Some thoughts on chemistry and biology

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During recent years, many members of the biological community have altered their research approach to include more quantitative and especially chemical techniques. As we chemists broaden our horizons and the biologists more sharply focus their view, we suddenly find ourselves, metaphorically at least, staring at each other. Sadly, for the most part, we are speechless.

Our lack of conversation is not the shock of suddenly meeting our counterparts face-to-face, but rather that we speak different languages. Chemistry has become a quantitative, if not mathematical discipline. Biology has more recently applied quantitative and mathematical methods to itself. Although the languages and traditions remain different, the convergence has resulted in a functional parallelism. What is site-directed mutagenesis or the polymerase chain reaction if not chemistry? What is the pursuit of enzyme-targeted pharmacological agents if not biology?

Can or will the biologists do chemistry themselves? Biologists can unquestionably make structural alterations in natural compounds. Site-directed mutagenesis is the replacement of an amino acid within a complex protein. The modern biologist has an arsenal of tools that may be used to alter one or more amino acids in a protein. After alteration, the biological assay will report what change in function the chemical variation has engendered. The question is whether or not the alterations will be understood in clear, structural terms from which mechanistic inferences at the molecular level can or will be drawn.

Chemists need to educate biologists about the meaning of structural alterations. The remarkable advances in spectroscopic and other analytical tools have permitted chemists to understand the consequences of structural alterations. At the present level of resolution, the biologist does not. In most cases, the biologist does not have the chemical training even to appreciate the problem. Chemists can—and should—help their biological colleagues to appreciate the issues.

The biologist, on the other hand, needs to appreciate the chemist's approach. When a biologist desires a solid state structure, he or she is willing to dedicate a graduate student or other coworker to the enterprise. The student will work, sometimes for several years in or with an X-ray lab, to obtain the structure of a protein important to his or her own lab. When the structure is solved, there is no doubt that colleagues from both labs will be coauthors on the resulting publication. This is not always so clear when a chemist contributes a special compound to an on-going research effort. The synthesis of a single chemical compound may appear minor, but it may have required enormous intellectual effort prior to synthesis. This may not be apparent to the biologist who, without malice, may underestimate the contribution.

A number of chemistry departments around the world have begun to evolve in the direction of biology. Indeed, chemistry departments everywhere have increasingly focused attention on either biology or materials or both. Some chemistry departments have even changed their names to indicate their broadened scope. New departments have arisen that are populated partly by chemists who wish to pursue biological, materials, or "nanotechnological" applications. These are certainly important initiatives that will keep the chemical sciences vital. A material question is whether or not the formation of new departments is "balkanization" or really makes sense.

Students typically are exposed to chemistry as an identifiable discipline at the high school or gymnasium level. Even in "advanced placement" or college level classes that are taught to pre-university students, the scope of such courses is limited. The limitations include the small number of students seeking advanced chemical studies at the pre-university level, the school facilities, and the training and experience of the teachers themselves. Many high schools are blessed with excellent students and wonderfully capable and dedicated teachers. Still, the proportion of both in any given setting may be small. In many communities throughout the world, there simply are not enough teachers or interested students to make advanced science courses a practical offering. This leaves the bulk of a basic chemical education to be acquired at the university level.

Throughout the world, education in chemistry follows a progression from "general" to organic to physical chemistry and is accompanied by the appropriate mathematics and physics courses. The details and even the extents of the programs vary by country so the discussion below is focused on the US, which is most familiar to the author. The comments, with the appropriate adjustments for the specific educational system, are extensible to chemical programs at large in the international community.

A typical undergraduate curriculum in the United States requires a student to study chemistry at successive levels beginning with the first or freshman year. This is a full year course and is the critical precursor to organic chemistry, the course that consumes the second year of study at the university level. Some curricula also require a course in analytical chemistry during the second year. A chemistry "major" (*i.e.* a student whose primary focus is chemistry) in the U.S. will typically take physical chemistry during the third (junior) year along with instrumental analysis. Various advanced laboratories and a one-semester inorganic chemistry course normally complete the undergraduate curriculum. Increasingly, a course in biochemistry is recognized as being useful for the well-rounded chemist. Even so, it is easy for an excellent undergraduate chemistry student to completely escape any contact with biology.

The lack of integration between chemical and biological curricula is unfortunate. For one thing, without the encouragement of a diverse academic program or wise counsel by interested faculty, the modern undergraduate chemistry student may completely miss gaining a perspective on modern biology. A course in biochemistry, for all its great value, does not typically deal with issues such as cell cycle, development, genetics, apoptosis, transport, membrane dynamics, fusion, endocytosis, and so on. This is not to diminish the importance of a rigorous course in biochemistry but rather to acknowledge that its coverage is necessarily limited.

Without some exposure to biology, how will the theoretical student know of the broad initiatives in biomedical computing? There is a critical need for computational biologists to address the enormous amount of information accumulating in genetic sequence projects. Who better than the theoretical chemist is there to deal with this information? Will the undergraduate chemistry major whose exposure to biology is limited consider computational biology as a career path? Will the student leaning toward analytical chemistry appreciate the vast need for methodology to assess and to quantitate biological processes? The development of analytical reagents suitable for application to biological systems is a frontier of paramount importance and potential impact. Who will develop the chemical methodology needed?

Nearly a decade ago, some faculty of the Washington University School of Medicine recognized the need to integrate quantitative scientists into the biomedical community. Of course, there have always been chemists, physicists, engineers, mathematicians, and others who have enjoyed productive and distinguished careers in medical schools. These individuals have often had highly collaborative research programs that it would have been difficult to undertake elsewhere. The scientists themselves have often been somewhat isolated in the sense that there was not a critical mass of like-minded individuals. Further, the natural affinity one might expect to exist between medical schools and chemistry departments is often impeded by distance. Simply put, medical schools and chemistry departments are typically in different geographical locations and even the smallest physical separations are often significant barriers to cooperation.

Interactions between the Washington University School of Medicine and its Chemistry Department are likewise impeded by a physical separation. The experiment that was tried involved the formation of a program in chemical biology in the Medical School. Chemically-oriented faculty within the Medical School and interested faculty from the Chemistry Department joined together to create a critical mass of about 20 faculty members. Joint seminars and journal clubs were organized and students were admitted to the program through the Medical School's normal pre-clinical recruiting mechanisms. It is the question of student recruitment that emerged as the major problem.

Undergraduates who are trained in chemistry typically apply to graduate programs in chemistry. This is perfectly reasonable. Most undergraduate advisors who teach in chemistry departments have probably never been in a medical school. Most of those who have visited will not have spent enough time in the environment to fully grasp the culture and perspective. Would most chemistry professors recommend that their talented graduates apply to a program in chemical biology in a medical school? The typical undergraduate chemistry major has little biological training and the mentor has little familiarity with a medical school environment. If the student takes the initiative to apply to a medical school to be educated in biologically-oriented chemistry, from whom will he or she seek advice? Will the student's advisor be able to proffer wise counsel?

Our decade of experience with the chemical biology program suggests that many of the excellent students who apply to our program are already "differentiated." They decided early, by whatever mechanism, that they were interested in chemistry in combination with biology. Many took courses offered in biology, biochemistry, or biophysics departments, some of which were taught by medical school faculty. In many cases, the interests of these students are often already beyond a chemical biology program and their graduate research projects could as well be conducted in a department of cellular biology or microbiology. The collaboration of excellent students with outstanding faculty is to be encouraged but cell biology is simply not bioorganic or bioinorganic chemistry.

The Chemistry Department at the Washington University has also recognized the advantage of closer collaboration with medical school faculty. The relationship expands their faculty base, the scientific expertise and course offerings, and the attractiveness of the Department to those students who are interested in biology but are not ready, for a variety of reasons, to change to a medical school environment. Mechanisms are currently being discussed that will lead to a mutually beneficial paradigm of chemistry-medical school cooperation.

This cooperation has been fostered, in part, by the National Institutes of Health. Jointly, the medical and main campuses have obtained a training grant from the NIH to foster interactions at the chemistry-biology interface. A number of "CBI" training grants have been awarded in the U.S. In the Washington University case, it served to dramatically change the level of interaction between the faculties and students and generally to enhance mutual respect.

The discussion above is focused on one case in one country. Undoubtedly both the issues and the innovations will find examples throughout the world.

We chemists tend to be somewhat parochial in our view of science and the world. Chemistry has been called "the central science." This important location in the landscape of science places upon us the burden of looking outward to expand our own horizons and the capabilities of our sister disciplines. Quantitative approaches and careful structural thought are benchmarks of the chemical discipline. Nowhere is the impact of the chemist's skills and perspectives of greater potential than on the emerging research areas in modern biology. A corporate research lab can assign individuals that have a broad range of expertise to undertake a specific problem. It is not so straightforward in most university settings. We need to think seriously about how cooperation can be fostered and what mechanisms will permit collaboration between the biomedical and chemical communities to prosper. Such interactions will require faculty, students at all levels, instrumentation, administrative and monetary support, and University-wide determination. Traditional administrative territories will be threatened by inter-campus and interdisciplinary cooperation. The universities that overcome these obstacles will achieve greatness in the 21st century. Those that think and act traditionally will not.