Translation of Basic Research into Useful Treatments: How Often Does It Occur?

William F. Crowley, Jr, MD

The article by Contopoulos-Ioannidis et al. (1) in this issue of the *Journal* addresses a much-discussed but rarely quantified issue: the frequency with which basic research findings translate into clinical utility. The authors performed an algorithmic computer search of all articles published in six leading basic science journals (*Nature, Cell, Science,* the *Journal of Biological Chemistry,* the *Journal of Clinical Investigation,* the *Journal Experimental Medicine*) from 1979 to 1983. Of the 25,000 articles searched, about 500 (2%) contained some potential claim to future applicability in humans, about 100 (0.4%) resulted in a clinical trial, and, according to the authors, only 1 (0.004%) led to the development of a clinically useful class of drugs (angiotensin-converting enzyme inhibitors) in the 30 years following their publication of the basic science finding. They also found that the presence of industrial support increased the likelihood of translating a basic finding into a clinical trial by eightfold.

Retrospective studies are often plagued by methodological concerns, such as the thoroughness of the algorithm, the completeness of the follow-up search, and the extrapolation and representative nature of the findings from these journals. These concerns are particularly appropriate for this article, especially because the algorithm used failed to unearth several key articles related to the cloning of growth hormone and cytokines. Not only did their algorithm miss these articles in the very journals they searched, but the proteins described therein have led to successful clinical trials and the subsequent development of therapeutic agents (2–4). Still, regardless of the study's limitations, and even if the authors were to underestimate the frequency of successful translation into clinical use by 10-fold, their findings strongly suggest that, as most observers suspected, the transfer rate of basic research into clinical use is very low.

It is important to recall that one of the attractive features of curiosity-driven research to many investigators is the unpredictability of its applications to any given field and hence its exciting potential to steer investigation in new directions. There are many examples of important solutions to clinical problems that have emerged from basic inquiries that could never have been predicted at their outset. Recent notable examples include the successful treatment of leukemia, which emerged from seemingly unrelated basic inquiries into the structure of a family of intracellular protein kinases (5,6); the use of bisphosphonates (originally used to dissolve boiler crud) and parathyroid hormone as powerful antiosteoporosis agents (7,8); and the Human Genome Project, whose applicability will be widespread, even beyond the initial expectations (9,10). Given this intrinsic unpredictability of how and when basic research becomes ready for clinical utility, a considerable breadth of basic research must be in place to sustain a robust program of bench-to-bedside transfer. Hence, use of the data by Contopoulos-Ioannidis et al. to limit basic research or prematurely mandate its clinical outcomes must be tempered by recognition of the often-meandering path and unpredictable outcomes of basic investigation.

As noted by the authors, sustaining a vigorous rate of transfer of basic findings into clinical application requires a stable and well-trained cadre of 'translational' investigators to patrol the borders of the basic/clinical interface. These investigators need to be recruited, educated, and continuously brought up-to-date in scientific techniques. The traditional 'translational block' occurring at this bench-to-bedside interface exists in part because of the attrition of such clinical investigators from academic health centers, a phenomenon addressed in previous reports from the Institute of Medicine (11,12). There are several reasons for this current dearth of translational investigators. The bench-to-human interface involves a dynamic agenda of scientific techniques. During the past decade, these techniques have varied from cellular and molecular biology, to genetics and genomics, to bioinformatics and proteomics. These tools that permit new basic truths to surface and that signal their readiness for transfer to human use are ever changing. Therefore, an equally dynamic educational training program must be devised that operates with similar flexibility at this critical interface if investigators are to continue translating new truths into clinical utility, and this has generally not been put together as a coherent educational program. Finally, such investigators have a traditionally short academic "half-life." Already late entrants into the research arena, clinical investigators are often early departures for other jobs such as departmental chairs, deans, or industrial positions. Their ability to talk many languages from basic research to clinical parlance to operational linguistics, all gleaned from their ability to survive and succeed in aca-

Am J Med. 2003;114:503–505.
From the Reproductive Endocrine Unit & Clinical Research Program, Massachusetts General Hospital, Boston, Massachusetts.

Requests for reprints should be addressed to William F. Crowley, Jr, MD, Reproductive Endocrine Unit/Clinical Research Program, Massachusetts General Hospital, 55 Fruit Street, Bartlett Hall Extension Room 511, Boston, Massachusetts 02114, or crowley.william@mgh.harvard.edu.

0002-9343/03/$–see front matter
doi:10.1016/S0002-9343(03)00119-0

demia, are much sought after in many arenas. The combination of all of these factors has led to a certain depletion of their ranks at precisely the moment when the environment needs them most.

Most clinical investigators acknowledge at least three subspecies to the genus "*Clinicus investigatorus*": translational researchers, clinical trialists, and outcomes/epidemiology researchers. Planning and sustaining an appropriately dynamic educational program for the translational investigators represents a real challenge to medical educators. Educational programs required by clinical trialists and outcomes/epidemiology researchers focus on questions that generally arise much later in the translation process, and can thus be planned with greater predictability. Consequently, there are several successful educational programs at leading academic centers with distinguished track records in training national leaders, but few that can claim similar success in educating translational investigators.

The interface between basic and clinical research also requires establishing and sustaining partnerships between bench scientists and translational clinical investigators, which are key to long-term success. However, our current academic systems are laden with disincentives to such mutually beneficial collaborations. Recognition and promotions at academic health centers, the virtually exclusive sites of translational research, and funding at the National Institutes of Health, are governed by an older, basic science model of success that focuses on individual independence and the emergence of intellectual leadership by a single investigator. However, many of the most challenging scientific opportunities in the future will be characterized to a much greater extent by teams, interdisciplinary studies, and group dynamics (13). For example, the searches for causes of polygenic disorders will require the combination of quantitative phenotyping of larger populations, bioinformatics, population-based genetics, and innovative statistics. This ensemble of skills is well beyond the capabilities of any single investigator. Clinical investigators who are capable of assembling and sustaining teams constituted from such diverse disciplines are likely to reap the richest rewards in the future. Currently, there are no systems to acknowledge, reward, or encourage these types of collaborations. Our academic systems, rather than being the leaders in this area, have positioned themselves such that they will now have to adapt post factum as these successful new models emerge. Conversely, industry, which understands the basic-clinical research interface and which has developed a well-structured reward system to encourage such collaborative endeavors, could emerge as the preferred site for such groundbreaking studies (12).

Finally, the authors discuss another problem regarding the basic science–clinical application interface. In their study, a strong prognostic marker of the successful translation of basic research into clinical trials was active involvement and support by industry for academic investigators. Academic health centers improve public health in two fundamental ways: conducting research and caring for patients. Industry develops drugs from basic insights derived from several sources, including academic centers, and they deliver these therapeutic innovations to patients in a market-based context. Academia and industry need each other to effect substantive improvements in health. Without substantive collaborations between the two, maximum advances in health care for the U.S. public are unlikely. Nonetheless, there are few examples of long-term, comfortable relationships between these two forces in health care. Perhaps the observations by Contopoulos-Ioannidis et al. may be used to develop better mechanisms that focus on the mutual opportunities instead of the obstacles between academia and industry. If developing a smooth interface between our well-phenotyped patient populations and our drug discovery efforts has ever been important, entry into the 'polygenic phase' of the genome era should reinforce this mutual need to redress the academic-industrial divide and prompt us to develop more effective collaborative models in the near future. The public assumes that the various components of the biomedical-industrial complex are working together harmoniously to help understand diseases and develop new therapies. They deserve nothing less.

REFERENCES

1. Contopoulos-Ioannidis DG, Ntzani EE, Ioannidis JPA. Translation of highly promising basic science research into clinical applications. *Am J Med.* 2003;114:477–484.
2. Goeddel DV, Heyneker HL, Hozumi T, et al. Direct expression in *Escherichia coli* of a DNA sequence coding for human growth hormone. *Nature.* 1979;281:544–548.
3. Goeddel DV, Leung DW, Dull TJ, et al. The structure of eight distinct cloned human leukocyte interferon cDNAs. *Nature.* 1981;290:20–26.
4. Goeddel DV, Ylverton E, Ullrich A, et al. Human leukocyte interferon produced by *E. coli* is biologically active. 1980;287:411–441.
5. Druker BJ, Talpaz M, Resta D, et al. Efficacy and safety of a specific inhibitor of the Bcr-Abl tyrosine kinase in chronic myeloid leukemia. *N Engl J Med.* 2001;344:1031–1037.
6. Druker BJ, Sawyers CL, Kantarjian H, et al. Activity of a specific inhibitor of the Bcr-Abl tyrosine kinase in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the Philadelphia chromosome. *N Engl J Med.* 2001;344:1038–1042.
7. Black DM, Cummings SR, Karpf DB, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. *Lancet.* 1996;348:1535–1541.
8. Neer RM, Arnaud CD, Zanchetta JR, et al. Recombinant human PTH (1-34) fragment [rhPTH] reduces the risk of spine and non-spine fractures in post-menopausal osteoporosis. *N Engl J Med.* 2001;344:1434–1441.
9. Venter JC, Adams MD, Myers EW, et al. The sequence of the human genome. *Science.* 2001;291:1304–1351.

10. International Human Genome Sequencing Consortium. Initial sequencing and analysis of the human genome. *Nature.* 2001;409: 860–921.
11. Kelley WN, Randolph MA, eds. *Careers in Clinical Research: Obstacles and Opportunities.* Washington, D.C.: National Academy Press; 1994.
12. Sung NS, Crowley WF Jr, Genel M, et al. Central challenges facing the national clinical research enterprise. *JAMA.* 2003;289:1278–1287.
13. Nathan DG. Careers in translational clinical research—historical perspectives, future challenges. *JAMA.* 2002;287:2424–2427.