Patient-Oriented Research: Principles and New Approaches to Training

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Remarkable advances in modern biology have enhanced our understanding of disease, permitting us to define—and potentially to treat—illness at the cellular and molecular level. The challenge we now face as physicians and physician-scientists is ensuring that these advances find expression in clinical practice. Thus far, the distance from the bench to the bedside has been surprisingly difficult to span, reflecting the need to develop broader, more integrative approaches to understanding how component molecules and physiologic systems function in the context of the whole person. Although there appears to be a consensus about the need to pursue such integrative, patient-oriented research, a mechanism for training future investigators in this discipline is less well established. In this essay, we present and develop the rationale for a set of underlying principles for patient-oriented research that can be used to guide appropriate training in this field. We also describe briefly a recently established prototype program—the Harvard initiative in Patient-Associated Science: Training, Education, Understanding, and Research (PASTEUR)—that we hope will help cultivate patient-oriented investigators and catalyze the evolution of patient-oriented research into a fully realized academic discipline. **Am J Med. 2000;109:136–140.** ©2000 by Excerpta Medica, Inc.

Despite a growing concern within the academic community about the decrease in physicians interested in biomedical research careers (1), we are impressed that the progress of modern biology is, in fact, stimulating more students than ever before to seek training as physician-scientists. The ability to characterize fundamental cellular processes has led to major advances in disease pathophysiology and has intensified interest in bringing molecular advances into the clinic. Yet the distance from the bench to the bedside has proved surprisingly difficult to span, reflecting the need to develop broader, more integrative approaches to understanding how component molecules and physiologic systems function in the context of the whole person. Whether this type of investigation is designated "clinical," "translational," "physiologic," or "patient-oriented" (the term we prefer), the underlying proposition seems clear, and perhaps even embarrassingly self-evident: the focus of this research is the patient in front of us.

Although there appears to be widespread agreement about the need for such integrative, patient-oriented research (2–15), the mechanism for training investigators to carry out such research is far from obvious. In this essay, we present and develop the rationale for a set of underlying principles for patient-oriented research that can be used to guide appropriate training in this discipline. We also briefly describe a pilot program—the Harvard initiative in Patient-Associated Science: Training, Education, Understanding, and Research (PASTEUR)—that we hope will help facilitate the development of patient-oriented research into a fully realized academic discipline. We offer these principles and program as a "template-in-progress," and hope that they will encourage further participation in this important ongoing dialogue.

PRINCIPLES OF PATIENT-ORIENTED RESEARCH

Principle One: The Patient Is the Focus

First, and most important, the focus of patient-oriented research is explicitly on the patient, and how to better understand the expression of disease within the person as a whole. To paraphrase Peabody (16), the secret to the study of the patient is in studying the patient. In contrast to research centered exclusively on what Haldane called "scraps and fragments" of people (2), patient-oriented research seeks not only to delineate component parts, but also to develop an understanding of how these different elements function together and are integrated in our patients.

Principle Two: The Patient and Physician Are Equal Partners and Share Responsibility

Patient-oriented research is not an emotionally detached academic exercise, but an intimate learning process, carried out in full partnership with the patient. We embrace the criteria of Goldstein and Brown [10] for patient-oriented research—that the patient and investigator shake hands at some point during the study—and the definition of clinical research, offered by Shulman and Varmus (8), as "research performed by a scientist and a human subject working together, both being warm and alive."

Forming this partnership will require both physicians

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and patients to modify their traditional roles. For physician-investigators, it will require the acknowledgment of ignorance: the ability to say to patients, "there are many aspects of your illness that we do not understand, but with you, we would like to learn more about." As this mutual exploration develops, the clinician-scientist must also be willing to allow more complexity and uncertainty than has typically been present in our thinking as reductionist investigators. For patients, the new partnership will require a recognition of the importance of research in understanding their conditions, and acceptance of the limitations of the physician's knowledge

Patients often distrust physicians and fear being used as guinea pigs, while physicians regret their patients' suspicion. But patients and physicians share the same goal: a better understanding of the disease in question and the development of improved treatment. It is thus imperative for physicians to regain their patients' trust and to demonstrate through their actions that participation in a clinical study is not the downside of admission to an academic medical center, but one of the attractions—the opportunity to be examined thoughtfully and studied carefully as an empowered, respected, and well-informed partner.

Principle Three: The Building Blocks of Contemporary Biology Are Tools in Developing an Integrative Understanding of the Patient and the Disease

Patient-oriented research accepts as its challenge both the need to understand the molecular basis of disease and the obligation to employ this knowledge in the care and treatment of patients. The ascendancy of molecular biology has transported the study of disease pathogenesis beyond the limits of broad, phenomenologic categorization into the more precise—and more useful—realm of molecular definition. Increasingly, studies of what initially appeared to be homogeneous disease entities have yielded remarkable assortments of genetic defects. Even when a single causative gene has been identified, such as in cystic fibrosis, the cellular pathophysiology often appears to be strongly influenced by the exact nature of the responsible mutation, findings with important implications for the development of treatments. Our progressive recognition of the importance of genetic variability on disease expression has given us the opportunity and the obligation to fashion treatments individually, guided by an unprecedented appreciation of the underlying biology.

However, although the reductionist paradigm that informs most contemporary biomedical research has facilitated the design and execution of elegant, well-controlled experiments, generalizing from these results to whole-body systems remains a challenge. Consequently, we must now determine how to incorporate molecular knowledge into a more expansive, integrative vision. We need to learn how to use the building blocks of contemporary biology as tools to understand patients and their disease. Particularly as we prepare to enter the postgenomic era, patient-oriented investigators will need to understand the basics of molecular biology to be able to frame questions in the most meaningful and effective fashion.

One prominent example of the increasing importance of molecular reagents in patient-oriented research is the explosion of interest in "surrogate markers," early prognostic signs that may be of great value not only to patients and their physicians, but also to investigators trying to understand disease pathogenesis, as well as to industry, whose ability to assess potential new therapies would be accelerated by the rapid evaluation of clinical response.

Principle Four: The Goal of Training Is to Teach an Intellectual Approach, Not Merely a Body of Knowledge, and to Empower Students (and Ultimately Physicians) to Ask Questions

The practice of medicine is more than the compassionate application of received wisdom; it is also the challenging of traditional dogma and the development of original insights. Placing renewed emphasis on the role of the clinician as investigator will help redefine the role of clinicians from "providers," whose goal is to assimilate and apply thoughtfully a given set of information, into physician-scientists, who routinely question old customs and actively explore opportunities to gain additional knowledge.

Many clinicians feel disempowered and believe that they have little to offer scientifically in the care and treatment of patients. One contributing factor may be the pervasive belief that to address a medical question meaningfully, one must either be in a laboratory, focusing exclusively on cells, gels, and DNA, or be conducting a large, elaborate, multicenter clinical trial. Either way, the result is to deemphasize both the primacy of the patient and the scientific value of clinicians' insights. This is particularly unfortunate, as the rate-limiting step in disease treatment is arguably not the shortage of bench researchers nor the shortage of large clinical trials. Rather, as Flowers and Melmon (17) have eloquently argued, it is the absence of a "clinical champion," a passionate clinician who has the skills to make relevant clinical observations as well as the technical background to frame the correct scientific question and seek (often through collaboration with dedicated bench researchers) a satisfying resolution.

The clinician is thus uniquely empowered to make a difference; the challenge is how to train this sort of clinician. Much of the knowledge base required of such a clinical-investigator is already taught in medical school, and much of what is not taught there can be provided through a program of additional courses (in areas such as principles of study design, and the methods and logic of trans-

lational research) and mentored research experiences. The greater challenge is to modify not the content of the medical school curriculum, but rather its purpose. We must reconsider the way in which medical students are taught to use the knowledge they learn, and aim to teach them not simply a vast quantity of information but an approach to knowledge acquisition.

As early as 1980, Eichna (18) described the medical school curriculum as "overstuffed," leaving the student with "no time to think, to wonder—just time to memorize facts" to pass a succession of competency examinations. In 1992, Ahrens (2) deplored the "boredom of rote learning" in medical school, adding that "our educational factories are turning out standardized, assembly-line products—men and women who are extremely well informed but not necessarily curious, imaginative, literate, or articulate." More generally, the concern is that in contemporary medicine we have created a culture that often seems to substitute recall for reflection, information for intelligence.

In graduate school, the goal is to teach students how to develop and frame scientifically meaningful questions; the role models are not the professors who have memorized the most information, but those who ask the most thoughtful, penetrating, and imaginative questions. We must incorporate elements of this culture into our medical education, and develop in students the ability to manipulate vast quantities of information and to ask clinically meaningful, physiologically-informed questions. Although the ability to think creatively and to ask useful clinical questions is admittedly difficult to evaluate and test in a standardized fashion, that must not stop us from attempting to cultivate such skills in our students.

Training in patient-oriented investigation, like training in biology and chemistry, is an evolving process. Medical schools should identify a group of patient-oriented investigators who can serve as models and mentors to students. From their first day of classes, medical students should begin hearing about—and from—these investigators. The preclinical curriculum should encourage students not only to accumulate information, but also to learn an intellectual approach that can be applied to daily clinical practice. The preclinical courses should also highlight the achievements of clinical research, point out important questions that demand resolution, and emphasize how much is not yet known.

During the clinical years, the questions asked on ward rounds should go beyond the usual recollection of facts ("What are seven causes of atrial fibrillation?" "What are the Ranson criteria?"), and should incorporate questions of mechanism and investigative approach, such as "Why might infection have led to atrial fibrillation in this patient, and how would you study this?" or "Why should this patient with pancreatitis have hyperglycemia, and how could this theory be tested?" Although it may be more comfortable to stick with questions of fact, for which there are arguably preexisting "correct" answers, such an approach ultimately does a great disservice to students and to patients.

Principle Five: Patient-Oriented Research Represents a Discrete Academic Discipline

While the basic research conducted in today's academic medical centers is informed by the standards, expectations, and paradigms of contemporary biology, the great progress that has been made in patient-oriented research is in large measure a tribute to the imagination and persistence of its practitioners, who often had to cobble together educational and research programs for themselves. Indeed, a unifying theme in the experience of today's patient-oriented investigators is the individuality of their paths en route to a shared destination. The evolution of patient-oriented research into a viable academic discipline would provide a home for students and investigators interested in its unique questions and methods. The recently established Association for Patient-Oriented Research represents an important step in this direction (15). We envision formal graduate programs in patient-oriented research, where interested students will acquire the broad perspective, fundamental skills, and ongoing mentoring necessary to develop and pursue vigorously a defined research interest within clinical investigation. The discipline is also expected to draw upon the resources and experiences of the pharmaceutical and biotechnology industries. Close collaboration between industry and patient-oriented investigators will help familiarize industry scientists, academic physicians, and students with an expansive range of investigational strategies and facilitate the identification of promising research opportunities.

Vitalized by the presence of physicians and scientists from both academia and industry who are passionate about the questions that clinical investigation proposes to address, patient-oriented research will reemerge as an academic discipline. It should provide an intellectual framework for translating advances in basic science into developments in medical therapy and enlarging the range of conceptual approaches to which students interested in biomedical research are exposed.

THE HARVARD PASTEUR INITIATIVE

The translation of the five principles of patient-oriented investigation into practice will require the thoughtful integration of a broad curriculum with a range of mentored research experiences, as well as an institutional structure that recognizes, values, and encourages patient-oriented investigation. In effort to explore how future patient-oriented researchers might be trained, and to begin to define

the core competencies that these investigators will require, we initiated the Harvard program in Patient-Associated Science: Training, Education, Understanding, and Research (PASTEUR). (Additional information regarding the PASTEUR program can be found at: http://www.hmspasteur.org.) The PASTEUR program seeks to introduce a group of medical students and interested graduate students to the technical skills, conceptual approaches, and mentored clinical research experiences necessary to conduct patient-oriented investigation, and represents an evolving experiment in medical education.

The PASTEUR program provides two types of instruction: didactic and mentored research. The didactic component includes lectures within preclinical courses, dedicated patient-oriented research sessions during ward rotations, and a "Clinical Champions" seminar series offering monthly talks by distinguished patient-oriented investigators. A case-based seminar course in patient-oriented research that can be taught at a range of levels, from undergraduate through advanced fellowship, is planned for the near future. The mentored summer research component consists of an 8-week experience that includes weekly didactic sessions addressing a range of topics in patient-oriented investigation. This summer, 22 first-year students have chosen to participate, and many of these students are likely to evolve their projects into more extended research experiences, continuing into the academic year. Although all of the present mentors are located within the Harvard medical community, future students will have the opportunity to participate in industry-based research projects as well.

The didactic and mentored-research activities are expected to stimulate the students' curiosity, develop their expertise, and encourage their commitment to patient-oriented investigation. We believe that the PASTEUR initiative will progressively enhance the emphasis of the medical school curriculum—clinical as well as preclinical—on scientific inquiry in general and on patient-oriented research in particular. Furthermore, by assembling a dedicated cadre of students and investigators, and iteratively developing a more precise understanding of the necessary skill sets, core competencies, and appropriate outcome measures, PASTEUR is intended to provide both the peer support and the intellectual foundation of a distinct academic discipline.

CONCLUSION

Physicians and physician-scientists have become increasingly concerned with ensuring that the tremendous advances they have seen in basic science find expression in clinical practice. While an understanding of the genetic basis of disease allows us to consider the development of molecular therapies, we have learned not to underestimate either the magnitude of this undertaking or the extent of preparation required. Indeed, this endeavor is much more difficult than most have anticipated.

As Goldstein and Brown (10) recently noted, paraphrasing Magritte, "a gene sequence is not a drug," and although the development of rational therapy for a disease may require an understanding of its molecular basis, the path from mechanistic understanding to clinical treatment is often difficult to define and hard to predict. Proteins often behave differently in test tubes than in cells, and cells behave differently in culture than as part of a vital organism. Finally, a patient's experience of disease reflects more than simply an underlying biologic defect. It is, to quote Eric Cassell (19), "a process inextricably bound up with the unfolding story of this particular patient." Thus, the critical question we are now struggling with as physicians and physician-scientists is how to avail ourselves of the advances in molecular biology without losing sight of our primary goal—the care and treatment of our patients.

We have identified five principles that we hope will inform the practice and training of patient-oriented investigators and encourage the evolution of patient-oriented research into a discrete academic discipline. Traditionally students and investigators interested in patient-oriented studies have been forced to rely upon a particularly stochastic and improvisational approach in their attempts to construct a research career; the substantial progress achieved by these pioneers reflects their insight, creativity, and remarkable determination. Now we must extend this progress and use this intellectual capital to grown the academic discipline of patient-oriented research. We must also introduce students to this discipline much earlier in their education, certainly at the beginning of medical school, and preferably during college, where the concept that the expression of complex biologic principles may be uniquely appreciated and examined in the human organism is often inadequately presented.

The continued cultivation of patient-oriented research along the lines suggested by the five guiding principles, and potentially mediated through programs such as PASTEUR, would have important implications for research and for medical education. This approach should facilitate the development of therapies based on an integrative model for the analysis of disease that is informed not only by the paradigms of modern biology, but also by the complexities of human illness.

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