Bringing the Basic Scientist into Human Disease Research*

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Many of us who are basic scientists give little thought to the implications that our research has for human disease until the time comes every few years to fill out the "Background and Significance" section on our NIH grant applications. However, the willingness of Congress to support our research has been based on the promise that basic research would ultimately benefit human health. With the current momentum in the biological sciences, the time seems to have arrived when that promise can be fulfilled. Do we need to concern ourselves with the application of basic science to human disease? I think we do. It is difficult for the more clinically trained scientists to keep up with, let alone exploit, the rapid progress in molecular biology without help from basic scientists. Moreover, the increased support that many of us would like to see for basic research will be much easier to justify if human health benefits. Finally, human disease research offers a tremendous new frontier for our students.

We are all aware of the fact that medical science is undergoing a revolution, whose origins and sustaining energies lie in basic research in the biological sciences. The first response of the agencies that fund medical research to this reality was an attempt to train renaissance men and women, scientist-clinicians educated both in basic research and clinical medicine. I believe there is now a general consensus that there will never be enough scientist-clinicians to do the job. Individuals willing and able to function well in both worlds are so rare as to assure that successful integration of basic science and medical science will require a joining of efforts between those who understand modern biology and those who concern themselves with human disease. However, there are substantial barriers between these two groups that need to be surmounted. On the side of the medical community, I perceive some confusion as to exactly what it is they want from basic science. All too often the need is stated as one of technology transfer, as if the bag of tricks resident in the molecular biologist's lab would, if moved to the clinical lab, satisfy the need. Biologists, for their part, are often quite content with the thrill of an ever-enlarging array of basic insights into biology and see human disease research as an application lacking intrinsic interest. Moreover, the future of medical science rests more with the scientists and clinicians who are being trained than with its current practitioners. In our medical schools and basic science departments, training is compartmentalized within departmental boundaries where clinical problems and basic science rarely meet.

One of the important goals of medical science in the next decade will be to identify the normal function of human disease genes. It is an activity that interests me as a geneticist and one that can serve as an example of the need for interdisciplinary activity. Technology promises us an increasingly precise map of the human genome, as well as clones and sequences of disease genes, but if we are expecting to learn the functions of disease genes from their sequence alone we will be disappointed. The first data from large sequencing efforts in yeast and nematodes reveal that the majority of coding sequences bear no resemblance to those in the existing database, some show regional consensus that may identify a known domain, and a few, probably less than 10%, display sufficient homology to suggest that the new gene is a functional homolog of a known gene. Disease genes are unlikely to give a different result. It is true that an enormous number of new sequences will be added to the database in the next few years, with the result that a new sequence will have a greater chance of matching another sequence, but in most cases we will be matching one sequence of unknown function to another sequence of unknown function.

Where does our understanding of function come from? Inactivation of a single gene in the genome of the organism is the only rigorous way to define the function of that gene in the life of the organism. Human genetic diseases are a tremendous resource of just such experiments of nature that provide information on the roles of genes in human biology. However, decades of research with bacteria, yeast, fruit flies, nematodes, and mice provide much more tractable models to further refine our understanding of the functions of disease genes. Fortunately, the unity of life has been well enough preserved through evolution to permit the exploitation of these model organisms to elucidate the functions of human genes. In the last few years, cell and developmental biologists have become aware of the fact that all eukaryotic organisms from yeast to humans use the same basic biochemical machinery (a conclusion that the students of intermediary metabolism

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had reached decades ago). It is common now to clone human genes for a large number of cellular processes from cell division to secretion by transforming mutant yeast cells with human DNA libraries. The homeotic genes, first characterized in Drosophila, are found in humans and appear to play analogous roles in vertebrate development to those they play in fly development. Findings like these have dramatic implications for disease research. Much of our understanding of human disease genes will come from their study in model organisms. A disease gene will be cloned from humans and sequenced, but its function will often remain mysterious until its homolog is identified and studied in bacteria, yeast, drosophila, nematodes, or mice.

I have given some thought to the question of how I, as a basic geneticist, might contribute to the investigation of human disease genes. I knew at the outset that I did not want to undergo retraining as an M.D. nor did I want to give up my own research program. I will relate two ideas that I am experimenting with in the hopes of stimulating further dialogue on this topic. The first idea seeks to encourage students who are training for careers in basic genetics to be more aware of the disease implications of their own research. The second idea seeks to make the expertise of an established genetics laboratory dedicated to basic research on a model organism available to medical scientists.

I teach a seminar in human genetics for graduate students who intend to do basic research in genetics. My purpose is to seduce the students into becoming interested in the relationship between whatever they work on and human disease. We read three papers each week and meet on Tuesday to discuss them. I know no more about the subjects than they do and so we sit around and ask each other a lot of questions. The format derives from my own experience of finding that I only get interested in something by puzzling over it. On Thursday we meet with an expert in the field, often a medical scientist who is one of the authors of the papers; the expert is instructed not to lecture but to let the discussion flow from questions that the students raise. When someone lectures, they often ask only the questions they can answer and students often get the erroneous idea that a lot is known. When students ask their own questions, they usually find that there are almost no answers to their questions and they may get interested in finding the answers. The students write a paper at the end of the quarter exploring the disease implications of their own thesis project. Every thesis project has disease implications, and the exercise of ferreting them out will, I hope, pique their interest in human disease and keep them attentive to this area throughout their careers. It may be working. The students like the class a lot, and I notice that many of them pick human genetics topics to present in our departmental journal club.

The second experiment is an attempt to make yeast available as a model organism for people training as medical researchers. When a medical scientist in Seattle inquires about the possibility of using yeast to study a mammalian gene, I invite them to send a postdoc to my lab for 2 to 3 months. They do whatever DNA constructions are necessary before coming to my lab so that their time can be spent learning how to push yeast cells around. Three months seems to be enough time for people to learn how to manipulate yeast, where we keep things, and to establish rapport with the people in my lab who can supply advice. After that period, I expect them to return to their home lab, but they are welcome to come over and use yeast media and get advice from people in the lab. This also seems to work. People who have started yeast work in this way have been able to continue it.

Most medical schools have bacteria, yeast, drosophila, nematode, and mouse geneticists around who could catalyze the analysis of human disease genes in these model organisms and who could stimulate their students to become interested in the disease implications of their research. Similar formats could allow biochemists and molecular biologists to contribute to human disease research, and I am sure that some do. However, it is not clear how to encourage people to take time and resources from their own research projects to participate in the goals of advancing medical science. I happen to have a history as a postdoc in Renato Dulbecco's lab so my research program has always been motivated by an interest in the disease of cancer, and my career is now secure enough that I can indulge myself in these experiments. My grants subsidize the work of medical scientists in my lab, but my competing renewals do not benefit from it. My department allows me to satisfy my teaching obligation in the human genetics seminar course in part because my salary is subsidized by the American Cancer Society.

However, the values that motivate research funding and career advancement are forcing young basic scientists to focus their full attention on their own research program. Little benefit would accrue to them by making their expertise available to medical scientists. Few training programs in genetics, biochemistry, or molecular biology would consider a course in human disease essential to their curriculum. To build more bridges between basic scientists and medical scientists, it will be necessary for medical school and university departments to reward faculty who help train their colleagues and for funding agencies to recognize such contributions in awarding grants. Training grants might encourage the teaching of human disease as a part of graduate education. The task may be difficult, but it is not insurmountable. In biotechnology firms, where personal advancement and the development of a useful medical product are one and the same, teams of basic scientists and clinicians often work well together.