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Presidential Address

On the Difficulty of Combining Basic Research and Patient Care

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In this paper I will express some concerns about the way that we are presently planning to perform medical research, both "basic" and "clinical," in the years ahead. I am particularly interested in the roles of MD and PhD investigators. Most of us have heard that the number of young MD's interested in research has dropped alarmingly in recent years. The reasons given for this include: the decreasing support of research and the competition involved in obtaining it, the frustration exhibited by older role models, the disparate financial rewards of research and practice, and the changed social situation for young physicians, including marriage, children, large debts, etc. [1]. All of these are valid reasons, but from my own experience, I suspect that there is another which has received less attention. Most young men and women enter medical school primarily to obtain the satisfaction of taking care of sick people. Almost all of the candidates I have interviewed in the past 10 years for our own pediatric residency program have chosen primarily to take care of patients. They may also hope to do some clinical research in order to remain in an academic environment, but they have little experience or understanding of how to go about this. Earlier, some of them had considered including laboratory research in their medical careers. But almost all of them recognized that to try to apply to clinical medicine the basic sciences which they had learned about in college and the first 2 years of medical school would be both increasingly difficult to do on a part-time basis and increasingly distant from their primary interests and goals. For a career combining the care of patients and laboratory research involving basic science, they see the need for extensive scientific training and then a life of long hours, repeated frustrations, and relatively little reward.

They are correct. Medical research has been evolving naturally into a more and more complicated field, no longer comfortable for a part-time investigator.

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If we encourage more than a very few, highly talented and motivated medical students toward a career combining medicine and basic science, I believe that we will be trying to "turn-back-the-clock" to a time when science was simpler and more easily supported. Many of my generation looks back on this period 2–3 decades ago as "the good old days." The availability of funds, the freshness of molecular biology, and the prestige of a research career allowed us to recruit with ease—and, perhaps, sometimes without sufficient discrimination! This "good-old-days" attitude persists. Now during the first 2 years of medical school, the basic science departments compete for the brightest students. MD-PhD programs are placed upon a pedestal, creating an atmosphere in which other medical students, who are interested primarily in taking care of patients, may be made to feel second-class. Later on, the current criteria for academic appointments and promotions reinforce this discrimination.

To get at this problem, first we need to emphasize the diversity of the medical research with which we are concerned, because some of this will be done best by MD's and some should be done by PhD's. Medical research constitutes a broad spectrum from molecular biology concerned with normal processes, through biochemical and biological studies of sick people, all the way to epidemiological studies on the natural history or therapy of disease. The training required for these types of work is not the same. For this paper, it suffices just to distinguish basic from clinical medical research, although, of course, this is too simple a classification. Nonetheless, to illustrate the difference between basic medical research and clinical medical research, let me digress to describe one area of basic research which is undeniably medical because it concerns aging and cancer, and which interests me particularly [2].

> All normal diploid cells are restricted to a limited number of cell divisions, with the exception probably only of stem cells. This lifespan is shorter for peripheral lymphocytes and for most epithelial cells than for fibroblasts. One reason we believe that fibroblasts have a limited number of cell divisions is because their lifespan is approximately inversely proportional to the age of the donor. Cell divisions can be used up in vivo as well as in vitro. In fact, cells in vivo probably never need all the divisions of which they are capable; and if they do run out of divisions, there are plenty of other cells to take over. To some extent, this limited lifespan can be increased by agents such as albumin, cortisone, or certain growth factors. But, eventually, for all these cells, a "crisis" and "senescence" occur. Is this due to the accumulation of spontaneous errors in the structure of DNA, or in the cell machinery which replicates DNA or which synthesizes proteins? Or is it due to a programmed terminal differentiation, analogous to that which occurs when precursor cells, such as erythroblasts or adipocytes, are induced to differentiate?
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> Fusion of senescent normal fibroblasts with advanced neoplastic cells can overcome the limited lifespan. These neoplastic cells have no limitation on lifespan, and are immortal by definition. How are they derived from normal cells? First, to become malignant, a cell must obtain a prolongation of lifespan. Initially, the cell need not be, and probably usually is not, completely "malignant" in the sense of being able to grow autonomously in vivo. Indeed, the increase in lifespan may be temporary. Also, the cell may still be responsive to the normal controls of growth through intracellular and extracellular mechanisms.
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> For some time, it has seemed likely that the initiation of a neoplasm is a multistep process. Very recently, exciting studies in three laboratories [3–5]—all reported in

one issue of *Nature* 2 months ago—have begun to separate the steps involved. These workers showed that the genes recognized in recent years as participating in the formation of tumors, called oncogenes, can function in an additive fashion in the transformation of a normal rat fibroblast into a neoplastic cell. These studies on rat fibroblasts clearly indicate that more than one step is involved in the transformation of a fibroblast from a normal to a neoplastic cell. The first step may simply involve a prolongation of lifespan, as mentioned earlier. Then, later steps lead to more clear-cut neoplastic behavior, including loss of growth control in vitro, and acquisition of the ability to grow progressively in nude mice or on the chorioallantoic membrane of the chick.

Incidentally, for some reason, human fibroblasts are more resistant to spontaneous or chemical transformation than are rodent fibroblasts. They may have better DNA repair mechanisms, or the fact that humans are not inbred like laboratory animals may be relevant. Human fibroblasts can be transformed with tumor viruses, such as SV40, and perhaps with chemical and physical agents, too, especially when the cells have been derived from individuals genetically susceptible to tumors. The work with rat fibroblasts, very likely, soon will be extended to human cells.

The idea that an established tumor progressively develops a more malignant phenotype has been accepted for some time. What is new is the recognition that even the first tumor recognizable in vivo has probably progressed through a number of stages from the normal cell. After escaping senescence, the cell must overcome local growth controls, such as growth factors and cell-to-cell contacts, and then must be able to survive nutritional and immunological obstacles before a clinically detectable neoplasm can arise. All this probably requires a number of discrete steps.

At some point in this sequence, essentially all tumors become aneuploid, although, at first, only slightly so [6]. When does this occur, and why? In the last 2 years we have begun to understand the connection between chromosome abnormalities and neoplasia, especially in Burkitt lymphoma and the other B-cell tumors of mice and humans. In these tumors, the chromosome abnormality is usually specific. It appears to result in the activation of a certain oncogene by translocation of this gene into proximity with immunoglobulin genes [7]. How activation of this oncogene occurs, and how it propels the cell toward malignancy, is not yet clear but should be explained soon. It is already likely that other oncogenes are activated also by chromosome translocations in other tumors. Alternatively, in some individuals with retinoblastoma or Wilms tumor of the kidney, loss of genetic material appears to be responsible, perhaps by removal of normal gene regulation.

All of this is very exciting! Although we do not yet know when in the steps leading to neoplasia aneuploidy occurs, nor its immediate consequences, it is satisfying to see the relation between chromosome changes and oncogenes beginning to be clarified. And it is even more satisfying to see the unfolding of the nature and the roles of the 20-odd oncogenes so far identified. Moreover, the study of oncogenes promises to elucidate not only the mechanisms of neoplasia but also those of cellular aging and perhaps of development. This is because oncogenes can prevent cellular aging, perhaps by interfering with a program of terminal differentiation in aging cells. And evidence is beginning to appear that the normal function of oncogenes may be in the control of developmental processes.

Research on these new cancer genes utilizes the tools of molecular genetics, and qualifies as both medical and basic, as mentioned earlier. Every investigator in the oncogene field knows that it is sufficiently complex, competitive, and rapidly developing as to demand full-time attention. It would be very difficult for a part-time individual to contribute significantly to this sort of research. I suspect that to be successful in this and similar areas of research, an individual

must spend at least 90% of his or her time in the laboratory. Other areas of basic medical research, such as immunology, virology, neurobiology, and endocrinology, are already, or will soon become, equally competitive, dependent on complex technology, and fast-moving—and equally difficult to perform successfully on a part-time basis.

How will this sort of basic research be organized in the future? Again, we have a model in the investigation of oncogenes. Probably all basic medical research requiring the tools of molecular biology will be done by teams working full-time in the laboratory. These will be made up mostly of PhD's, concentrating entirely on their research and in close and rapid communication with others in similar laboratories nearby and elsewhere. It has become abundantly clear that this is the organization necessary to obtain the results which all of us want!

The physician-scientist trained both in medicine and in basic research is going to find it increasingly hard to stay at the forefront of such basic research if he or she continues to care for patients more than a minimum amount of time. On the other hand, there are several appropriate and satisfying careers for such an individual. One involves the translation into clinical medicine of the advances in basic research which relate to the pathogenesis and therapy of disease, the recognition of important problems amenable to basic investigation, and the testing in patients of the hypotheses derived—in short, the role of intermediary between the basic research laboratory and the clinic. Another career combining research and patient care, already well represented, involves the study of a particular disease both in the clinic and in the laboratory. The focus upon an abnormal process rather than a normal one, and especially if the condition is rare, avoids competition and permits the work to proceed at a less urgent pace! There are a number of individuals pursuing this sort of career—often with notable success. But it is my impression that usually they have not had much guidance in getting where they are, as for example, concerning how much basic science training they needed, and when and where they should have gotten it. Yet another career option combining research and clinical care involves epidemiological studies directly with patients concerning the causation, natural history, and therapy of disease. Nowadays, these clinical investigators must have considerable knowledge of epidemiology, biostatistics, and experimental design—topics largely ignored in medical schools until recently.

We need to develop and to make better known these career paths for the clinician interested in medical research. We need to expose medical students to the excitement and challenge of research on diseases in humans much earlier in medical school, at the time when now they are being drawn toward the basic sciences. As I have stressed, the first step is to recognize how difficult it will soon be for all but a very rare individual to conduct basic medical research and care for patients simultaneously. Then enlightened planning can begin. We should recruit the MD or PhD degree candidates who are the most appropriate on the basis of background, maturity, personality, and goals. While it is difficult to recognize and measure such personality traits, it has been suspected for some time that different characteristics mark the individuals suitable for laboratory research and for clinical

practice [8]. Currently, admission committees to medical schools seem to be trying to combine these characteristics. Next, MD's and PhD's should be trained differently both before and during graduate school, emphasizing humanistic aspects, sensitivity, and communication skills for MD's and rigorous scientific preparation for PhD's. In addition, PhD's interested in basic medical research should be provided sufficient knowledge of medicine, and, subsequently, sufficient access to patients, to facilitate this research.

We need to train medical students in a more individualized fashion suitable for their future careers. A minimum "core" training of 3 years may be sufficient for many physicians, with less exposure to the basic sciences and more emphasis on clinical skills and the psychosocial aspects of medicine. A fourth year would be available, as presently, for consolidation of this clinical education. For medical students motivated toward clinical investigation, the fourth year could be used for specific training in biostatistics, epidemiology, and experimental design, plus introductory research involving humans. This might well justify a Master's degree in clinical investigation, which would enhance the prestige of such a career. Finally, highly qualified and motivated students should continue to study for both the MD and PhD degrees, but with a realistic expectation of the difficulty of a combined career, unless the time for patient care is to be kept to a minimum.

Finally, we need to encourage the creation of more teams for medical research. As mentioned earlier, most of the members of these teams will be PhD's working full-time, plus those few MD's or MD-PhD's who are well trained in science and can devote 90% of their time to the laboratory. In addition, there will be the MD's who wish both to take care of patients and to relate as clinical investigators to the basic research of the team. In such teams, I hope that PhD's and MD's will find more appropriate, complementary, and satisfying roles, based on different talents, training, and interests.

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