THE LAST WORD/

by Arthur Kornberg

THE UNIVERSAL LANGUAGE

The basic medical sciences, which in my school-days were completely discrete, have now effectively merged into a single discipline. This astonishing unification is based largely on the expression of anatomy, pathology, bacteriology, physiology, and genetics in a common tongue: chemistry.

Anatomy is studied as a continuous progression from molecules of modest size to the macromolecular assemblies, organelles, cells, and tissues that make up a functioning organism. The transformation of genetics has been even greater. It is no longer a question of whether we *can* sequence the 4-billion base pairs of the human genome. The questions are rather: "What will it cost?" and "Should we do it now?" By manipulating DNA, we create new species at will. As the effects of this more profound grasp of chromosome structure and function become manifest, the impact of this revolution in human understanding on both medicine and industry will prove far greater than even extrapolations from the current successes of genetic engineering.

But where has the development of the new branch of biochemistry, called molecular biology, fallen short? In its rapid and turbulent growth, molecular biology has washed away much of the bridge between biology and chemistry. In the rush and excitement of the new mastery over DNA, attention in biochemistry departments has been sharply shifted away from chemistry and toward major biological problems of cell growth and development. Training in enzymology and its practice have been neglected. Most biochemistry and molecular biology students are introduced to enzymes as commercial reagents, and they treat them as faceless buffers and salts. As long as this inattention to enzyme chemistry and basic biochemistry persists, the fundamental issues of cell growth and development will not be resolved, and applications to degenerative diseases and aging will be delayed.

Molecular biology falters when it ignores the chemistry of the products of the DNA blueprint, which make up the integrated machinery and framework of the cell. Molecular biology appears to have broken into the bank of cellular chemistry, but, for lack of chemical tools and training, it is still fumbling to unlock the major vaults.

We now have the paradox of the two cultures, chemistry and biology, growing farther apart even as they discover more common ground. For the chemists, the chemistry of biological systems is either too mundane or too complex. As a result, they are drawn in the opposite direction, toward a deeper understanding of atomic and molecular behavior. With occasional gestures in the direction of biology, chemistry departments still retain the classical separations into the discrete divisions of organic, physical, and inorganic-analytical chemistry. Perhaps they can now ignore the analysis and synthesis of proteins and nucleic acids because these procedures have become straightforward enough to be machine-programmed and -operated. But the structure-function relationship of these macromolecules is another matter. Polymer chemists, for example, are frightened away not only by the size and complexity of macromolecules, but even more by their association with water, a habitat that introduces unacceptable complications into otherwise satisfactory calculations.

On the other hand, biologists now obtain commercial kits with which they measure and use enzymes and manipulate genes. This enables them to set their sights on important questions beyond the current reaches of chemistry. In these research studies, the effects of manipulating the cell's genome and the actions of viruses and various agents are almost always monitored with intact cells and organisms. Rarely is an attempt made to examine a stage in the overall process in a cell-free system. This reliance in current biological research on intact cells and organisms to fathom their chemical operations is a modern example of the "vitalism" that befell Pasteur a century ago, and that has permeated the attitudes of every generation of biologists before and since.

The reductionist approach that I am espousing has had major success in this century in explaining body metabolism and how it is affected by inborn errors, drugs, and disease. Can we come as close to understanding the mind and human behavior? The first and most formidable hurdle to accept, without reservation, is that the form and function of the brain and nervous system are simply chemistry. Brain chemistry may be novel and very complex, but it is expressed in the familiar elements of carbon, nitrogen, oxygen, phosphorous, and sulfur that constitute the rest of the body. Brain cells have the same DNA all cells do; the basic enzyme patterns are those found elsewhere in the body. Hormones once thought unique to the brain are now known to be produced in the gut, ovary, and other tissues, and even in plants or protozoa. In brief, my plea is for a major focus of research on brain chemistry, in animals and humans, normal and sick. With the application of simple biochemical techniques, we will be able to map and assay a number of specific brain functions. Further advances will come rapidly when additional chemical techniques are developed to explore the nervous system. In the next decades we will see astonishing revelations about memory, learning, personality, sleep, and the control of mental illness.

In resolving the conflicts between the biological and chemical cultures, and educating both scientists and lay people, we must strive to understand as much of life as we can in rational terms. Much of life can be expressed in chemical language. Chemistry is an international language linking the physical and biological sciences. We must teach the language of chemistry early in grade school and continue its use in high school. It is a language that enables us to make the clearest statements about our individual selves, our environment, and even certain aspects of our society.

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