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Presidential Address

The Impact of the Revolution in Biology on Clinical Investigation

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Since custom demands that I address you this morning, I have considered a number of subjects that might be of interest to you and to which we might direct our attention. As a biologist engaged in the study of man, the clinical investigator is keenly sensitive to the social, political, and intellectual climate of our human society. I was tempted, therefore, to speak of the turbulence of the atmosphere in which we live; of the clash of the world's rival political philosophies; of the revolts of the colored peoples of the world against deprivation and indignity; of the grave medical problems generated by the growth of our population; or of the influences of governmental support for biological and medical research on American medical education. I was tempted too to speculate on the potential implications for medical science of spatial exploration, which has made a reality of what was fantasy only a short time ago. But though these questions are tempting and invite discussion, you may be relieved to know that I finally decided that I might better discuss the impact on clinical investigation of the revolution in biology, a revolution in which clinical medicine is a very active participant.

Biology and the natural sciences related to biology are advancing at an explosive pace. Let me indicate just a few of these advances. The mechanisms of biosynthesis of nucleic acids and of proteins are rapidly being elucidated. The transmission of genetic information from DNA via RNA to proteins is being delineated. The nucleotide code for each of the amino acids is largely established. The determination of the fine structure of the gene and of the colinearity of its structure and of the structure of the proteins whose synthesis it controls is well under way. The genetic control of regulatory processes in cellular metabolism is increasingly understood. The mechanisms of viral invasion and replication and the role of viruses in the etiology of animal tumors are being defined. The physical and chemical properties of macromolecules are being correlated with their biologic function, as, for example, in the determination of the detailed structure of the active sites of enzymes. The functions of structural constituents of cells, such as the endoplasmic reticulum, or the ribosome, or the lysosome, are being revealed. These are but examples of the extraordinary advances that have occurred in recent years. But clinical medicine too has shared in this crescendo of discovery. In the past

fifteen years we have savored the recognition of numerous new diseases; we have witnessed the extraordinary growth of human genetics; our understanding in all branches of internal medicine has been greatly enhanced, and there have been monumental achievements in pharmacotherapy and in surgical treatment.

In the advancement of knowledge in the biological sciences, the clinical investigator has an important role to play. For the most part, he plays this role as a member of a Department of Medicine, or of another clinical department, in a university medical school. I hope that you will permit me to say that the Department of Medicine occupies the cardinal position in the medical school and serves as the principal bridge between the basic medical sciences and clinical medicine. With growing recognition of the necessity for maintaining close integration in the teaching of the basic medical sciences and clinical medicine, various curricula have been designed to meet this objective. In the final analysis, however, the teaching of clinical medicine in terms of a deep understanding of the basic medical sciences is best done by physicians who themselves are well trained, both in clinical medicine and in one or more of the basic medical sciences, in other words, by well integrated physician-scientists who are engaged in creative scholarship.

This objective is so easy to state but so difficult to achieve. For of all the problems faced by the clinical investigator, the most critical is the intellectual and emotional challenge of achieving and maintaining both clinical excellence and excellence in medical scientific investigation. It is true now, and it will be increasingly true in the future, that the clinical investigator must be prepared to utilize and to develop the most advanced and sophisticated concepts, methods, and techniques of the basic medical sciences. But he also feels deeply the need to be an expert and knowledgeable physician and teacher of medical students and house officers.

It is obvious that if he is to be successful in the achievement of medical scientific and clinical excellence, the clinical investigator must be intelligent, exceptionally hard-working, and, of equal importance, he must have a deep and genuine interest in clinical medicine. And he also needs just a little bit of luck. With these prerequisites, a program of clinical and scientific training will help to prepare him for the long road ahead. Let me emphasize that there is no unique formula for the edu-

cation and training of a clinical investigator. There are numerous examples of brilliant men who, largely self-taught, have made great contributions in clinical investigation.

The essence of fundamental investigation lies not in whether it is done in a preclinical or in a clinical department, in a laboratory, or on a ward. It is rather the quality of the question which is asked and the quality of the experiment which is designed to answer the question that determine whether research is fundamental in character. But as the medical sciences become increasingly complex and difficult, it is clear that the clinical investigator who hopes to ask and to answer questions of fundamental importance will require advanced scientific training as well as the excellent clinical training offered by our best internship and residency programs.

In seeking to achieve excellence as a clinician and as a scientist, many a clinical investigator feels himself riding two horses, often with a sense of their incoordinate pacing or of his inadequate mastery of them. He feels an enormous challenge to his intellect and to his capacity for hard sustained work. He may find himself frustrated at times, unable to devote himself as fully as he would like to his clinical and teaching responsibilities or to his investigative work.

It is worth noting, therefore, that in meeting the challenges of modern science, the clinical investigator is afforded major opportunities. Careful study of the human organism in health and in disease can provide stimulating leads to an understanding of fundamental physiologic or chemical or physical processes. One need only reflect on such classic examples as the studies on pernicious anemia that led to the discovery of vitamin B<sub>12</sub> and the mechanism of its absorption; or the observations in a variety of clinical disorders associated with hyperglobulinemia that are leading to important advances in our knowledge of protein structure and synthesis; or the studies in the human endocrine diseases that have provided essential data for an understanding of the physiologic roles of endocrine secretions. A striking example is afforded by the history of studies in sickle cell anemia, which ushered in a whole new era of molecular diseases. Sickle cell anemia was first described by J. B. Herrick in 1910 who noted the peculiar elongated and sickle-shaped red cells in an East Indian medical student in Chicago. In 1927, Hahn and Gillespie, studying a child with sickle cell anemia, indicated that the basis of the sickling phenomenon is an abnormality of the hemoglobin and that with deoxygenation, sickling occurs, whereas the oxygenated cell does not sickle. In 1940, Ham and Castle noted that the viscosity of sickle cell blood was greatly increased on deoxygenation, and Sherman observed that the deoxygenated sickle cell displayed birefringence in polarized light. In a conversation with Pauling, Castle mentioned the likelihood of molecular orientation as a basis for the sickling phenomenon. With these clues, Pauling and Itano in 1949 carried out their brilliant experiment that demonstrated a difference in the electrophoretic behavior of normal human hemoglobin and of

sickle hemoglobin. Shortly thereafter Harris demonstrated the formation of sickle-shaped tactoids in stroma-free solutions of deoxygenated sickle hemoglobin. This was clear proof that the abnormal shape of the sickle cell is a function of its hemoglobin and not of the cell membrane. Electrophoretic techniques were quickly employed to study the genetics of this disorder as well as of the other hemoglobinopathies that were soon discovered. And then in 1956 Ingram demonstrated that normal human hemoglobin and sickle hemoglobin differ by only one amino acid residue, the substitution in sickle hemoglobin of valine for glutamic acid. A single gene defect was shown to be responsible for a single amino acid substitution. These studies, which began with careful and astute clinical observation, have led to major advances in human genetics and in our understanding of the structure and mechanism of synthesis of proteins. In several respects, modern molecular biology has been fathered by clinical medicine.

As clinical investigators, we want to do more than to discover leads, important and crucial as these are. We want to be able to follow these leads in depth and to explore their significance. It is for this further exploration that advanced scientific training is usually essential. Armed with such training, the clinical investigator who is alert to nature's experiments in man can make contributions to medical science that are of major importance. He is doing so now and I am confident that he will do so in the future.

I have spoken until now of the intellectual and emotional impact of the revolution in biology on the clinical investigator. But more important, I believe, is the much broader question of the impact of this scientific revolution on our society and on the contributions of clinical medicine and clinical investigation to our society.

The achievements of modern science and technology and of modern medicine have resulted in the prolongation of the average human life span and in diminished infant and child mortality. The consequent rapid rise in the world's population, though an impressive testimonial to the advancement of science, is nonetheless a cause for much concern because of the economic and political problems that have been created. But for us as clinical investigators there is yet another series of questions with which we must wrestle.

The science of human genetics, which has grown so rapidly in the past two decades, has already revealed an enormous number of human hereditary disorders, and the number appears to increase with every passing day. There are at least 60 disorders linked to the X-chromosome alone and another 20 that are probably linked to it. There are more than 400 autosomal dominant and at least 175 autosomal recessive genetic disorders. If the estimate is correct that man has approximately 40,000 to 50,000 genetic loci, then we have so far recognized genetic substitution or mutation in only about 1% of the total. If we further assume for man a spontaneous mutation rate similar to that which obtains in other higher

forms, then we may expect an appreciable and steady increase in the number of newly created as well as newly recognized genetic disorders.

But the rate of mutation may be further accelerated by environmental factors or mutagens such as chemical agents that are poured into the air we breathe, added to the food we eat, or dumped into the water we drink. And I need not speak of the obvious mutagenicity of ionizing radiation. Clearly there is reason to expect that the rate of genetic mutation in man will increase.

As physicians we have the responsibility of healing the sick and of prolonging life. But we must realize that in genetic and evolutionary terms, such successful prolongation of life may often aid in the propagation of deleterious genes. The very successes of clinical medicine, which may permit the preservation and dissemination of harmful genetic traits, may create grave problems from the standpoint of human evolution. It is obvious that as physicians we shall continue to do our utmost to heal the sick and to prolong life. But I believe that we have an equal responsibility to do all that is possible to render the deleterious gene harmless and to foster favorable progress in man's evolution.

The challenge that is offered to us as clinical investigators is formidable. It involves the recognition of known hereditary disorders and the discovery of new ones; the discovery of the latent asymptomatic carriers of mutant genes; the determination of the nature of the genetic defect, ultimately in terms of the modification in the gene and the modification in the gene product; the determination of the factors in our environment that are

beneficial and of those that are harmful to individuals genetically predisposed to human diseases; and the institution of measures designed to prevent the symptomatic expression of the genetic disorder. We may find that the elimination or attenuation of harmful factors in our environment will require major changes in our social and cultural patterns; if we are convinced that such changes are wise and necessary, I hope that we shall accept our social responsibility and shall help bring them to pass.

I should not close without saying a word about our good fortune in being clinical investigators at this point in history. I realize that life in academic medicine is not easy; we seem chronically harried and harassed with too little time to think; the calm contemplative existence we yearn for is often supplanted by committee meetings, project site visits, time sheets, and querulous comments of seemingly unsympathetic editors or obtuse referees; and the wives and children of young investigators are not convinced that academic medicine has been admitted to the affluent society. Granted these irritations, which I hope will be remedied, I feel that we are extraordinarily lucky to be taking part in the greatest leap forward in man's knowledge of living matter that has yet occurred. We live during a glorious era in science, and we are very fortunate indeed that our work is so much fun and is such high adventure. The meetings of these societies testify to the vigorous healthy state of clinical investigation today. I hope that you will all continue to prosper in your work and that you will enjoy your adventure to the full.