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The Two Cultures: Chemistry and Biology[1]

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Much of life can be understood in rational terms if expressed in the language of chemistry. It is an international language, a language for all of time, and a language that explains where we came from, what we are, and where the physical world will allow us to go. Chemical language has great esthetic beauty and links the physical sciences to the biological sciences. Unfortunately, the full use of this language to understand life processes is hindered by a gulf that separates chemistry from biology. This gulf is not nearly as wide as the one between the humanities and sciences on which C. P. Snow focused attention. Yet, chemistry and biology are two distinctive cultures and the rift between them is serious, generally unappreciated, and counterproductive.

The historical roots of chemistry and biology are intertwined in many places, and the conflicts between the chemistry and biology cultures go far back as well. A particularly fascinating example is the attempt to understand the fermentation of sugar to alcohol by the yeast cell. It had been known for over 6000 years that the insipid juice of the crushed grape can be transformed in a few days into an intoxicating, tasteful wine. But the nature of the fermentation remained a total mystery until nearly the 19th century, when it became known that the compound fermented by grape juice was sucrose and that the principal products were alcohol and carbon dioxide.

Alcohol fermentation could have been solved by any of the great chemists of the early 19th century. Berzelius of Sweden or Liebig and Wohler of Germany might have succeeded except for their neglect of biology and their failure to recognize the central role of yeast in fermentation. Pasteur, an equally great chemist, did appreciate the role of yeast, but his exaggerated immersion in biology caused him to neglect his chemical roots and miss discovering that enzymes are the vital force of fermentation. To what extent the yeast cell and its chemistry are responsible for making wine and brewing beer became the subject of one of the most protracted and vitriolic polemics in science.

From the 17th century on, since Antony von Leeuwenhoek first saw yeast cells in fermentation sediments, many believed these globules to be the driving force of the process. Against this view, the chemists, despite prescient ideas about catalysis of chemical reactions, were contemptuous of attributing the chemistry of fermentation to yeast cells. How tragic that these outstanding scientists who correctly focused on the chemical

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essence of the fermentation process were so blind to the biological entity responsible for this chemistry. They discarded the baby with the bath water.

Against this background, Pasteur did his epochal work confirming and extending the earlier experiments on the preeminence of the living yeast cell. In the 30-year war of words with his enemies in chemistry, Pasteur emerged the clear victor, but at an intolerable cost. Pasteur, who as a youth discovered stereochemistry, now allied himself with vitalism. Having failed to extract a juice from the yeast cell that would convert sugar to alcohol, he concluded that nothing short of a living cell could carry out this complex chemical reaction. And so the discipline of modern biochemistry remained unborn for over 30 years until Eduard Büchner, in Munich, near the start of this century, accidentally discovered fermentation by yeast juice steeped in sugar. With this discovery, biochemists could then sort out the molecules responsible for the chemistry that ferments sugar to sustain the life of a yeast cell and power the muscle of an animal.

Observing the plot and nearly all the characters in the yeast and muscle stories to be the same, the unity of biochemistry throughout nature was unmistakable. Found subsequently in virtually all aspects of cellular growth and function in plant, animal, and microbe alike, this unity is one of the major revelations of our century.

It might have been expected that the separation between chemistry and biology in the 19th century would have been bridged by the emergence and growth of biochemistry in this century. In biochemistry, one could fulfill the wish to understand the chemical basis of cellular function in fermentation and photosynthesis, in muscle contraction and digestion, and in vision and heredity. Despite its enormous success in solving these and other problems, biochemistry has nevertheless failed to fill the gulf between chemistry and biology. Instead, as I shall discuss, biochemistry itself is being pulled apart by the separate drifts of the two cultures from which it was assembled.

By 1950, organic chemistry had been enriched by more than a century of impressive achievements. Organic chemists had prepared and characterized the sugar and amino acid substrates and products of enzyme reactions. They belonged to a proud and venerable science. Insights into the structure and reactivity of carbon compounds had made possible the synthesis of the extraordinarily complex alkaloids and antibiotics found in nature. The problem was that organic chemists placed arbitrary boundaries on their science. Although, in their pursuit of natural products, they might still eagerly seek the challenge of an Amazonian butterfly pigment, they would not accept nucleic acids, proteins, and enzymes as proper natural products. I recall in an organic chemistry textbook of 1960 a reference to the importance of proteins "as a *source* of amino acids for living cells". This is like saying the importance of an automobile is as a source of its parts.

When a National Academy of Sciences committee surveyed the status of chemistry in 1964, chemistry was defined as "the research activities of chemistry departments in this country". There was little recognition of the chemical research in biochemistry and biology departments. Nucleic acids, proteins, and enzymes had been excluded from the province of legitimate chemistry, and chemists had excluded themselves from the essence of biology. Major changes have taken place in the past 20 years. A 1985 report on the status of chemistry claims its share in the advance of genetic chemistry and takes pride in its future. Increasingly, young professors in chemistry departments are pursuing problems of biologic significance. Yet, a recent recipient of the Nobel Prize in chemistry, when asked by a newspaper reporter whether he considered applying his novel technique to the study of enzymes, replied: "I'm not about to switch from science to religion."

Chemists were not alone in ignoring the chemistry of living things. The physicists, who during the post World War II period turned their attention to biology, generally focused on genetics and hoped to avoid chemistry for which they had little patience. Those who applied physical methods to determine the structure of proteins and nucleic acids expected that they could infer biological properties directly from the structures of these molecules and thereby bypass biochemistry.

Many biologists were just as eager to remain clear of chemistry. Particularly so were those concerned with systematics, evolution, and behavior. Even those biologists who realized that enzymes and proteins determine the shape, function, and fate of cells and organisms shuddered at the multiplicity of enzymes and their chemical complexity.

Having criticized the biologists for their lack of appreciation of chemistry and the chemists for their disinterest in biology, one might hope that the gap between them would be filled by biochemistry. Biochemistry, by using the techniques and principles of both chemistry and biology, contributed in the past decade to an extraordinary coalescence of both cultures: the development of genetic chemistry. As most everyone is aware, recombinant DNA technology has made possible the mass production of interferons, interleukins, rare hormones, and superior vaccines. The impact on medicine and the pharmaceutical industry have been nothing short of revolutionary, and agriculture will soon follow. Even more profound than the feats of genetic engineering is what this conjunction of chemistry and biology has done to erase the sharp boundaries that had separated classical compartments within the biological and medical sciences.

The basic medical sciences, which in my school days were completely discrete from one another, have now effectively been merged into a single discipline. This astonishing development, this unification, is based largely on the expression of anatomy, pathology, bacteriology, and physiology in a common tongue, the language of chemistry. Anatomy, the most descriptive of these sciences, and genetics, the most abstract, are now simply 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. A serious question only 40 years ago was whether genetic phenomena operated by known physical principles. Of course we now understand and examine genetics, heredity, and evolution in simple chemical terms. Chromosomes and genes are analyzed, synthesized, and rearranged.

It is no longer a question of whether we *can* sequence the 4 billion base pairs of the human genome. *Rather*: "What will it cost?" and "Should we do it now?" By manipulating DNA, we modify 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 medicine and industry will prove to be far greater even than extrapolations from the current successes of genetic engineering.

Where has the development of this new branch of biochemistry, called molecular biology, fallen short? In its rapid and turbulent growth, molecular biology has washed away much of the bridge to chemistry. In the rush and excitement over the new mastery over DNA, attention in biochemistry departments has been sharply shifted to major biological problems of cell growth and development and away from chemistry. Training in enzymology and its practice have been neglected. Most biochemistry and molecular biology students are introduced to enzymes as commercial reagents and treat them as faceless as 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 their application to degenerative diseases and aging will be delayed.

Molecular biology falters when it ignores the chemistry of the products of the DNA blueprint—the enzymes and proteins, and their products—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 physical understanding of atomic and molecular behavior. With occasional gestures in the direction of biology, chemistry departments still retain the classical separations into 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 nucleic acids and proteins but even more by their intimate association with water molecules, a habitat which introduces unacceptable complications into otherwise satisfactory calculations.

Pharmaceutical chemistry was until recently the bastion of organic chemistry. Many thousands of compounds were synthesized each year in the search for alternative or superior drugs for the treatment of various diseases. After many years of this kind of effort, the likelihood of discovering winners among antibiotic, antiulcer, antihypertension, or anticancer drugs has become rather slim. At the same time, the requirements by the Federal Drug Administration for safety and efficacy have become increasingly rigid. The development of a new drug through the many required trials to the point of FDA approval now costs over $100 million dollars and takes 8–10 years. Two major pharmaceutical companies have each spent over 200 million dollars annually for 10 years without a significant new drug to show for it. No wonder that the research orientation and the leadership in the pharmaceutical industry have been shifting from chemistry to biology. With the dramatic entry of genetic engineering, there is the prospect that these techniques of molecular biology can be used to prepare natural hormones, interferons, interleukins, and other body substances in quantity and to use them to correct imbalances and deficiencies of these substances in disease states. Furthermore, the techniques of genetic chemistry make it possible to probe basic body mechanisms and understand metabolic traffic well enough to use these agents to enhance our well-being. The executives of the pharmaceutical industry, generally trained in business and law, often see more clearly than the scientists they employ the urgent need to merge the cultures of chemistry and biology.

Let us examine the status of biology. Previously a loose confederation of botany, zoology, genetics, and museum departments, biology is now coalescing because of its use of chemical techniques and language. Evolutionary biology, organismal behavior, and cellular physiology are finding common explanations in the genes and proteins that can be traced through evolution to their current locations and functions. Biologists now obtain commercial kits with which they measure and use enzymes and analyze and manipulate genes. This enables them to set their sights on important problems beyond the current reaches of chemistry. For example, popular interest now centers on understanding the growth and development of cells and tissues. Many laboratories are preoccupied with the origins of cancer and hope that studies of cancer processes will also provide insights into the normal patterns of growth and development. Enormous efforts are devoted to AIDS, both to the virus itself and on how it undermines the immune system.

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 an 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 as we have metabolism? The first and formidable hurdle is acceptance without reservation that the form and function of the brain and nervous system are simply chemistry. I am astonished that otherwise intelligent and informed people, including physicians, are reluctant to believe that mind, as part of life, *is* matter and *only* matter. Perhaps the repeated failures of science to analyze social, economic, and political systems have perpetuated the notion that individual human behavior cannot be explained by chemistry and the physical laws that govern all matter in the universe.

Brain chemistry may be novel and very complex, but it is expressed in the familiar elements of carbon, nitrogen, oxygen, and hydrogen and of phosphorus 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.

Despite the stunning successes of genetic chemistry and the promise of understanding the brain, the importance of chemistry as the foundation of all medical and biological science is not commonly appreciated. Failure to recognize this simple truth, as I have mentioned, is common among both physicists and biologists. As for the public, distinctions among the natural sciences have little meaning. Few can even distinguish an atom from a molecule, a virus from a bacterium, or a gene from a chromosome. It is no wonder that journalists and lawmakers keep asking us whether a molecule, a virus, or a cell is living. They become impatient when we fail to give them a straight and simple answer as to where and when life begins and ends.

"Better things for better living ... through chemistry" was the slogan of the Du Pont Company advertising campaign for many years. The purpose of the slogan's message was to inform the public of the value of plastics, herbicides, and industrial chemicals for our individual and collective well-being. The campaign was successful for a time in promoting good will for chemistry and the Du Pont Company. Then, "through chemistry" was dropped when it became known that these chemicals, as is true of all things, natural or man-made, can be toxic too. In the food market recently, I overheard a little girl saying: "Mummy, you shouldn't buy that. It has chemicals." What is worse, neither the child's mother nor the store clerk found her remarks strange or disturbing.

No advertising campaign, or our educational system, including the excellent Nova television programs, has taught the public that life is a chemical process. These efforts have not made it clear that the human organism, its form, and behavior are determined by discrete chemical reactions, as are its origin, its interactions with the environment, and in important respects, its fate. A lack of public understanding is evident by the ways in which people commonly refer to the success of a collective social effort, such as a winning football team or business group, as having the right chemistry. How do they judge whether the chemistry is right? They apply the litmus test.

In resolving the conflicts between the chemical and biological cultures, and educating both scientists and lay people in this regard, 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 links the physical and biological sciences, the atmospheric and earth sciences, and the medical and agricultural sciences. Chemical language is rich and fascinating and creates images of great esthetic beauty. We must teach it 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.

By the same token, 3 billion years of cellular evolution has perfected molecules and molecular societies of awesome chemical sophistication. The chemist interested in catalysis, stereochemical specificity, polymer structure, metallic–organic reactions, surface effects, and a hundred other facets of chemistry will be challenged and instructed by the myriad of forms in biology. At a social level, the urgent need to understand the chemistry of heredity and nutrition, of health and disease, will prove to be the most intimate and compelling means for informing our citizenry of the importance of chemistry.

In a cross-cultural forum provided by a recent meeting of the American Association for the Advancement of Science, I was led to wonder whether a sociological study of chemists and biologists might be helpful in understanding their different styles. Are chemists more conservative, analytical, and clannish than biologists? Are biologists more artistic, eclectic, and right-brain dominated than chemists? Which of the language barriers is more formidable and needs earlier imprinting? How much of the cultural difference between chemists and biologists is attributable to highly evolved training and vocational patterns? What are the consequences of most chemists being employed in industry and most biologists in academia? This sociological investigation could start off without threat of racial, political, or sexual opposition. Insights gained from such a study might be useful for science training and practice in the future.

In the long view, these cultural differences between chemistry and biology are dwarfed by our overall devotion to the larger culture of science. It is the discipline of *science* that enables *ordinary* people, whether chemists or biologists, to go about doing the *ordinary* things, which, when assembled, reveal the *extraordinary* intricacies and awesome beauties of nature. Science not only permits them to contribute to grand enterprises but also offers them a changing and endless frontier for exploration. I like the remark of Einstein, who has proven as quotable in philosophy as in physics. He once said: "The most beautiful experience we can have is the mysterious. It is the fundamental emotion that stands at the cradle of true art and true science. Whoever does not know it and can no longer wonder, no longer marvel, is as good as dead."