Basic science and clinical medicine

Problems and opportunities at the interface[1]

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The author discusses the relationship between clinical medicine and basic research, and suggests that an effort should be made to encourage close communication between practitioners in both disciplines. The author's experience in the Cardiac Unit at Massachusetts General Hospital is discussed as a specific example of a program that has evolved into an amalgam of clinicians and scientists, producing many examples of cross-fertilization between basic research and clinical application. The practice of both disciplines together, and not in separate laboratories or distant departments, stimulates pertinent questions and clinical responses, and minimizes the delay between discovery and application.

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Clinical medicine today is beset with both great opportunities and great problems. The very issues of health care delivery and cost containment that dominate our present discussions blind us to future developments that are certain to change the fundamentals of the practice of medicine. We are in the midst of an incredible revolution in biology, where the ability to understand and manipulate the bases of life itself is almost within our grasp. The structures of oncogenes and lipoprotein receptors are now part of common laboratory talk. Yet how do these basic discoveries translate to the evaluation and care of the patient?

Consider that much of what is expensive in medicine is directed at attacking the end stage of a disease. The high technology of which we are so proud is aimed largely at

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the salvage of patients who have already traversed a long and downward-sloping road. Cardiac catheterization, coronary angiography, angioplasty, coronary bypass surgery, and cardiac transplantation are activities that have already brought medical care costs well beyond 11% of the gross national product. Yet they would fade into insignificance if coronary arteriosclerosis did not occur. The second major killer, and consumer of resources, is cancer. A definitive diagnosis and intervention at the earliest stages of neoplasia would do away with the need for increasingly expensive and complex scanners, mutilating surgery, and debilitating chemotherapy. Why is the vision of clinicians so constricted that they can only view the end of a disease process and not see its beginning?

I believe, as C.P. Snow has suggested in another context, that we suffer from two coexisting but inadequately communicating cultures: the culture of the clinician and the culture of the basic biological investigator. What is clearly needed for the most efficient translation from discovery to practice is not only better communication but happy cohabitation. I should like to enumerate some of the reasons why effective interaction is scarce, and how it can be made to occur.

It is a paradox that in this fertile garden of ideas that characterizes modern biology, the number of physicians selecting a career in research is continually diminishing. My distinguished predecessor in the Page Lectureship, James Wyngaarden, has sounded the alarm and called the clinical investigator "an endangered species."[1] He has clearly plotted the progressively smaller number of MDs who are recipients of research fellowships, and of new research project awards. Faculty positions in medical schools, both at junior and senior levels, are often difficult to fill, yet clinical practice in the most desirable locations is overserved. While new diseases may still be discovered through bedside observation, many of us are turning our backs on the potential for really understanding and solving the problems presented by the major killers of the young and of those in their most productive years. Most analyses of the reasons for this distortion in career choice focus on the issues of opportunity, security, and relative financial reward. I do not believe that these are the central issues. To be sure, the bright young physician with many career choices may well think that the clear disparity of financial reward between practice and an academic career, with the uncertainty concerning the government's commitment to the support of medical research, is an important factor to be considered in selecting a career. Yet there are many equally talented young people who make an earlier choice of a scientific career, leading to the PhD degree, where the same securities and rewards are not an option and the attendant uncertainties a given.

James Wyngaarden has led the NIH to improve opportunity and security for the young physician-investigator. There are new young investigator awards and clinician-scientist awards that provide five years of secure support for the fledgling clinical researcher. Voluntary organizations, such as the American Heart Association, have also provided similar awards, though necessarily on a smaller scale. Penury is no longer a prerequisite for embarking on the path of clinical investigation. Yet I believe that, although these measures are certainly necessary, they are, standing alone, insufficient.

The wonders of modern biology can be neither comprehended nor appreciated without background or exposure. Training in medical subspecialties has become so complex and demanding, both in the body of knowledge that must be mastered and in the techniques that must be learned, that little time is left for even superficial familiarization with the rapidly advancing frontier of science. The third-year cardiac fellows of 1984, while entirely up-to-date in clinical cardiology, are operating on a biological base that dates back to 1976, material learned during the first two years of medical school. They have heard of gene cloning and monoclonal antibodies but know nothing of their substance or their potential application to the art. Neither existed at the time they studied biochemistry or immunology. An occasional lecturer at Grand Rounds or an article in *Scientific American* is insufficient to arouse any more than idle curiosity. They listen avidly and incorporate into their body of knowledge advances in electrophysiologic testing, angioplasty, and coronary endoscopy, but are incapable of looking beyond immediate application. In past eras the physician was drawn from the problems at the bedside to investigation of pathophysiology. The tools needed could be easily envisioned. Science progressed slowly and the means for research were rather quickly mastered. Today the physican does not even know

the vocabulary of the discipline needed to answer the question.

Can one be satisfied with compartmentalization? Should not the basic scientist pursue the questions that he or she is most competent to address and the clinician be left to apply the discoveries to the problems of the patient? I do not believe that this kind of duality is optimally productive, nor will it bring the fruits of discovery most rapidly to application. The fundamental biologist pursues curiosity about life's processes. Not often enough is there motivation to address the perversions of these processes that constitute disease. It is the clinician who thinks of disease daily, and is most qualified to ask questions about application. Yet the clinician no longer has the background to link biology with pathophysiology.

Even at most of our academically oriented teaching hospitals, residency training is designed so that the mastery of clinical skills is divorced from the teaching of biological science. The typical training of a future medical investigator begins with several years of residency, an intense experience, during which there is little opportunity to think about anything except the care of the patient. This period is usually followed by clinical training in a specialty, again with little exposure to investigation. At the end of about five to six years of clinical practice, with very little time for contemplation or reading outside of a clinical field, the physician is expected to begin scientific studies anew. It is not at all surprising that a sudden departure from the familiar is difficult and daunting to all but the most directed. Even the MD-PhD student is so removed from research experience that the very concepts and techniques with which the thesis project was pursued have been left behind by the rapid evolution of the field.

Selection of residents poses an additional problem. Of course lip service is given to the "renaissance man," who knows science and clinical medicine equally well. Unfortunately these individuals are all too rare and thus clinically motivated applicants are given preference because they have the interest and the stamina to stay up all night and accomplish the required work load. In the minds of most intern selection committees, delivering patient care efficiently takes preference over the ultimate career path for which the potential trainee is destined.

At the institution I know best, the Massachusetts General Hospital, the housestaff seems to know everything about the current progress in clinical practice and yet almost nothing about the exciting advances in fundamental knowledge that are occurring within the same hospital complex. Often they have not even heard of discoveries in molecular biology or fundamental physiology that are discussed in scientific circles around the world. Should not the institutions that pride themselves on producing the medical faculty of the future seriously examine the work load and structure of their housestaff programs to determine whether they are a barrier to participation in the excitement of fundamental science?

I should like to discuss a potential solution to this dilemma and show by example that it is possible to join preeminent research and first-rate clinical practice into a single entity. This effects what cannot be accomplished even by optimal collaborative interactions among disparate and separate elements.

I propose that the ideal clinical research environment contains within the same unit of organization the entire spectrum of relevant activities, from the most advanced clinical practice, to excellent applied research, to fundamental investigations. The medical school, on a single campus, that has both basic science and clinical faculties, does not satisfy this model. It must exist, quite complete, in the microcosm of a single unit or department. It is the physical proximity of common space that allows excitement and enthusiasm to flow among individuals who are pursuing different kinds of activities. It must also be an environment where flights of fancy are encouraged and not denigrated and where the burden of daily patient care is not permitted to overwhelm the clinician, so that contemplation, correlation, and undirected discussion are possible. Competent clinicians, who also are adept practitioners of science, must be visible role models to blur the boundaries between the two cultures. Details of organization are not important as long as any connection is possible.

I should like to discuss a specific example, because an exposition of data is always instructive. The cardiac unit at the Massachusetts General Hospital is an amalgam of clinicians and scientists. I would like to dissect its origins and expose its present method of operation. It has been developing in its present form for twenty years and there are now sufficient graduates who have established themselves in careers in clinical

investigation that the influence of their training can be assessed (*Table*).

The interface between science and medicine has interested me since the earliest days of my training. In the middle of a very good and highly clinically oriented internal medicine residency at the Massachusetts General Hospital, I went to study protein chemistry with Christian Anfinsen at the National Institutes of Health. This was a period when many physicians sought scientific training at NIH, but not everyone elected to go into in a laboratory that seemed to be so far from clinical medicine. I had already become dissatisfied with what I considered to be superficial explanations of pathophysiology and was looking for a more profound insight into biology. The problem that Anfinsen set was a very fundamental one indeed. He asked how proteins, which have a three-dimensional structure, were specified by DNA, which has only linear or two-dimensional information in its base sequence. The colinearity of the base sequence of the DNA and the amino acid sequence of a protein was already well appreciated, but where were the instructions for three-dimensional folding? The experimental design conceived was elegant in its simplicity. A small enzyme from bovine pancreas, ribonuclease, was known to be nearly spherical in shape. It was constructed of a single polypeptide chain that folded in a convoluted manner to form the sphere. We attacked the structure, breaking all the bonds that held it together, except those connecting the amino acids in their linear array. Then, the unstructured, loose, and moving chain was left alone to see what happened. Remarkably, it reassembled. It found its way back to its original spherical shape and the enzyme regained the activity that had been lost in the course of the violence we had done to it. Clearly the information for three-dimensional shape was contained entirely in the amino acid sequence and thereby in the sequence of bases in DNA.[2-4]

While I was working in the Anfinsen Laboratory, I was asked by the Chairman of Medicine at MGH, Walter Bauer, to come back and head the Cardiac Unit. Before my visit, I was rather skeptical that I would be willing to leave the proteins that provided so much excitement, regardless of the prestige that this position would bestow on a man in his early thirties. Dr. Bauer dispelled all doubt by telling me that he did not care what research I did, because no matter how basic, it would eventually find application in cardiology. As will become apparent shortly, he was entirely correct.

After some training in cardiology, I moved to MGH and began independent laboratory research. The problem of protein folding still fascinated me but I decided that the greatest challenge lay in understanding how antibodies worked. Here was a very large group of proteins, very similar in amino acid composition and general structure, yet each had a unique capacity to recognize a different antigen. Linus Pauling had hypothesized that the antigen imprinted itself on a protein, forming a complementary shape. Thus the key created the shape of its own lock. This flew in the face of the conclusions drawn from the ribonuclease experiments. I repeated the same experiment with antibody and soon concluded that this set of proteins followed the same rules as all others.[5] There was no imprinting process beyond the information contained in the DNA specifying the amino acid sequence of the antibody.

It now became extremely interesting to decode the amino acid sequence of the antibody combining site, and to relate it to antibody specificity. It was desirable to develop methods of protein sequence analysis in the laboratory. Per Edman had just published the startling results of his automated protein sequencer[6] and, though we were but a small laboratory appended to a clinical service, our team did not hesitate to construct one, since these devices were years away from commercial development.[7] The postdoctoral fellow involved in this project, Michael Waterfield, now working at the Imperial Cancer Research Institute in London, has continued to work on research close to clinical problems, most recently distinguishing himself with an important discovery relating growth factors to oncogenes.[8]

We soon discovered that, although we could sequence proteins more easily using our new device,[9] antibodies were not very good candidates. They were not pure proteins, but incredibly diverse mixtures. It was essential to find a homogeneous antibody and we thought one might result upon immunization with a pure antigen.[10] Looking around for small peptides that could be bought cheaply, I found angiotensin, then available as a drug. Antibodies were generated in due time[11] and examined as candidates for sequence study. They were not the pure proteins that I sought and this direction of inves-

tigation was about to be abandoned when a colleague suggested that angiotensin antibodies might have other applications.

The role of the renin-angiotensin system in circulatory regulation was poorly understood. A significant impediment was the inability to measure the components in a clinical situation. At the urging of my colleague Lot Page, I used the antibodies that had been generated for other reasons to develop an immunoassay for angiotensin.[12] This quite naturally led to a series of studies in renin-angiotensin-aldosterone control that has formed one of the major themes of this laboratory up to the present time. Immediately some very talented clinicians saw the relevance of this kind of study to clinical problems and came to work in the laboratory. Suzanne Oparil, who is now a distinguished investigator in the field of hypertension at the University of Alabama, was a very clinically oriented cardiology fellow at the time. She used immunological and peptide chemical methods to study the conversion of angiotensin I to II[13–15] and the physiologic control of renin release. Much later, Victor Dzau, now Associate Professor of Medicine at Harvard Medical School and Chief of the Vascular Unit at the Brigham and Women's Hospital, also established a research career on the chemistry of the renin-angiotensin system after starting as a clinical fellow. Thus we moved in gradual steps from the structure of the antibody combining site to clinical studies in hypertension. Participating in these studies were many clinically oriented fellows who gained significant insights into immunology, protein, and peptide chemistry in the course of their studies.

It was about this time that a medical resident by the name of Robert Lefkowitz began to work in the laboratory. He had applied for a cardiac fellowship a year thence, but I had some doubts about accepting him because he seemed destined for a career in clinical practice. While he had worked at NIH prior to residency, he had seemed disappointed with his experience. Now, as the 1983 recipient of the Lita Annenberg Hazen Award for Excellence in Clinical Research and as Professor of Medicine at Duke University, Dr. Lefkowitz writes, "Despite the house rules against doing research during elective rotations, I arranged to work surreptitiously in Ed Haber's laboratory. . . .There, at odd hours of the day and night . . . I began experimenting again. Though remarkably crowded, the contact with Ed and the immunochemists in his lab rapidly expanded my scientific horizons."[16] Would his career have been different if he had not been so stimulated?

Table. Careers of graduates of fellowship program 1965 to 1981*

	Number	Percent
Academic	104	76
Professor	(17)	
Associate professor	(23)	
Assistant professor	(46)	
Instructor	(18)	
Research institutes	5	4
Private practice	25	18
Industry	3	2

* Not including those presently in training.

Thomas Smith, the 1983 recipient of the Rosenthal Award for Clinical Research of the American Heart Association and now Chief of Cardiology at Brigham and Women's Hospital and Professor of Medicine at Harvard Medical School, came to the laboratory first as a medical student and then as a clinical fellow. He questioned that if antibodies could be used to measure minuscule concentrations of angiotensin, why could they not also determine plasma concentrations of the useful but troublesome drug digitalis? This led to the development of one of the most widely used clinical immunoassays today,[17] a method that has had significant impact on our understanding of the clinical pharmacology of the digitalis glycosides.

Since very selective antibodies for digitalis were available, he wondered whether or not it might be possible to use them as specific antidotes for the drug. Of all agents used in the treatment of cardiovascular disease, digitalis is the most difficult. The appropriate therapeutic dose is very close to the toxic dose. The knowledge in the laboratory of antibodies and their chemistry permitted the purification of a specific antibody and its cleavage to smaller active fragments. These were then used in the treatment of life-threatening digitalis intoxication, resulting in dramatic improvement of patients on the brink of death.[18] This rapid transition from an idea, to a specific antibody, to an immunoassay, to an innovative therapeutic modality could only occur in a laboratory that was working at the interface between clinical medicine and fundamental research.

A next logical step was the application of antibodies to diagnosis *in vivo*. A strong interest in ischemic heart research developed in the cardiac unit. It became desirable to be able to determine, as precisely as possible, the size and location of a myocardial infarction. Normally antibodies do not penetrate cells. A dead cell, however, is leaky and allows the entrance of antibody molecules. Antibodies specific for myosin, a constituent within the cardiac cell, tagged with radioactive markers were used effectively to locate and size myocardial infarcts.[19] Bringing to bear two techniques current in the laboratory, peptide synthetic chemistry and monoclonal antibodies, Dr. Gary Matsueda, a peptide chemist, in a sense seduced to work on clinically oriented problems by his environment, produced a selective antibody to fibrin that did not cross-react with fibrinogen.[20] These antibodies provide the means for visualizing thrombi in living animals (and later patients) as they are being formed. They also provide the potential for mapping fibrin deposits on atherosclerotic plaques *in vivo*.

The latter two pieces of work have been especially effective in uniting the clinical investigators who were examining coronary thrombosis in humans with the fundamental investigators in the biochemical laboratory. The groups meet together regularly and it is remarkable to observe the rapidity of translation of a fundamental discovery to clinical application or, alternatively, the use of a fundamental approach to examine a clinical problem. How often does the clinician have at hand the ability to use protein chemistry, peptide synthesis, monoclonal antibodies, and recombinant DNA methods to answer queries? Having the methods and their practitioners *in situ* is very different from negotiating with a reluctant collaborator in another department.

Is it desirable for everyone to participate in research? To bring the reluctant clinician to the bench is a grave error. One must be drawn there by interest and enthusiasm. Will everyone exposed to the right environment succeed? Certainly not, though a subsequent career in either clinical practice or patient-oriented research cannot be deemed a failure. An education in the possibilities of modern biology as well as the discipline of rigorous experimental work cannot but contribute to the clinician's abilities.

For medicine to take maximal advantage of the dizzying progress in biological research, both disciplines must be practiced together and not in separate laboratories or distant departments. They will feed and stimulate one another. The basic investigator can ask pertinent questions because the clinician conveys concerns and then, in turn, the clinician is able to bring to fruit the seeds germinated in the scientist's laboratory. In this setting, the much-lamented lag between discovery and application is minimized. It is also an ideal environment for stimulating the student to enter research because discovery is very close to translation.

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