

Summary of lecture by S. E. Luria on
Molecular Biology: Past, Present, and Future

Molecular biology concerns microbiologists because of both the role they have played in its development and the opportunities and responsibilities it creates for them. Molecular biology may be defined as the program to interpret the specific structures and functions of organisms in terms of molecular structures. It differs from classical biochemistry, which dealt with the chemical reactions of metabolism, by focussing on the machinery rather than the substrates of life. It is that part of biochemistry that deals with the specific structures of genes and gene products and the relation of those structures to functions.

The roots of molecular biology are the structural approach -- purification and physicochemical analysis of specific classes or species of macromolecules -- and the informational approach -- the inquiry into gene structure and gene function.

The structural approach, applied to enzymes, has revealed the key role of primary structure (amino acid sequence) in determining molecular structure, including the complex forms that generate active sites (illustrated with the egg white lysozyme) and allosteric sites. New powerful methods are now at hand to deepen our understanding of the relation of protein conformation to enzyme action. Enzyme regulation can occur by covalent as well as noncovalent changes in protein structure and entire new fields of studies are now open.

The greatest triumph of the structural approach to molecular biology -- Watson and Crick's double-helix model of DNA -- has merged the structural with the informational approach, which had progressed

through the recognition of gene-enzyme relation, the use of phage multiplication as a model for gene replication, the proof of the DNA nature of genetic material of bacteria and phage, and the fine structure analysis of these genetic systems. The DNA structure sparked the flourishing of discoveries in molecular biology -- messenger RNA, the genetic code, and the nature of mutations. Major problems of DNA structure and function remain unsolved, such as the mechanism of DNA replication, the mechanism of homologous pairing, and the role of minor bases of DNA.

The gene has emerged, not as a molecule, but as a segment of a nucleic acid continuum. This has revealed the need for molecular signals indicating where genes begin and end. The signals have partly been deciphered, both as signals on mRNA; indicating where polypeptides will start or stop being made, and as signals on DNA, indicating where synthesis of mRNA units by RNA polymerase will be initiated and terminated. At this level, signals exist for regulatory actions, determining how much of a gene product will be made. Remarkable feedback loops provide uncanny precision of functional regulation of specific genes.

We also observe macroregulatory phenomena, which switch on or off entire groups of genes -- as in the changes in RNA polymerase specificity that accompany sporulation or phage infection in bacteria. Caution is needed before applying such findings in bacteria to the interpretation of developmental changes in higher organisms, in which the modes of gene function may be very different. Thus, for example, in the eucaryotic nucleus RNA synthesis proceeds without concomitant protein synthesis.

The molecular genetic studies of bacteria and phage have clarified the organization of the bacterial genome, its complexities, and its changeability by the addition or loss of plasmids and by the transfer and integration of episomes or of DNA fragments. Apart from the insight into the evolution of the bacterial genetic systems, these phenomena have made it possible to isolate specific genes or groups of genes in the test tube. Coupled with the possibility of synthesizing specific DNA sequences, these discoveries suggest that in the future genetic engineering may become feasible, even in higher organisms including man. The opportunities, dangers, and responsibilities potentially generated by these scientific advances need to be considered and publicized well in advance of their actual realization in order to avoid possible disasters and to foster enlightened applications.

An area of great interest, both practical and theoretical, is that of RNA genes in certain viruses. It has recently been found that some carcinogenic RNA viruses generate in their host cells a DNA transcript which may conceivably become integrated into host cell chromosomes. The possible relation to carcinogenesis, as well as the implications for the problem of early and current gene evolution, are terribly exciting.

Recently the attention of some molecular biologists has turned to what may be called "supramolecular biology" -- the study of the organization of macromolecules to form molecular complexes, membranes, and cellular organelles. This represents an effort to interpret not only molecular function, but also cellular function in terms of molecular structure. In addition to seeking an understanding of the

functional organization of assemblies of proteins and other molecular species (including the role of membranes in DNA synthesis, active transport, and oriented biosynthesis of cellular wall components) one asks a deeper biological question: is all specificity of cells derived solely from the gene structure, or is some information for cellular organization provided by the existing organization itself, acting as a directive primer for growth and possibly evolving in parallel with gene evolution?

Finally, the question should be considered whether molecular biology is a "useful" or an "esoteric" branch of science. Undeniably, molecular biology represents one of the intellectually most satisfying achievements of scientific endeavor and, as such, is a significant part of the cultural patrimony of mankind. Molecular biology has until now progressed mainly on its own internal momentum, receiving little stimulus from practical problems, but has discovered phenomena of great potential implications for human welfare -- or human mischief -- depending on what use society will make of this knowledge.