Chemistry — the *lingua franca* of the medical and biological sciences

Despite a large cultural difference between chemists and biologists, chemistry is becoming the common language for all the biological sciences. Now the challenge is to teach the language of scientific achievement to the public and to our representatives in Washington.

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Genetic engineering and related biotechnologies represent the most revolutionary advance in the history of biological science. We have an inexhaustible supply of genes and simple and efficient techniques to track and capture them. The term revolutionary is generally overused, but not here. The effects of this advance on medicine, agriculture, and industry can hardly be exaggerated.

Yet even more revolutionary, but generally unnoticed, is a development that lacks a name or obvious applications. I refer to the coalescence of the numerous basic medical sciences into a single, unified discipline, which is providing us with a more fundamental understanding of nature and will inevitably lead to even more remarkable and unanticipated practical applications. This unified discipline of biological science has emerged because it is expressed in a single universal language, the language of chemistry.

Much of life can be understood in rational terms if expressed in the language of chemistry. It is an international language, a language without dialects, 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. Yet when I took my training in medicine, the importance of chemistry was hardly noticed.

When I entered medical school in 1937, research and teaching in the sciences basic to medicine were carried out in many discrete departments: anatomy, bacteriology, physiology, biochemistry, pathology, and pharmacology. They were as separate as the departments of physics, chemistry, and biology were then and still are today. Departments of genetics and neurobiology did not yet exist in medical schools. The situation now is radically different. Research and teaching in all the basic science departments are interdependent and really indistinguishable.

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The current unity of the basic medical sciences has come about because these previously diverse disciplines are now expressed in the common language of chemistry. Anatomy, the most descriptive of these sciences, and genetics, the most abstract, have become chemistry. Anatomy can and should now be studied as a continuous progression from molecules of modest size to the macromolecular assemblies, organelles, and tissues that make up a functioning organism. The transformation of genetics has been even greater. A serious question only 50 years ago was whether genetic phenomena operated by known physical principles. Of course we now understand and examine genetics and heredity in simple chemical terms as DNA.

One language, two cultures

In our dedication to understanding all of life as chemistry, we must take account of a century-old rift that has separated the cultures of chemistry and biology. It might have been expected that this rift would be bridged by the emergence of genetic chemistry. Paradoxically, chemistry and biology seem to be growing farther apart even as they discover this common ground. This rift, although not as wide as that (dramatized by C.P. Snow) between the sciences and humanities, is nevertheless serious, serious enough to raise our concerns.

Having thought and written on this two-culture problem for some years [1], I have come to wonder whether the divisions between chemists and biologists might be driven by some basic differences in their emotional and cultural patterns. Almost all the chemists and biologists I have asked about this agree that chemists and biologists do belong to separate cultures.

Chemists seem more conservative, analytical and clannish. They focus on molecules: an exotic alkaloid, antibiotic or arcane pigment. They seek the challenge of a molecule with many chiral centers at the very limit of synthetic difficulty and vie to obtain it in the fewest steps with the best yield. They obtain precise data with relatively few and elegant techniques. To them, the chemical

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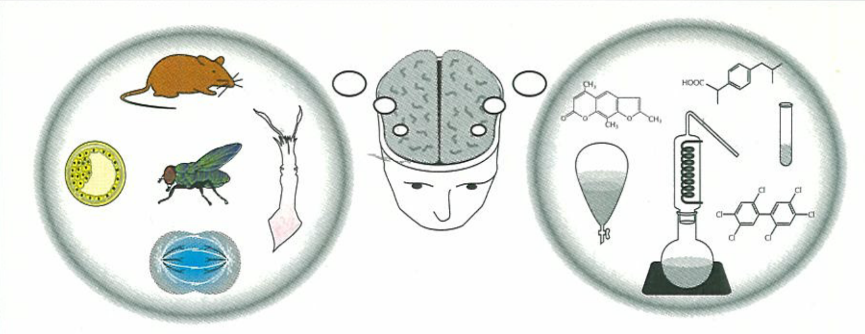

Fig. 1. The rift between the two cultures of chemistry and biology might derive from the apparently more right-brain-dominated character of biologists and left-brain-dominated character of chemists.

monotony of proteins and nucleic acids overrides their biological importance.

Biologists on the other hand seem more artistic, eclectic and right-brain dominated. They focus on complex phenomena in cells and organisms, using a wider range of techniques with less precision (Fig. 1). They welcome mysteries and complexities and some are disappointed when the veil over a phenomenon lifts to expose molecular details.

In essence, for the chemist, the chemistry of biologic systems is either too mundane or too complex. For the biologist, the intricacies of organic synthesis and the mathematical rigor of physical chemistry are beyond reach and irrelevant. Of course there have been some illustrious exceptions, scientists who bridged both cultures. Pasteur was one, and, in our generation, Linus Pauling was another. Oswald Avery, working at Rockefeller, was obsessed with the pathogenesis of lobar pneumonia and pursued a phenomenon of pneumococcal strain transformation to the point of discovering that DNA is the molecule of heredity. More and more scientists are now following their lead, producing a remarkable blending of the two cultures. In recent history there has been a striking collection of major chemical advances driven by basic biological questions. Perhaps the cultural differences are becoming less important as the interest of the problems becomes clearer to both sides.

Science as the enemy

Of greater concern than the cultural rift between chemists and biologists is the rising tide of public fear, distrust and rejection of science, both chemical and biological. Chemistry has had a poor image for some time. 'Better things for better living . . . through chemistry' was the DuPont slogan for many years. The slogan informed the public of the value of plastics, herbicides, detergents and industrial chemicals for our individual and collective well-being. Then the slogan was abbreviated to: 'Better things for better living.' The words 'through chemistry' were dropped when the public became aware that chemicals, as is true of all things, natural or man made, can be toxic too. A few weeks ago, a large bank in New York, The Chase Manhattan, merged with an even larger bank, The Chemical Bank. Not surprisingly, the new and now the very largest bank will not have chemical in its name. In fact, the only times we hear something good said of chemistry these days are references, as in newspaper articles, to the good chemistry of a winning football team, or the improved chemistry between Israel and Jordan.

The image of biologists has not been doing well either. Hollywood has chosen them as their recent villains. Lacking communists as culprits, and squeamish about racial bashing, hit movies — for example, 'Lorenzo's Oil', 'The Fugitive', and 'Jurassic Park' — have demonized doctors and scientists. Never mind that well-controlled studies now show Lorenzo's oil is of dubious value [2], that criminal activity by a major drug company as in 'The Fugitive' is exceedingly uncommon, and that we all know the cloning of a whole dinosaur genome in 'Jurassic Park' to be utter fantasy.

Perhaps Hollywood has taken its cue from Congressional committees and the headlines they generate that make it seem science is wracked with fraud. Congressmen and reporters fail to recognize that the practice of science defines rather strict boundaries for behavior which are effective in all but the very rare instance, one in a thousand or less, of the irrational and the criminal. In the practice of science, the more startling the claim, the more it attracts attention, and if false, the sooner it is exposed.

Learning from bacteria

In my research, I have adhered to two articles of faith: that the study of enzymes can bring us to the core of biology and that the enzyme systems of *E. coli* and prokaryotes will be prototypical for all forms of life. Because of the universality of biochemistry, our studies of how *E. coli* replicates its own genomes and those of its plasmids and phages have anticipated the enzymes of eukaryotic replication: the helicases, topoisomerases, polymerases, primases, ligases and binding proteins. There are fascinating variations, but the basic themes are much the same.

Not only has *E. coli* blessed us with insights into the mechanisms and machines of catalysis and regulation of the basic biochemical processes, but it has also been instructive in social behavior. There are its well-studied tropisms for attractive foods and places, avoidance of the obnoxious, the inclinations to form colonial societies, the appetite for sexual congress, and how it copes with stress. *E. coli* in stationary phase turns on and turns off hundreds of genes. Based on a complex medley of signals, the *E. coli* culture knows that it has not simply missed its lunch, but that feasting is over and a period of famine and stress lies ahead. The major adjustments in the physiology and morphology of cells, including newly discovered mechanisms for adaptive mutations, enable it to endure the stresses and deficiencies of hard times. I am coming to believe that what we learn from organisms in the stationary phase will have profound significance for how we as humans cope with not only the biological issues of mutagenesis, carcinogenesis and aging but also the social issue of diminished support for science.

In the last decade, with more drastic reduction in support for a larger enterprise, science has entered the stationary phase. We may succeed with sufficient effort to secure brief bursts of growth here or there as with microbial or human cultures. But for the survival of science, so crucial to our civilization, we must now be resourceful in adapting to the stringencies of the stationary phase.

I will venture an admonition and a reflection. In the stationary phase, we have become ever more vulnerable to the severe cuts in federal support now proposed in Washington. We must not let anyone be deluded into thinking that these cuts will be replaced to any significant extent by scrounging among private and industrial sources. Over 90 % of the support for the revolutionary advances in biomedical sciences in the post-World War II period came from the NIH. No industrial organization would have invested many millions of dollars annually, for decades, in projects that have no direct relevance to marketable products or devices. We must make it clear to citizens and legislators that virtually all the important advances in medical science in the past century started from curiosity about questions in physics, chemistry and biology utterly unrelated to any of the uses that had stemmed from these basic discoveries.

We are urged to do: strategic basic research! Targeted basic research! How can we make clear the oxymoronic nature of these terms? The major problem is how to make the public understand that too much focus on practical results is actually counterproductive. Even to scientists it may seem unreasonable that the best way to solve an urgent problem (for example, to find a cure for a disease) is to pursue apparently unrelated questions in basic biology or chemistry. Call it counterintuitive or difficult to assimilate — but it is a fact that the pursuit of curiosity about the basic facts of nature has proven throughout the history of medical science to be the most practical, the most cost-effective route to successful drugs and devices. Investigations that seemed totally irrelevant to any practical objective have yielded most of the major discoveries of medicine. X-rays were discovered by a physicist observing discharges in vacuum tubes, penicillin came from enzyme studies of bacterial lysis, the polio vaccine from learning how to grow cells in culture, genetic engineering and recombinant DNA from reagents developed in exploring DNA biochemistry.

As scientists, we lack the skills and resources to make our case effectively. What we must do — and I have urged this for many years — is to organize the resources that we do have and employ professional media personnel, who will be effective in conveying the important message that basic research is the lifeline of medicine. University presidents and trustees, research foundations, disease organizations, professional societies and pharmaceutical companies should stop competing with each other and band together. They should contribute the resources needed to lobby vigorously with people skilled in media communications — such as science journalists — whom we as scientists would inform eagerly of the material needed to make our case. If the National Rifle Association can be so effective with its message, why can't we do at least as well with a far better one?

A final reflection. In the face of so much uncertainty, would I, today, recommend a career in science to my grandchildren? Emphatically yes! Science is unique among all human activities — unlike law, business, art or religion — in its identification with progress. As for the means to do science, I think back to 1943 when I was studying rat nutrition at the NIH and decided that research was more attractive than the clinical medicine I had been trained in and had chosen to do. There were no grants then, laboratory resources were meager and academic jobs were almost nonexistent. Biochemistry was a cottage industry. Those were not the good old days.

Yes, I've been poor and I've been rich. Rich is better. But rich or poor, science is great! To frame a question, be it ever so humble, and get an answer that opens a window to another question, and to do this in the company of like-minded people with whom one can share the thrill of unanticipated and extended vistas, is what science is all about. Pasteur, during his last hours, attended by his devoted pupils, kept repeating his favorite words: "Il faut travailler." It is the work itself that will sustain us in the difficult days and years ahead.

References

1. Kornberg, A. (1987) The two cultures: Chemistry and Biology. *Biochemistry* **26**, 6888–6891
2. Aubourg, P., *et al.*, Bougnères, P.-F. (1993). A two-year trial of oleic and erucic acids ('Lorenzo's oil') as treatment for adrenomyeloneuropathy. *New Engl. J. Med.* **329**, 745–752.

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