). In addition to the increasingly reductionist approach to understanding medical and biologic processes, a second major change in medical research occurred in the last quarter of the century: the expansion of epidemiologic research and the advent of the clinical trial as a tool to answer important scientific questions.

During the past 20 years, both the physician-scientist and the clinical epidemiologist/clinical trialist have thrived. In the reductionist disciplines of molecular and cellular biology, extraordinary advances have been made. Equally impressive have been the increased understanding of populations that have come from expansion and refinement of the sciences of epidemiology, outcomes research, and clinical trials.

However, with these advances has come an unanticipated liability: the withering of the clinical investigator. Early warnings of this process were raised 15 to 20 years ago (3,4), and within the past 7 or 8 years the extent of this liability has become apparent (5–7). Like all good Monday morning quarterbacks, it is now easy to appreciate why the problem occurred. In the 1960s and 1970s it was assumed that physicians who also developed expertise in one of the fundamental sciences by obtaining a PhD degree would use their knowledge of the fundamental science to address problems in the clinical arena. In retrospect, this assumption was naive. The physician-scientists were being trained to be reductionists. The fundamental research approaches they were learning did not lend themselves to an understanding of human physiology or pathophysiology. As a consequence, physiology as a discipline atrophied. In many medical schools, it became extinct, as pointed out by Feinstein (8) in this issue of *The American Journal of Medicine.* Physiology does not readily lend itself to a reductionist approach. Indeed, by its very nature, it uses the tools of integration to understand complex processes. Thus, it would seem unlikely that scientists trained in a reductionist environment would develop research careers in the fields of human research. Rather, they would spend their time in the fields of the fundamental scientific laboratories in which they were trained, far removed from the bedside. This prophecy has been fulfilled, as very few graduates of the MD, PhD programs have careers in the clinical sciences.

The other end of the medical research spectrum also has contributed to the decline of the clinical investigator. The collection of data from large populations and the increasingly sophisticated statistical techniques to analyze these large databases have substantially changed the way public funding agencies and academic medical communities address medical questions. The large population-based studies have addressed many questions related to health and disease that appeared difficult to achieve by any other technique. Supplementing this approach was the randomized clinical trial: the gold standard of the "evidence-based medicine" group of investigators. The approach taken was to gather data from large populations and then to evaluate the approach to treating disease by comparing the efficacy of one agent with another for the treatment of a specific disease, assessing the clinical relevance of the results using clinical trial technology. The most valuable of these trials were those that used "hard" end points, such as death or significant disability. Neither the reductionist basic scientist nor the evidence-based scientist required or used physiology as a major discipline within their thought processes. In many circumstances, both groups had come to the conclusion that physiologic-based studies were too difficult or too fraught with errors and, therefore, not sufficiently rigorous to answer the types of scientific questions that

Am J Med. 1999;107:522–524.

From the Harvard Medical School, Brigham and Women's Hospital, Boston, Massachusetts.

Requests for reprints should be addressed to Gordon H. Williams, MD, Endocrinology-Hypertension Division, Harvard Medical School, Brigham & Women's Hospital, 221 Longwood Avenue, Boston, Massachusetts 02115-5617.

0002-9343/99/$–see front matter
PII S0002-9343(99)00303-4

needed to be addressed. This thinking appeared to extend from whole animal to human physiologic or pathophysiologic studies.

During the past decade, however, it has become increasingly evident that clinically relevant progress in medical research at the cellular/molecular or population levels cannot long exist in the absence of science that is based on organ and organism physiology (9). Integration of both ends of the medical research spectrum is the critical step that needs to be taken. From the reductionist camp it became clear that the number of paths that one could travel in terms of cell or gene physiology was far too many, particularly when it was likely that relatively few would be important to understanding human diseases. Which ones were important, however, could not be determined in a reductionist environment. Similarly, the population-based studies often did not give precise enough answers for the individual patient.

What began as a slow trickle of concern in the late 1970s and early 1980s has become a torrent during the past 5 to 6 years (5–7). Nearly all now agree that there are substantial training, research funding, and career development deficiencies in patient-oriented research. Several steps have been taken at the NIH to correct these problems, including redesigning the review of clinical research grant applications, the development of a specific training program for clinical investigators (the K30 program), and specific salary awards for clinical investigators (K23, K24 programs).

One can divide medical research into three fundamental disciplines (Table): population-, patient-, and laboratory-based. At one level one can assume all these disciplines are clinical research. However, as pointed out by Feinstein and as suggested by other authors, the weak link in our current medical research establishment lies at the level of physiology and pathophysiology, either in studies of humans or whole animals and organs (shaded area in Table). Feinstein has rightly noted that a critical change in our educational approach will be necessary to repair this deficit. What if we do nothing? Plausible but extreme consequences were provided by Varki (9) in his 1999 American Society of Clinical Investigation Presidential address. While it is unlikely, given the changes that have been made, that the dire circumstances outlined in his "Nerfiex Commission Report" will actually occur, it is certain that substantial additional steps will be required to restore the balance in our medical research establishment. As important as changes in programs and funding goals are, there also needs to be a fundamental change in the medical scientific community's assessment of each other's worth, as well as a targeted approach to addressing the primary deficit in the physiology component of our education and research endeavors. There have been several promising signs that

Table. Structure of Biomedical Research Enterprise

	Population-oriented		Patient-oriented			Bench-oriented	
Approach	Outcomes Research	Clinical Epidemiology	Clinical Trials	Clinical Pharmacology	Human Physiology, Pathophysiology, and Genetics	Animal Models	Cellular and Molecular Biology
Material	Databases		Individual Patients			Animals	Cells
Specialized Infrastructure	Computer Facility		Clinical Trials Center		Clinical Research Center	Transgenic Facility	Laboratory
Training Program	Masters in Public Health		Masters in Clinical Science			PhD	

institutions are addressing these problems. To put these efforts in perspective, however, there are only two newly created clinical research review committees at the NIH, while a 1996 report suggested that there will need to be 5 to 10 times that number (10). The K30 clinical training programs, while providing funding for clinical research at more than 30 institutions, provide, on average, funding at a level one fifth to one tenth of that provided by the MSTP program preparing individuals for MD, PhDs in the reductionist sciences. Promotions committees at most academic institutions, particularly the intensive research institutions, still evaluate promotion of clinical scientists using the same criteria that are used in evaluating bench scientists. The fundamental discrepancy between the loan burden of scientists involved in bench compared with clinical research has not been resolved. Finally, a major return to integrationist physiology-based training at our medical schools has yet to be achieved. While each of these issues has their individual champions, it is likely success will occur only when an integrationist approach to all issues is used.

REFERENCES

1. Thorn GW. A department of medicine, 1963–1973. *NEJM.* 1964; 270:2816.
2. Hollenberg CH. Training of the physician scientist. *Can Med Assoc J.* 1969;100:6035.
3. Wyngaarden JB. The clinical investigator as an endangered species. *NEJM.* 1979;301:1254–1259.
4. Kelly WN. Personnel needed for clinical research: role of the clinical investigator. *Clin Res.* 1985;33:100–104.
5. Ahrens EH. *The Crisis in Clinical Research: Overcoming Institutional Obstacles.* New York and Oxford: Oxford University Press; 1992.
6. Kelly WN, Randolph MA, eds. *Careers in Clinical Research: Obstacles and Opportunities.* Washington, DC: National Academy Press; 1994.
7. Williams GH, Wara DW, Carbone P. Funding for patient-oriented research. Critical strain on a fundamental linchpin. *JAMA.* 1997; 278:227–231.
8. Feinstein AR. Basic biomedical science and the destruction of the pathophysiologic bridge from bench to bedside. *Am J Med.* 1999; 107:461–467.
9. Varki A. Executive summary of the Nerfiex Commission report. *J Clin Invest.* 1999;104:S1–10.
10. Clinical Research Study Group. An analysis of the review of patient-oriented research (POR) grant applications by the division of research grants. Bethesda, Md: National Institutes of Health; 1994.