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THE ROLE OF MOLECULAR BIOLOGY IN HEALTH AND MEDICINE

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A major current concern in the area of health relates to delivery of medical care with emphasis on the relative shortage of physicians. Because the time spent in medical education and specialty training has been increasing over the past 50 years in response to the advances in scientific knowledge and technology to the extent that a period of 12 years (4 pre-medical, 4 medical, 1 interne and 3 residency) is usually spent before practice is undertaken, the medical profession and some medical educators are talking about a shorter curriculum with less emphasis on the natural sciences. The currently popular concept of "relevance" has led to the assignment by some of "less relevance" to the natural sciences and "more relevance" to the social sciences (including psychiatry) as related to medicine.

Historically, it is worth noting that the major thrust and impact of the Flexner Report in 1910 was that of stressing the scientific basis of medicine and the necessity for structuring medical education and practice on the scientific principles of the natural sciences of chemistry, physics, biology, etc. The great advances which had been made in the period of 1875-1910, particularly in the areas of bacteriology and the role of bacteria in disease, and in the discipline of pathology as developed particularly by Virchow in terms of a cellular basis of disease, were compelling reasons for introducing these new sciences into the medical curriculum. Indeed, the microscope became a symbol of medicine along with the stethoscope and reflected the commitment of medicine to a scientific basis.

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The exciting and very rapid advances in the natural sciences in the past 25 years have served to pose a dilemma for medicine. On the one hand, exciting new discoveries were being made in the areas of biochemistry, genetics, virology, pharmacology, etc. which required a more sophisticated level of science comprehension than was possible for most physicians. At the same time traditional and empirical practices of medicine were being challenged by the newly emerging concepts and laboratory techniques suitable for application to clinical problems.

A prominent and most promising feature of the emerging new areas of the biological sciences was that of a molecular basis for understanding complex biological events. In essence, the newly emerging concepts of molecular biology were extending, if not replacing, the cellular basis of biology to a more fundamental level, viz., the molecular. While biochemistry is in its very nature oriented to a molecular view of cellular functions, it had been concerned, particularly for the past 30 or so years, with applying techniques for the main purposes of isolation, identification and characterization of molecules such as vitamins, lipids, carbohydrates, etc. and with the energetics of living systems. With the development of new techniques in the physical sciences, rapid advances began to be made by the biochemist in the isolation and characterization of macromolecules such as proteins and nucleic acids. As the biochemist became more adept at understanding the primary, secondary and in some cases even the tertiary structure of macromolecules such as proteins and nucleic acids, (including genes and viruses) events of the greatest scientific importance occurred particularly in the area of biochemical genetics, viz., the establishment
of DNA as the primary genetic material, the chemical and physical nature of DNA and above all else the "cracking" of the genetic code inherent in the DNA molecule. This intellectual tour de force opened up a vista of scientific possibilities yet to be fully appreciated. At this point one might say that molecular biology emerged—but it should be noted and even emphasized that molecular biology is not in fact a discipline but rather a way of thinking and developing concepts about biological events. The underlying basic discipline for molecular biology is in fact today chiefly biochemistry.

With the development of new concepts about genetic transcription and translation, regulation of cellular processes, differentiation and development, etc., it was to be expected that new concepts in molecular terms would emerge, particularly in pathology, to replace—or at least to extend—the cellular basis of disease developed by Virchow. As a matter of fact, the molecular view of biological processes has led to a breakdown of the traditional boundaries which earlier distinguished anatomy, microbiology, physiology, pathology, pharmacology, etc. from one another. New journals have even emerged with such titles as, "Experimental and Molecular Pathology", "J. of Molecular Pharmacology", "Molecular and General Genetics" etc., etc. The molecular concepts of biological processes aligned with biochemical techniques have thus begun to emerge as a feature shared to an increasing extent by all the basic sciences of medicine. The significance of this trend is not so much that distinctions are disappearing, but rather that new concepts are emerging. This development is not simply one of substituting one set of words or interpretations for another, but rather is
one which will permit for the first time an experimental approach to problems heretofore considered too complex to yield to experimental approach. Thus, investigators are now designing experiments to yield information on such complex systems of the brain as memory, mentation, etc. The advances in biochemical techniques and the new concepts of molecular biology have led to major new advances in subcellular anatomy, microbiology (and in particular virology), physiology, immunology, pathology, pharmacology, genetics, etc. The full impact of these new concepts are yet to be fully appreciated and exploited in the fields of medicine dependent on these basic disciplines. While there is a gap—and always will be and should be—between the implication of a new concept in the basic sciences and the application of this new concept to clinical problems, the gap today seems to be disconcertingly large and growing larger. In my view, the primary reason for this is that the basic scientist is pursuing his research with a greater commitment than is the clinician to comprehend and apply the results of the new research findings. If this position is valid, then it follows that the clinician can not afford to be educated and trained with less science, but rather, to be effective, he must be trained with more science.

Because time will not permit a systematic review of the many areas of exciting new developments in molecular biology and biochemistry which give promise of great importance when developed to the point of application in the clinic, I have decided to limit my comments to the area of molecular mechanisms involved in cell regulatory processes.
The problem of regulation of the cell to maintain its steady state functions has begun to yield information of great interest to the biological scientist as well as to the clinician. While the biochemist has been relatively successful in defining the energetics of the cell in terms of specific reactions involving the conversion of chemical bond energy of food stuffs to the energy required to do mechanical, osmotic, biosynthetic, electrical etc., work, mainly through the generation of ATP, the capacity of a specific cell and the whole organism to regulate these processes has begun to be appreciated only recently. While energy production and effective utilization of transduced forms of energy are of fundamental importance and basically similar in principle, if not in detail, in all cells, we now recognize that other forms of control are much more subtle and meaningful in the maintenance of functional health and survival of a cell or organism. It goes without saying that if a cell or whole organism cannot generate the energy necessary for effective function and regulation, particularly in higher animal forms, the organism will not survive. As a matter of fact one has to accept the fact that if an organism survives at all, it does so because it can generate the energy necessary to do so. What is less clear is the nature and latitude of the regulatory processes which determine the survival of a given cell or the whole organism.

The regulatory processes which operate from the stage of the fertilized ovum and lead to the differentiation and development of the fetus, and postpartum the regulatory processes which operate through growth, maturation and finally death are conceptually being developed and experimentally approached. While the model for much of the thinking about higher animal
forms such as man is based on the models of microorganisms such as *E. coli*, cells of higher animals must utilize similar regulatory processes to one degree or another in addition to the controls inherent in a cell which has its nuclear DNA in a segregated cellular organelle surrounded by a nuclear membrane, and its DNA bound to a family of proteins known as histones plus a multiplicity of regulators at the level of hormones.

It is accepted that all the biological information that the adult human has potentially and/or actually is encoded in the DNA of the fertilized ovum from which he develops. A clear understanding of how this information is transcribed, translated and finally regulated is necessary before one can appreciate the regulatory aspects of this process as the most basic consideration in the health and disease of a cell or organism. While the basic model of transcription of DNA via messenger RNA and the translation of messenger RNA on ribosomes into specific functional proteins is still not complete, it is nevertheless adequate to explain the specific macromolecular defect in many cases of hereditary disorders involving a genetic defect or mutation. A considerable number of hereditary disorders have now been described in which the lack of a specific enzyme (e.g. phenylalanine hydroxylase deficiency in phenylketonuria) or a specific amino acid (e.g. hemoglobin S in sickle cell anemia in which a valine residue replaces the glutaminy1 residue in position 6 of the *β*-chain of normal hemoglobin A), can be explained on the basis of a mutant gene unable to code specifically for the necessary amino acid sequence required for a functional enzyme or protein. While the processes involved in transcription of DNA and the translation of messenger RNA are far from being completely understood,
meaningful questions can now be asked on the basis of the available concepts which can be experimentally tested.

Once the differentiated organism has developed to the stage of an adult animal, the role of the regulatory processes in maintaining the steady state functions of the individual cell and whole organism becomes a predominant consideration. While the DNA of muscle, liver and kidney cells, e.g., all contain the same genetic information, it is clear that each cell of these organs is regulated to carry out specialized functions peculiar to that organ. While all the cells are programmed to produce the enzymes necessary for energy production and utilization, the cells of each organ also have the means of expressing themselves by synthesis of the unique macromolecules which are necessary for the specialized function of that organ. In essence then, the genetic information in each cell is programmed in terms of a type of repression and derepression of specific genes, inducers, plus other types of regulators. Because the macromolecules of each cell have a finite half-life time, there must be regulatory mechanisms in the adult cell which turn the genetic information on and off by some kind of a feedback or other mechanism.

A second level of regulation relates to the translation process. There is now evidence that the translation of messenger RNA, formed by the chromatin template of nuclear DNA, either before, during or after attachment to the ribosome is subject to regulatory factors. Levels of transfer RNA (needed for converting amino acids into aminoacyladenylates for conversion into peptides), initiation and termination factors (needed to indicate initiation and termination of the peptide chain on the messenger RNA), special binding
factors, etc. are known to operate in regulation at this level. Many hormones are now thought to exert their regulatory effects in animal systems by affecting the transcription or translation (or both) processes.

Regulation is also known to occur at the enzyme level in the way of feedback inhibition, conformational changes, specific activators and inhibitors, enzyme turnover, etc.

An area of emerging importance is that of the role of functioning membranes as regulatory systems. The animal cell has an elaborate system of membranes involving not only the surface of the cell, but also all of the intracellular organelles such as mitochondria, nucleus, microsomes, endoplasmic reticulum, golgi apparatus, etc. These membranes serve to compartmentalize certain cellular functions and thus provide a system for regulation in the way of control of transport in and out of specialized areas of the cell.

The purpose of this excursion into regulation is primarily to call attention to the fact that we are on the brink of a new set of concepts which will hopefully provide a more basic understanding of the physiology of the cell and the organism. These new concepts provide a new basis for understanding disease in all of its aspects whether the disease is a result of genetic defect, bacterial or viral infection, toxic agents, neoplasia, nutritional deficiency, etc. It is safe to predict that the unifying theme in the newer pathology will be in terms of a failure in cell regulation at the molecular level, irrespective of the etiology. It follows then that concepts of diagnosis, prognosis and therapy must be based on these concepts if a rational basis for the practice of clinical medicine is
to emerge and replace the large areas of empirically based medical practice. However, we will realize this goal only if it is recognized as a primary purpose of medical education and training. This of necessity must mean a more profound level of science training and education rather than the trend to less profound and more superficial science.

The limited if not erroneous view of the fundamental basis of disease is revealed when the clinician talks—and even writes textbooks on the subject—about so-called metabolic diseases. It must be emphasized that basically all diseases are primarily the consequence of a cellular metabolic disorder. This is as true of a bacterial or viral infection, or a coronary occlusion as it is of diabetes mellitus. The argument that this term is a convenient basis for classifying a group of diseases does not relieve the clinician who subscribes to this of the burden of ignorance of what is the underlying basis of all disease.

In countries with major problems of medical care and limited scientific traditions and research experience, a serious problem will exist in the attempt to apply the newly emerging scientific principles to clinical situations. The effective application of scientific principles requires the availability of a group of basically trained scientists to be certain that the principle is not only understood to begin with, but also is being appropriately applied and critically evaluated. After all, the great value of a scientific principle is that if fully and critically understood, it will permit a practical application free of empirical considerations. Since the clinician may not in all instances be sufficiently well trained to comprehend, appreciate, and effectively utilize the full potential of all of the new developments in the basic sciences, it goes without saying that any
commitment of a society to deliver effective medical care must at the same time accept a commitment to train and maintain a sizeable group of basically oriented scientists.

Finally, a word should be mentioned about current nutritional research. First off, it seems very clear to me that we have today all the basic knowledge needed regarding essential nutrients but what we lack is the effective means in the different countries for application of this knowledge in the prevention or treatment of primary nutritional disorders. In addition we lack a meaningful definition of health and what constitutes a departure from good health. While there is uncertainty as to the quantitative requirement for one or more nutrients in one situation or other, this search for a magic number seems not likely to yield anything more than a series of quantitative limits which may be relevant to the requirement of a given individual but of limited value as an index of nutritional adequacy—or of good health.

The area of nutritional research which remains to be explored in any depth has to do with that of regulation of cell function. It is obvious that in any overall process there will be a rate limiting requirement for any essential ingredient of that process, and any level below that rate-limiting requirement will affect, perhaps in an all-or non-manner, the operation of that process. What we need to know are the consequences of regulatory failure or inadequacy of any of the multiplicity of regulatory processes which result from dietary restrictions. At the same time, we have to know what degree of adaptability exists and the limits of this adaptability in the regulatory process affected by dietary restriction.
(Dr. Waterlow has discussed this matter in a recent publication (1)).

The means of regulation of cell function are complex and finely con-
trolled; the limits of adaptability in any given dietary situation are
not well understood. The kind of information needed will result not
from the perpetuation of traditional experiments in human nutrition, but
rather from experiments designed on the basis of the newer concepts of
molecular biology and cell regulation. It is thus likely that well
designed animal model systems will be needed to exploit these newer
concepts before suitable experiments can be designed for use with the
human.

References

(1) Waterlow, J. C. Observations on the mechanism of adaptation to low