Future of Chemistry | Special Issue 150 Years of BASF

DOI: 10.1002/anie.201410884

Reinventing Chemistry

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change · chemistry · science

The End of One Era and the Beginning of Another

Nothing goes on forever. The years following World War II were very kind to chemistry. The research universities and the chemical industry—one of the most beneficial partnerships our technologically sophisticated society has seen—developed the forms that we know. Industrial chemistry became a core part of the industrial world; academic chemistry explained how atoms and molecules made reality happen.

How did it start? World War II generated a flood of technology relevant to chemistry. High-octane fuel and synthetic rubber were the first of many major expansions of the chemical industry. Catalysis—especially heterogeneous catalysis—became the core of large-scale synthesis. Methods to separate molecules revolutionized purification. New forms of spectroscopy uncloaked molecular structure. Quantum chemistry rationalized chemical bonds, and molecular orbital theory made these rationalizations relevant to complex molecules. Computers, and computer-aided simulations, began their development. The technical and conceptual capabilities of chemistry increased enormously. At the same time, the economic reconstruction of Europe and Japan, and the rebuilding of the U.S. infrastructure, provided expansive commercial opportunities. Although the rapid growth of chemistry initially concentrated in the United States, it soon spread across the developed world.

It was a very easy time for chemistry: complex organic synthesis, quantum chemistry, laser spectroscopy, production of polyolefins, organometallic chemistry, molecular beams, medicinal chemistry, and countless other areas developed and flourished. The range of commercial and scientific opportunities was very large.

This prolific era is over, and chemistry is now facing classes of opportunities, and obligations to society, that are even *more* interesting, but entirely different. They will require—I believe—a new structure for the field, and raise a fundamental question: "What must chemistry be in the future?" It has been the field of science that studied atoms, bonds, molecules, and reactions. And 50 years from now? Will it still be the study of molecules and what they do? Or will it deal with complex systems that involve molecules, in any form—in materials science, biology, geology, city management, whatever—"chemical" or not? Any simple definition of the field of chemistry—or at least any definition as simple as "atoms, molecules, and reactions"—no longer seems to fit its potential, its obligations to society, or the complexity of the challenges it faces.

Throughout the productive postwar period, "chemistry" always blended the practical and conceptual. This postwar era simultaneously developed academic chemistry—to analyze and understand complexity—and industrial chemistry—to produce the chemicals used by society.[1] The two are sometimes described as separate, and even antagonistic. Far from it! The interchange between them—albeit usually unplanned and often haphazard—provided extraordinary benefits to both. The discovery of useful new phenomena—often in industry—offered starting points for academic scholarship. The universities, for their part, developed theoretical and mechanistic understanding, which reappeared in industry as better processes and new products. Academic research generated new analytical methods, which the manufacturers of commercial instrumentation converted into easily used, highly engineered, and indispensable tools for chemical research. Both industrial and university researchers developed new synthetic methods and new materials. Computation and simulation changed the definition of an "experiment" for both. Everyone won. This stimulating exchange of information between academic and industrial laboratories continued until the 1980s, and then slowed.

The post WW II era has now ended. Since the 1990s, the chemical industry has focused on process improvement, and has introduced few fundamentally new products. Although academic chemistry has migrated into new fields (biochemistry, materials science, and computational chemistry are examples), and academic departments have proliferated, the historical core disciplines have drifted more toward "iteration" and "improvement" and away from "discovery."

The depletion of the vein of new ideas and commercial opportunities that marked the end of the postwar period was inevitable: nothing goes on forever. And the issue is certainly not that society has run out of problems for chemistry to solve. In fact, I would argue the opposite: that chemistry may now be the most important of the sciences in its potential to impact society.

So: what are these new problems? How must chemistry change to address them? What's next? The science and technology that developed in this period will continue as the foundation of whatever the field becomes, but the most urgent opportunities now lie in new directions. Exploiting

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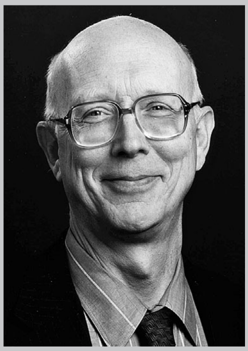
these new opportunities will require new skills, and a new structure for the field.

Three preliminary points: opinions, vocabulary, and summary. First, this Essay is a perspective, not a classical review of the literature. I will offer opinions, but state them—at least in some cases—as assertions, primarily to save space; for the shorthand, I apologize. I intend to offer ideas and opinions for discussion, not facts.

A second matter—and one closely connected to a major point of the Essay—has to do with vocabulary. One of the internal quarrels in chemistry—and other fields of science—concerns the relative value of research that is (ostensibly) based purely on curiosity, and research that is (possibly) based purely on solving problems. Here I will make no distinction between the two—between basic and applied, or between science and engineering—not because they are not different, but because they share a common purpose, because they overlap so greatly that it is often impossible to tell them apart, and because they must work together seamlessly if they are to solve the problems they face. I will use the word "fundamental" to describe all academic research and nonproprietary industrial research; that is, all research that contributes to a common, public pool of knowledge."[2] "Fundamental research" includes curiosity-driven research, problem-based research, empirical research, theoretical research, computational research, and other flavors of research. I also emphasize that when I use the word "chemistry," I (usually) intend it to be shorthand for "Chemical science and engineering."

Third, I will summarize my perspective in five points:

1) Chemistry is ending an era of extraordinary intellectual growth and commercial contribution to society, powered by an explosion of science and technology, and a parallel and mutually beneficial expansion of academic and industrial chemistry. The close links between the two were mutually deeply beneficial.
2) Although this era is over, the new opportunities that have appeared are, if anything, even greater—both in terms of intellectual challenge and in terms of potential for impact on society—than were those in the rich period now past.
3) These new opportunities are, however, much broader in scope and greater in complexity than the simpler, previous problems, and require new structures and methods. Chemistry is no longer just about atoms and molecules, but about what it, as a field with unique capabilities in manipulating molecules and matter, can do to understand, manipulate, and control complex systems composed (in part) of atoms and molecules: its future extends from living cells to megacities, and from harvesting sunlight to improving healthcare. To deal efficiently with these problems, academic chemistry will need to integrate "solving problems" and "generating understanding" better. It should teach students the skills necessary to attack problems that do not even exist as problems when the students are being taught. Industry must either augment its commodity- and service-based model to re-engage with invention, or face the prospect of settling into a corner of an industrial society that is comfortable, but largely irrelevant to the flows of technology that change the world.
4) In the new era, both academic and industrial chemistry (ideally with cooperation from government) would benefit from abandoning distinctions between science and engineering, between curiosity-driven understanding and solving hard problems, and between chemistry and other fields, from materials science to sociology.
5) In short, chemistry must expand its mission from "molecules," to "everything that involves molecules." For academic chemistry, this expansion will provide fresh intellectual and practical challenges, and fulfill its ethical obligations to the taxpayers who pay the bills. For industrial chemistry, the expansion of scope would open the door to new commercial opportunities, and to future growth. For government and for Society, it would build some of the capability needed to solve problems that currently seem insoluble.



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70 Years

Three groups cooperated to build modern chemistry: the universities, the chemical industry, and governments. The foundation of the enterprise was the chemical industry, which had existed for a century.[1] The first *new* foundation stone was what we now call the "research university."[3] This new type of university was invented in the U.S., and included among its responsibilities—beyond teaching undergraduates—the conduct of research, as an element of national strategy, and the creation of technology, both sponsored by the government. It was a product of post-war concerns about national security.

The "research university." The research university was a utilitarian construct,[3b] based in the perception that science and technology had played a crucial part in determining the outcome of WW II,[4] and that it was appropriate (and, in fact, strategically critical) that the government build a capability in universities that supported national needs in technology. The very influential document used to justify the use of federal funds to support academic research—"The Endless Frontier"—was written by Vannevar Bush.[3b,5] Its argument was that technology was useful in supporting three objectives important to society: national security, health, and jobs. It was not a paean to unfettered academic research to be paid for by taxpayers.

In the 1960s and 70s, the Cold War was in its most unstable phase, the scientific establishment was relatively small, and there was lots of money. Physics—for its relevance to the Cold

War, microelectronics, and Sputnik—was the dominant scientific ideology. Curiosity-based research—"playing"—was easy to justify, and because of the wealth of scientific opportunities, often productive. From this period came the delicious idea of "entitlement:" that is, the theory that a good use of public funds was to give them—without attached strings—to scientists in universities, with the understanding that their published, public research would provide a pool of knowledge from which technology could be drawn.

The contradiction between the utilitarian intent of "The Endless Frontier," and the understandable desire to have a research stipend, without obligation, has been one source of conflict and argument in academic science, and in science policy, ever since. The argument "pro-stipend" is that (as a singular example) curiosity-driven research led to quantum mechanics (certainly the most important of the discoveries of the last century), and later to areas such as genomics. "Directed research," so the argument goes, "could never do better than that." The argument "con-stipend" is that the money for research comes from taxpayers (who expect and deserve something in return), that undirected research often becomes directionless research (and has, in any event, a *low* yield of important science and technology), and that working on real problems results in better fundamental science than working without constraints (Figure 1). As one example, the Internet—certainly one of the most important scientific tools ever developed, started as a redundant communication system linking ballistic missile silos. As another, the response of the biomedical world to the emergence of AIDS, and the subsequent, absolutely remarkable advances in treatment of viral disease, have been claimed to be based on a foundation in undirected research in virology. An alternative argument is that the response to AIDS was made possible by targeted research in a number of areas, from Nixon's "war on cancer" (which assumed, largely incorrectly, that cancer was a viral disease, but which provided a critical foundation in retrovirology) to the industrial pharmaceutical research that led to the first HIV protease inhibitors, and ultimately to triple therapy. The overall effort was a brilliant success, but it is difficult—even in retrospect—to separate the contributions of "directed" from "curiosity-driven," and of academic from industrial. Whatever the reason, the mixture worked, *very* well: chemistry was prodigiously productive (Figure 2).

Regardless of this history, academic scientists became accustomed to little or no accountability in their research, and universities became accustomed to overhead on research grants as a source of operating income. The many "easy" opportunities for discovery—combined with the system of academic incentives and rewards (which is *still* in place)—favored a style of research involving a single investigator and graduate students, generally without collaborators.

Darwinian evolution of subfields. Chemistry started an era of expansion with a traditional structure of subfields: organic, inorganic, physical and analytical chemistry. Although it has worked hard to maintain this disciplinary structure, unacknowledged convergences and

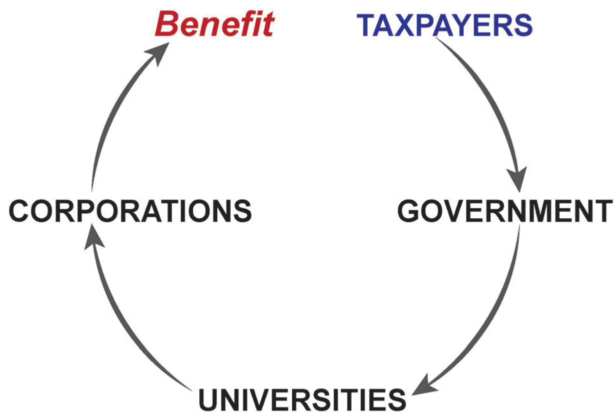

Figure 1. "Follow the money!" Taxpayers (individuals and corporations) provide money to government, on the hopeful theory that good will come of it, and because they have no legal alternative. Government provides a small amount to academic scientists (largely to stimulate long-term, early-stage research in areas with broad social benefit), and to industry (largely to purchase specific services—which may include research and development—and products). In an ideal world, corporations and universities work together to generate the technologies that provide the benefit to taxpayers. Support for universities is not an entitlement, it is an investment by taxpayers; but whether the resulting obligation to them is best discharged by unconstrained research, or by research directed toward the solution of a problem, is a matter of opinion.

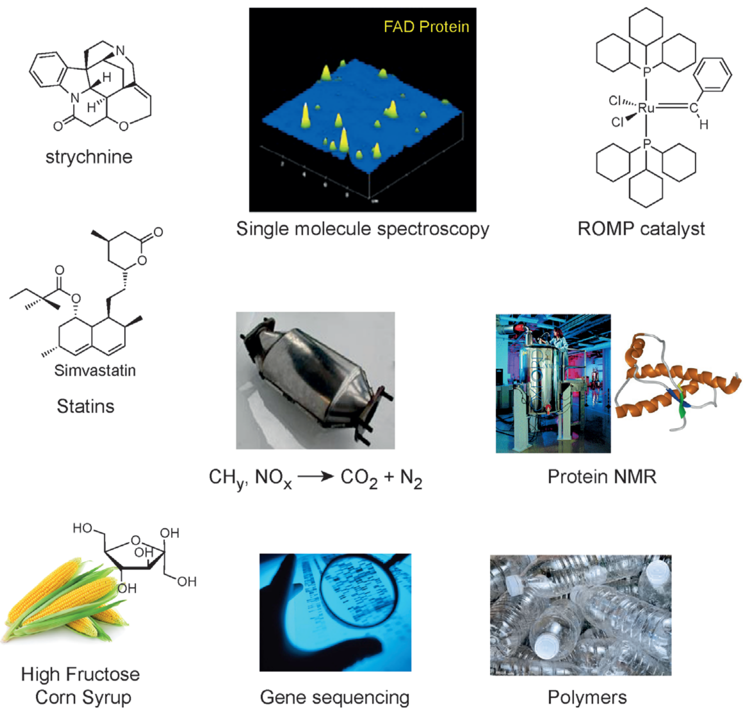

Figure 2. Chemistry has been extraordinarily creative and productive in the last 70 years. Examples (a small number, chosen idiosyncratically, from a list of hundreds) range from strategies for the synthesis of complex molecules to production of commodity polymers, and from new types of catalysts and reagents to drugs, foods, and systems for control of pollution. Analytical methods provide a common enabling theme.

easily recognizable mutations in fields evolved a different structure. Synthesis of structurally complex natural products—a dominant early specialty—was arguably as much a product of the new instrumental methods—the HPLC and VPC and NMR and MS and X-ray crystallographic methods that made it possible to determine complex structures—as of the sophisticated synthetic strategies developed to make these structures. Similarly, the combination of organic and inorganic chemistry, new structural methods, and catalysis led to organometallic chemistry and organometallic catalysis. Chemistry and biology fused to create biochemistry—the most popular of today's subfields.

Materials science was another product of this era. It is particularly relevant to questions of "directed" vs. "undirected" research, in the sense that this now-respectable academic field was intentionally constructed by the U.S. government to fill a need. Its origin was a set of interdisciplinary laboratories founded and supported by the Department of Defense and the National Science Foundation in the U.S. to provide, in universities, some of the types of multidisciplinary expertise found in the major corporate laboratories of GE, Boeing, IBM, Bell Labs, and DuPont, and required for military systems.

The explosion of interest in biochemistry came, of course, partially from the fascination of biology, but partially from the enormous financial support provided by the National Institutes of Health, urged on by a public eager to live as long as possible.

So, the evolution of academic chemistry as a field was never a simple result of unfettered, curiosity-driven research: it was the product of a much more complicated set of processes, involving changing scientific opportunities, discoveries and developments in industry, national priorities, the exploitation of technologies developed for other purposes in WW II, the geopolitics of the Cold War, the co-evolution of analytical systems and scientists using those systems, and the development of computers, lasers, gene-sequencers and other tools with broad impact. Also, importantly, it reflected the choices of students and young faculty: each subfield, as it bloomed (and faded), was evaluated through the eyes of fresh graduate students and starting faculty for fundamental scientific interest, for the availability of funds, and for the eventual prospect of jobs and opportunities for advancement.

Academic chemistry is now conservative, individualistic, and competitive. Now, at the end of this remarkable and complicated post- WW II period, chemistry, and especially academic chemistry, has expanded enormously. There may now be, if anything, too many (rather than too few) universities with aspirations to research, and in some countries, there is too little money to sustain individual, isolated programs at productive levels. (It is not that academic chemistry is underfinanced: financial support from most governments has continued to grow, if unevenly, and in ways that depend sensitively on the state of economies, but that the ratio of funds to investigators has shrunk.)

The system of incentives evolved in the university world has, however, not changed much over the last 50 years, and still favors small, competing research groups, with funds distributed by peer review. Tenure and other related forms of academic employment are still based largely on evaluations of *individual* scientists: universities do not trust themselves to evaluate the "creative" contribution of a single person to a collaboration. The processes used to award tenure increasingly depend upon numbers that are easy for computers to calculate, but difficult for humans to interpret (awards, publications, dollars under management, "H-index"). This style of evaluation favors research in well-established (and well-populated) disciplines, where there *is* a group of "peers" with opinions on the quality of the work, rather than exploratory work. It also favors a style of research centered on small, isolated research groups, and not on the larger collaborations usually necessary to attack "big" problems.

Tribalism and competing disciplines: A (probably inevitable) side effect of a structure for academic chemistry that favors non-cooperating, individual research groups is the emergence of tribalism based on technical specialties. Chemists usually identify themselves as members of specialist groups: "synthetic organic chemists," "bioinorganic chemists," "surface," "mass spec," "physical-organic," or whatever chemists. Whether these groups are, in fact, granfalloons (in Kurt Vonnegut's classic definition),[*] or whether they serve some function in dissemination of information, and in competition for funds, students, and space, is unclear. They do, however, impose a barrier to a student who wishes to contribute to an area that does not fit into an historically recognized discipline (research in sustainability or climate change, energy conservation, public health, and complex systems are examples). And tribes generally are at war with one another as a matter of principle.

The chemical industry—from partner in discovery to specialist in product development. The chemical industry was the core of chemistry before the research university was invented. Its role as producer of fuels and chemicals on commercial scales is well understood and appreciated. Its role as a creative force in invention is sometimes less well recognized, and one of the unfortunate changes in the chemical industry has been its gradual but progressive withdrawal from long-term, fundamental research. In its heyday, however, it—in a sense—embodied the style of research in which groups of scientists and engineers—in collaborations—took on very large, important (both commercially and societally), problems for which there are no solutions, and invented the science *and* the technology that was required to solve them. Examples of areas which have been—in large part—invented and developed by industry include heterogeneous catalysis, synthesis of monomers and production of polymers, small-molecule pharmaceutical chemistry, organometallic chemistry, much of electrochemistry and energy storage, materials science, and much of surface science. The DuPont Central research laboratory (under the direction of Earl Muetterties and George Parshall) provided an example; it was, for many years, arguably the world's center of fundamental research in organometallic chemistry.

[*] A granfalloon "... is a group of people who affect a shared identity or purpose, but whose mutual association is actually meaningless." (K. Vonnegut, *Cat's Cradle* and Wikipedia).

In the first half of the postwar era, industry was an equal partner with the universities in the development of new areas of chemistry; in the second half, economic pressures—and a decrease in the number of opportunities that were perceived to be economically realizable—caused industry to focus on short-term product development, rather than to contribute actively to the development of new areas of large-scale chemistry.

The changes that forced large companies out of long-term research are relatively straightforward to understand: the goals of capitalism and the public markets, and incentives for senior management, both favor investments in which financial returns are expected to be short-term. Research is generally a long-term investment. The question of whether the short-term approach is the best for companies and stockholders is a complicated one to answer;[6] if the chemical industry were expanding, and demonstrating profits based on successful research, it could do as it wished. In the face of pressure for profitability, much of industry has chosen to emphasize the management of existing businesses, rather than to try to create new ones: research in the chemical industry is now often considered as an expense, rather than an investment.

This choice of direction has had several consequences: 1) it has ended (or constrained in scope and character) the unique and mutually beneficial intellectual partnership between industrial and academic chemistry that characterized the 1960s to 1980s (Figure 3). 2) It has increasingly limited the number of jobs for chemists in industry, and made a career in industrial chemistry less attractive for students choosing what to study. 3) It has limited the options for chemistry to explore new areas, since many of these areas (e.g., the materials science of porous media under hydrostatic pressure, or "fracking"; understanding if there is new chemistry—especially chemistry relevant to sequestration—that can be applied to carbon dioxide; the management of flows of material, energy, and information in cities; the development of new strategies for using solar energy) require the kinds of resources and skills in large-scale project management that only industry can provide. Industry continues to place a few large-scale bets in research (for example, synthetic biology to make fuels and specialty chemicals), but the number and audacity of these bets have declined sharply. Even the pharmaceutical industry—a long-term contributor to, and user of, sophisticated synthetic organic chemistry—increasingly considers synthesis a valuable, but primarily technical skill, and has turned to organismic and disease biology as the source of new products and services.

The narrowed focus of industry on maintaining profitability in commoditized product lines, in a business environment in which costs due to regulation (especially environmental regulation) and safety are increasing, has had another important effect. It has made the chemical industry seem relatively uninterested and uninvolved in research whose outcome might have social benefit rather than financial return. There is a wide range of problems—environmental maintenance, sustainable practices, reduction in the costs of healthcare, areas of national security (e.g., defense against chemical and biological terrorism; emerging disease), education, raising the standard of living of the poor—in which

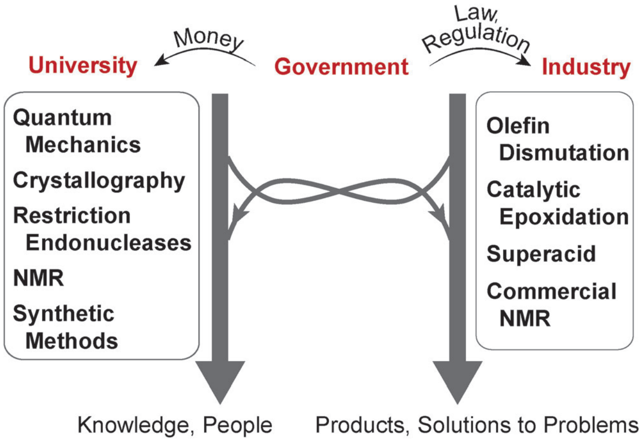

Figure 3. The interaction between academic and industrial research is sometimes simplified to a linear process: academics *discover* and *understand* new phenomena ("curiosity-driven research") and industry *commercializes* these phenomena. The reality is much more complicated. In particular, and especially in chemistry, both have contributed to discovery and invention, although universities tend to carry out much of the work in scholarly investigation (understanding mechanisms, developing complex synthetic methods, understanding model systems, and validating new analytical procedures), and industry develops large-scale and practical multistep syntheses, and carries out the capital and engineering-intensive development required for commercialization. As a few examples, university research produced quantum mechanics, crystallography, and restriction endonucleases, which have been indispensable in both academic and industrial research. Industry discovered the first examples of olefin dismutation, and its development into a broadly useful class of reactions for complex organic synthesis by Grubbs, Schrock and others occurred in universities. Observation of the acidity of silica–alumina supports for cracking and reforming catalysts in petroleum companies stimulated, in part, Olah's work on fluid superacids in the university. NMR was discovered as a phenomenon in the university (in physics), but would never have become the indispensable tool—NMR *spectroscopy*—for organic and biochemistry that it now is without enormously sophisticated, conceptual and technical development both academically and in commercial instrument companies.

societies may have substantial interests, but in which the opportunities for profitability may be limited, or in which it may be necessary to develop a new kind of business. It has sometimes been possible to justify product development focused on areas of social return for their potential benefit in public relations, to provide windows into possible new business areas, and to avoid the appearance that companies are exclusively financially self-serving. The disinterest in social return has placed the chemical industry increasingly in the position of appearing to be a necessary, valuable, but not necessarily attractive part of the industrial economy. That strategy may not be the best for it in the long term.

So, as with the research universities (albeit for totally different reasons), industry has become more conservative, more financially oriented, and less exploratory, as it extracts as much value as it can from the last set of problems, tries to understand the conflicting advice about "innovation" with which it is flooded,[7] and considers how, and if, to participate in whatever comes next.

Government. Government plays a complex, and often maligned, role in the chemical enterprise. It provides the funds for much of academic research. It channels industry through laws, regulations, and taxes, and it also provides revenue as a purchaser of services and products. One of the most interesting developments in the relationship between government and universities has been in peer review. Peer review was originally established to place the responsibility for allocation of government funds—to individual projects, according to their technical merit—in the hands of scientists, rather than bureaucrats. Two things have gone wrong. First, the peer review system has moved from one centered in elite science to one that is populist. (Even to use the word "elite" now evokes a shiver of discomfort from the politically sensitive.) I would argue that science is, at its core, an elitist activity: not everyone can do it, not everyone can judge it, and only unusual people do it really well. This point of view is at odds with one that says that support for science—since it comes from taxpayers broadly—should be distributed broadly by a peer-review process that is itself demographically representative and anonymous. Second, governments have decided that they have priorities in technology, and that they should be entitled to direct the research focused on those areas of high priority. The first part is undoubtedly correct; the question of whether government program managers are also competent as research directors is more arguable. Regardless, the peer review system has evolved from one of "keeping academic research out of the hands of government bureaucrats" to "evolving government bureaucracy to direct academic research."

Government, for all of its idiosyncrasies, also still sometimes serves another vital and increasingly neglected function; that is, protecting and supporting research activities that are intended to generate a social rather than financial return, or that require a long time to accomplish. Unfortunately, research in laboratories—whether in university or industry—can take a technology only so far, and full-scale implementation of any new technology to the benefit of society almost always requires industrial participation in some large-scale, for-profit form. Government can start and enable programs, but it is usually industry that provides products as perceptible benefits. Academics can, of course, provide valuable understanding.

What's Next? Unlimited Opportunity, But in New Classes of Problems

Coming out of this extraordinary era of the 50s to the 80s, chemistry has a certain intellectual and organizational style; and although there are certainly still opportunities that fit that style, the perception—by society, and probably by most chemists—is that chemistry is less exciting than biomedicine, brain science, "social engineering" (that paradigmatic hybrid of computer science, electronics, sociology, and advertising), studies of climate change, astronomy, and a number of other fields. The increasing evolution of the chemical industry toward a commodity-and-service business model leaves it unarguably essential, but not exciting. Does this mean the field is over?

No. It is not over. Of course not! In fact, a look at the problems facing society, and the requirement for the skills of chemistry that can be applied to the solutions of these problems, indicates exactly the opposite. But the structures that served so well in the past will not do equally well in the future. What is called "chemistry" now may be only a distant cousin to the chemistry of 50 years from now.

One change is that some of the chemical "opportunities" are now urgent necessities. Academic scientists are uneasy when faced with "timelines" and "deliverables." Some of the problems facing society (for example, climate change, management of energy production and use, lowering costs of healthcare and distributing its benefits) must, in fact, be attacked immediately, and finding approaches to their solution is urgent. Other, seemingly less urgent, enigmas (for example, understanding the molecular basis of life) will be entirely based on curiosity (although even they offer—in the undefined future—avenues to new technologies and jobs). While there are many problems to which chemistry is *the* discipline offering the most plausible expertise, how will the participants (research universities, industry, government, and interestingly, in the future, foundations) set priorities? Who will do what, in what order? How long will it take? Table 1 contains examples of challenges.[8] Some are obvious. Some are "inevitable," in the sense that it is certain that the problem is real and *will* be addressed somehow. (The only question is "How?") Some come simply by assuming that common wisdom is wrong. Some are purely my personal opinion.

Table 1: What's next?

	New Classes of Problems
1)	What is the molecular basis of life, and how did life originate?
2)	How does the brain think?
3)	How do dissipative systems work? Oceans and atmosphere, metabolism, flames.
4)	Water, and its unique role in life and society.
5)	Rational drug design.
6)	Information: the cell, public health, megacities, global monitoring.
7)	Healthcare, and cost reduction: "End-of-life" or healthy life?
8)	The microbiome, nutrition, and other hidden variables in health.
9)	Climate instability, CO_2, the sun, and human activity.
10)	Energy generation, use, storage, and conservation.
11)	Catalysis (especially heterogeneous and biological catalysis).
12)	Computation and simulation of real, large-scale systems.
13)	Impossible materials.
14)	The chemistry of the planets: Are we alone, or is life everywhere?
15)	Augmenting humans.
16)	Analytical techniques that open new areas of science.
17)	Conflict and national security.
18)	Distributing the benefits of technology across societies: frugal technology.
19)	Humans and machines: robotics.
20)	Death.
21)	Controlling the global population.
22)	Combining human thinking and computer "thinking."
23)	All the rest: jobs, globalization, international competition, and Big Data.
24)	Combinations with adjacent fields.

Although I chose the particular problems in this Table to illustrate the need to rethink what chemists should know in the future, many people would construct similar lists. Let me discuss each of them briefly, since their connections with "chemistry," as it currently defines itself, may, for some, not be immediately obvious. And if some now seem closer to science fiction than to the usual content of a fine chemical journal such as *Angewandte Chemie*, consider—100 years ago—how ludicrous proposals would have seemed to double the human lifespan, assemble the world-wide web (whatever that might be), eliminate polio and smallpox, define the molecular structure of a biological assembly to be called "the ribosome," or explore Mars by sending robots using rockets guided by computers. All, of course, happened. Chemistry tends to be excessively modest in its ambitions. Excessive ambition might sometimes be a better strategy.

1. What is the molecular basis of life? Isn't understanding "life" a subject that falls in the intellectual purview of biology? (Figure 4) No. Life is an expression of molecular chemistry—a remarkable network of molecules, catalysts, and reactions. It is also chemistry operating in a way that we (or at least I) do not understand. The cell is an assembly of reacting and interacting molecules. The molecules are not alive; the reactions are not alive; so how does the cell become alive? The answer to this question seems non-obviously obvious: "life" appears to be the name we give to the astonishing behavior of a particular set of reactions, operating in a constrained environment called "the cell." It is like a flame, only much more complicated. A flame burns oxygen and methane, and generates heat and light. A cell "burns" oxygen and glucose, generates heat, and makes another cell. And life is much more difficult to understand than a flame in another sense: unlike a flame, we do not know how life started. A spark ignites a flame in a mixture of oxygen and methane of the right concentration. How could the much more complicated components of life put themselves together from the disorganized chaos of prebiotic Earth, and make the much, much more complicated networks of reactions we call the cell?[9]

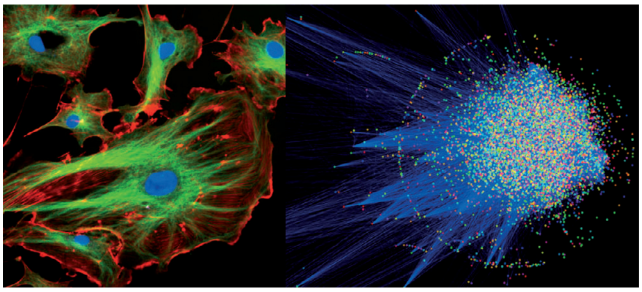

Figure 4. Left: A cell with fluorescent labeling of some of its internal structure. Right: A diagram of an "interactome". Points represent proteins, lines interactions between them. The network of interactions—and probably most importantly the control of catalytic activities of enzymes by metabolites and signaling molecules—is enormously more complicated than suggested by this diagram, and well beyond the reach of current understanding of complex, dissipative systems.

2. How does the brain think? That life is simply molecular behavior is disconcerting; that human thought is more of the same is even more so. Yes, there are the detailed and fascinating biochemical questions of neurotransmitters/receptors and protein synthesis and transmembrane electrochemical potentials, but the deeper question—probably one more at the border of chemistry, cognition, and physics than chemistry and biology—is the basis of sentience and self-awareness. Is thought—is Bach's "Well-tempered Clavier"—simply molecular behavior (albeit of a complicated sort)? Or is there something else there? Are we missing something fundamental? (I do not mean to minimize the interest in arguments about "emergence" as "something new" vs. "incomplete understanding" in complex systems, only to reemphasize that the empirical foundation of "thought," so far as we now know, is simply interacting molecules, and hence, chemistry.)

3. Dissipative systems. Oceans and atmosphere, metabolism, flames. Chemistry tends to study systems at, or moving toward, thermodynamic equilibrium. They have seemed complicated enough. But the most interesting systems in the world around us—life, thought, combustion, ecosystems, traffic, epidemics, the stock market, the planetary environment, weather, cities—are "dissipative;" that is, their characteristic and most interesting features only emerge when there is a flux of energy through them.[10] Studying dissipative systems has, of course, been a subject of physical science for decades, but, unlike equilibrium systems, understanding dissipative systems— both theoretically and empirically—is still at the very beginning.

4. Water, and its unique role in life and society. Water is an astonishing liquid: there is nothing like it. Understanding water is crucial at almost every level, from the very practical to the very conceptual. How will it be possible to generate the pure water needed for human life, and the much larger quantities of water required for consumption by plants, as the climate changes, and as the energy used to generate and transport it is constrained? Why is water the unique fluid in which life occurs? What is the role of water in the myriad of processes—from catalysis to molecular recognition—that make up metabolism in the cell?[11] (It is remarkable that most discussions of biochemistry focus so intently on the organic molecules that make up the cell, and so completely ignore the water that is the major component of living systems: conceptually, we often discuss life as if it occurred in a vacuum. Although computation has now reached the point where it can begin to help in understanding water, we still do not understand most of its mysteries.)

5. Rational drug design. So-called "rational drug design" has been a familiar problem for decades. One promise of genomics has been that it would give rise to a process in which sequencing the genome would allow the prediction of the amino acid sequence of a protein; the sequence would allow prediction of protein tertiary structure; the protein structure would lead to identification of the active site; and with a three-dimensional model of the active site, chemists could design and synthesize tight-binding ligands. In this process, only the "sequencing" works, after 50 years of effort. Making a drug is, of course, much more complicated than making

Figure 5. One of the new constructions of humankind is the "megacity:" a city with a population of greater than 50 million people. Managing these ensembles requires both knowledge and technology to solve problems at every level, among which are: mass transport of water, food, materials of construction, power, heat, pollution, and waste; control of disease; and management of education, self-governance, rumor, unrest, and crime. Chemistry is uniquely experienced in making sensors, in managing large systems of sensors, in dealing with problems in transport of materials, energy, and waste, and in developing appropriate technologies for sustainability and public health. Based on its experience with modeling large numbers of interacting molecules and particles (e.g., statistical mechanics and colloid science), it may also have more to offer to the science of sociology and related areas concerned with large numbers of interacting people than one might expect. (Photo left: David Iliff. License CC-BY-SA 3.0. Photo right: YGLvoices. License: CC-BY-2.0).

a tight-binding ligand, but the ability to design ligands rationally would be enormously helpful. So, after decades of work by very able researchers, the solution of the problem still escapes us. It has been so difficult, that I must wonder—in the sense explained so compellingly by Thomas Kuhn—if our understanding of the problem is not missing some crucial element.[12]

6. Information: from the cell, and public health, to megacities, and global monitoring. Because computation has become so powerful and so inexpensive, there is a tendency to think of all information in terms of binary bit strings.[13] It is not clear how best to describe "information" in all the problems with which chemistry deals. The often-heard phrases "What is the information content of an active site?" Or "What is the information content of a cell?" or "How much information is necessary to model the global climate?" may not be best answered using just what can be immediately coded in a bit string. And other, fundamentally empirical, questions about information abound in chemistry. For example, if one wishes to monitor global climate, or manage the flows of matter, energy, waste, people, and disease into and out of a megacity (Figure 5), what should be the nature of the suite of sensors involved, and how should the enormous quantities of data generated be processed and interpreted? Questions about the generation, collection, and uses of information in complex physical systems are, of course, only questions partially addressed to chemistry; chemistry has, however, probably the deepest fundamental knowledge of their physical bases, and of the methods used to collect the relevant data, and will thus be essential to answering them.

7. Healthcare and cost reduction: "End-of-life" or "healthy life"? The type of healthcare prevalent in most of the developed world has a capitalist, for-profit, focus on treating established disease, usually at end-of-life.[14] In fact, much of the increase in lifespan that we have enjoyed in the last century has come—not from high-technology medicine—but from public health: clean water, pollution control, airbags, traffic lights, safe food, antibiotics, vaccinations, even an even-handed legal system. A focus on a "healthy life," coupled with reducing the cost of healthcare, generating new technologies for public health, and extending their benefits across classes of society is squarely within the purview of chemistry, and is a key objective of most societies.

8. The microbiome and other hidden variables in health. The current enthusiasm for understanding the role of the microbiome[15]—the "bugs in our gut"—in human health may or may not be sustained as the subject is explored, but the idea that there are hidden variables—nutrition, exercise, environmental exposures, complex patterns of inheritance and susceptibility—that are not a central part of the current paradigm (or dogma) of "diagnosis and treatment" offers another set of fundamental problems appropriate for chemistry.

9. Climate instability, CO_2, the sun, and human activity. Perhaps the most pressing scientific problem facing humankind is understanding the influence of human activity on the environment, and the most pressing technological problem is understanding what to do about it. This problem is enormously significant practically and economically, and is enormously complicated scientifically. One of the mantras of business schools is "If you can't measure it, you can't manage it!", and chemists are masters at the measurements needed to understand these interactions. And if we ever seriously consider implementing so-called geoengineering—

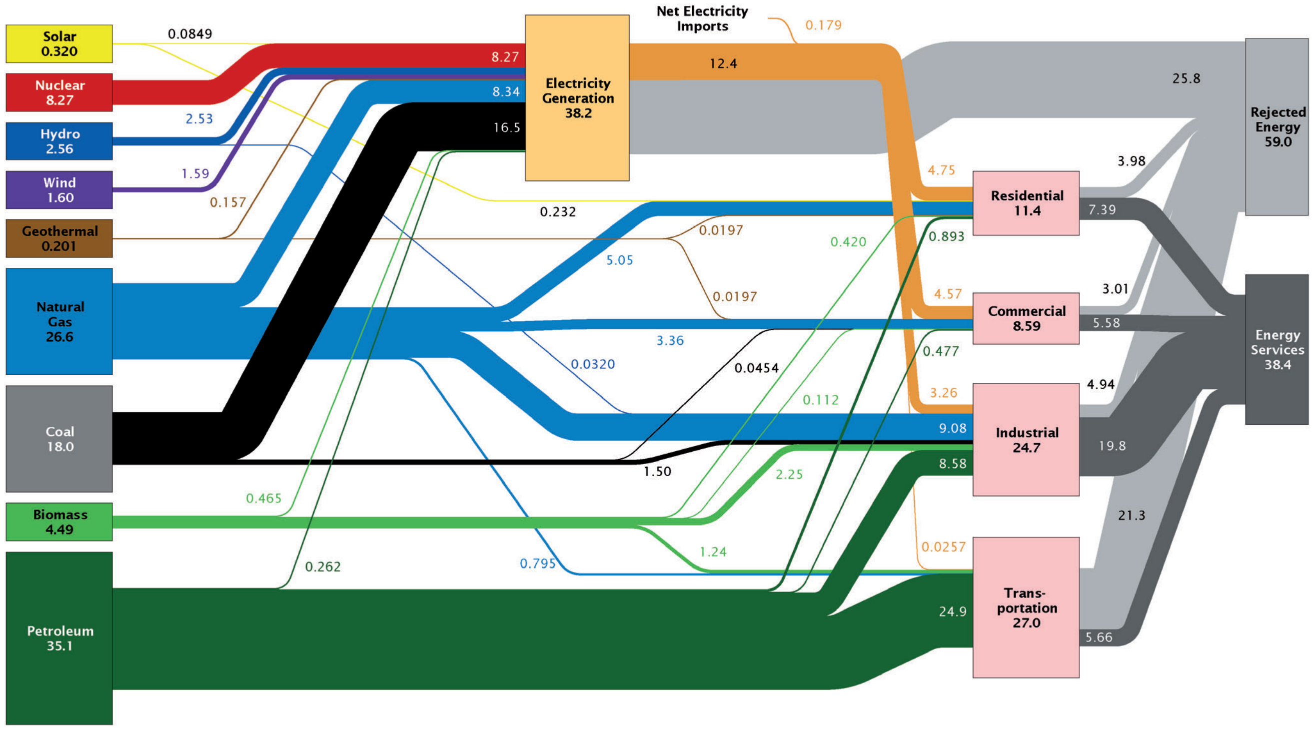

Figure 6. A schematic diagram showing the flows of energy in the U.S.; these flows vary from region to region in the world, but any diagram suggests countless opportunities for intervention and improvement, many involving chemistry. The inertia of large energy systems is also enormous: the fact that ≈80% of the energy is now generated by burning fossil fuel will take decades to change significantly. (Figure 6 was prepared by Lawrence Livermore National Laboratory under sponsorship by the U.S. Department of Energy: https://flowcharts.llnl.gov/).

the intentional modification of global climate (for example, by injecting sulfur-containing aerosols into the atmosphere, or forcing large blooms of algae in the oceans), estimating risks and benefits will require combinations of the skills of chemistry with those of many other areas, from geology and oceanography to economics, public policy, and politics. Geoengineering would also require acute sensitivity to ethical issues, since experiments influencing the habitability of earth, if they were to go wrong (as do many experiments), could have memorably unfortunate consequences.

10. Energy generation, transportation, use, storage, and conservation. Most of the CO_2 injected into the atmosphere by humans is the result of the combustion used to generate energy (Figure 6).[16] Again, every aspect of energy generation, transportation, storage, and conservation has chemical components, from understanding the very interesting practicalities of familiar (but not necessarily well understood) processes—from fracking to sequestration, and from the design of photovoltaics to storage of nuclear waste—to inventing radically new approaches to energy generation and use. More importantly, the question of how these processes, and their consequences, influence oceans, atmosphere, and climate are critical for large-scale action.

11. Catalysis (especially heterogeneous and biological catalysis). One of the uniquely important skills of chemistry is catalysis. Given its pervasive importance, it is astonishing how much we still do not know about this subject. Although the Haber–Bosch process for synthesis of ammonia (first commercialized by BASF around 1913) led the way into today's universe of commodity catalysts, we still do not understand (beyond a superficial level) the mechanisms of these processes that generate fuels, chemicals, and materials. As an indication of the limitations of our understanding, consider the difficulty of designing a new heterogeneous catalyst, understanding the complexities of enzymatic catalysis, and, especially, designing catalytic networks in which there is feedback and control operating between different parts of the networks (as there is in the cell).

12. Computation and simulation of real, large-scale systems. Will we, at some point, be able to simulate a cell, from the molecular level up? What about an ocean? Design a *drug* (not just a ligand)? For all the continuing expansion in the power of computing, and the optimism (with good historical foundation!) that more bits thrown at a problem often leads to better results, what are the limits to simulation, and what are the approximations that will be most useful, in bridging molecular and macroscopic phenomena? And will there be alternatives to current methods of digital computation? Quantum computing? New uses of analog computing, or neural-net-like systems? Neuromorphic systems? Then, beyond simulation, there are the problems of theory. Is there an analytical approach to solve large sets of coupled, nonlinear differential equations that describe life, or megacities, or planets? How should one analyze the behavior of complex systems (and, in fact, *is* there a single theory for such systems)?

13. Impossible materials. Will it be possible, eventually, to make a high temperature superconductor? What about a transparent, liquid ferromagnet, or a truly biocompatible neural prosthesis? A material that was a better thermal conductor than diamond, but inexpensive and oxidatively stable, would be most useful. Active, adaptive, matter that mimics some of the features of tissues provides many targets. Most "impossible" materials that one can imagine seem impossible because they have not been made, not because there is a sound theoretical reason that they cannot be made.

14. The chemistry of the planets: Are we alone, or is life everywhere? Planetary discovery is a field that has undergone recent and revolutionary change: we now know that many (perhaps most) stars have planets, and some of those planets will support liquid water. We will be able to visit the planets (and their moons) in our solar system, but not—in any foreseeable future—those in others. What will we be able to make of them, and particularly of the possibility that they might support life, either like ours, or perhaps entirely different? If "life" is a molecular phenomenon, life involving systems of molecules other than the ones that have led to us seem possible. And inferring that life was probable (or inevitable) on other planets would be a kind of second Copernican revolution: it would complete the displacement of humankind from a unique place at the center of the universe, to the much less exalted position as one of many forms of life, on many planets, circling many suns. From "crown of creation" to "common as grass." It might be good for our humility.

15. Augmenting humans. Humans are remarkable; perhaps with augmentation, they could be even *more* so. Augmenting human capabilities could take many forms, most with strongly molecular and biochemical components. To take just one example, the human nervous system operates using electrical potentials generated from gradients in concentrations of ions between the cytosol and the extracellular medium; computers operate using electrical potentials generated from gradients in the concentrations of electrons in circuits fabricated in doped silicon. Connecting these two systems is an arrestingly difficult problem with a strongly molecular component. Augmentation could apply to senses, memory, information processing, and physical abilities. Augmentation applied to behavior and emotion would be much more complicated ethically. Of course, Facebook, Twitter, and the other avatars of social engineering have already augmented electronically (for better or worse) the ability of our children to communicate, and their ability to form communities, so some changes are already underway.

16. Analytical techniques that open new areas of science. Analytical chemistry is a much more important area than it may seem. Dyson, Galison, and others have argued convincingly that one of the most important steps in opening new areas of science is developing new analytical techniques that make possible relevant measurements.[17] (As an example, consider the indispensable contribution of chemical methods to gene sequencing, of spectroscopy to organic synthesis, and of lasers to everything). Chemistry is still in a period of very active development of new analytical techniques, and probing molecular behaviors and motions at the subcellular level, addressing individual cells, exploring the deep brain (especially in humans), and (at the other end of scales of sizes) developing the measurement infrastructure for managing megacities, healthcare systems, and atmospheres, all represent enormously interesting and challenging problems.

17. Conflict and national security. Terrorism by small groups has come to be the equivalent of war using conventional armies—in impact on societies, if not in ultimate potential for harm—as a concern of national security. Although terrorism has historically been confined to relatively small events, acts involving nuclear, chemical, or biological weapons have the potential to be another matter entirely. Defense against this type of terrorism involves chemistry at every stage—from intelligence, and management of a terrorist event, to cleanup, forensics, and restoration of function.

18. Distributing the benefits of technology across societies: frugal technology. Most of the people in the world live in conditions that we—in the developed world—would consider unendurable poverty and instability. Extending the benefits of technology to these societies—for ethical reasons, to promote regional and global stability, and, in the long term, to create markets, jobs, and an expanded middle class—requires a business model that does not fit well with short-term capitalism. Technology that is successful in developing economies must give the highest possible ratio of benefit to cost (both measured somehow). Taking an expensive technology and making it inexpensive and robust is not straightforward. Often, in fact, it is best to invent new solutions to the problem altogether. Chemistry has been a key to development of *sophisticated* and *expensive* technologies; it also has the potential to be a major contributor to the development of *frugal* and *accessible* technologies. Developing a solution to a problem that is simultaneously inexpensive, functional, rugged, and profitable is usually more difficult than developing one that is simply complicated and expensive.[18]

19. Humans and machines: robotics. What is the "next big thing" in technology (after the World Wide Web)? Robotics is one candidate. It is an area that is in the early stages of explosive growth. It has the potential to provide new efficiencies, and capabilities that human workers cannot match, and, perhaps, to release humans from some of the drearier parts of a working life; it also has the potential to displace humans from jobs, when jobs are already in short supply, increase consumption of energy, and perhaps generate—in combination with computer "intelligence"—a kind of non-human competitor for humans. Understanding how to make robots that remove humans from dangerous situations, or that substitute for them in unpleasant ones, or that work with them as assistants (so-called "collaborative robots"), while minimizing the costs and dangers of doing so, is a challenge with many components in materials science and in chemistry. Developing new forms of robotics will, of course, also require close cooperation between chemistry and the other components of this dynamic and quite unfamiliar field.

20. Death. We mortals find death obsessively and enduringly interesting. We spend enormous effort to avoid it. We do not, however, have a precisely defined idea of what it is. What does the death of a living organism really entail? What molecular, cellular, and organismic processes are essential for life and death, and where is the boundary between them? Is death a binary process, a gradual one, or a complex system of processes? Understanding death, like understanding life, is a subject that can involve molecular science at many levels, and have conceptual, ethical, and practical outcomes.

21. Controlling the global population. Standard of living is, in some broad sense, the ratio of resources to population. Population control is a complex problem, with elements from contraception to education.[19] There are components to it, however, to which chemistry must contribute. For example, reversible male contraception provides an obvious path to limit unwanted pregnancy. Decreasing infant mortality, and improving the health of children, provides a less obvious path to the same end, by decreasing uncertainty in the number of babies to have to produce the desired number of healthy, working young adults (who are the only support available to many families in the developing world). Building better public water systems is even less obvious, but equally important. Making potable water available frees young girls—in many societies—of the obligation to fetch water from distant wells, and allows them to go to school. Improving the level of education of women is one of the best ways to limit population growth. So, chemistry is involved in many aspects of this problem, from medicinal chemistry to PVC pipe.

22. Combining human thinking and computer "thinking." Humans think. Computers compute. But as computations become more complex, the distinction between computation and thinking becomes more and more difficult to make. Building the bridge between human thinking, and the information processing activities of computers and systems—whether simply computation or machine intelligence— will require building bridges between them. Google Glass and similar systems may be a primitive first step, but what would a USB port for the brain look like? Among other characteristics, it might have a neural-to-electrical interface, which we cannot presently begin to design at the molecular level.

23. All the rest: jobs, globalization, international competition, and big data. Against the background of these problems, there is a tsunami of other changes coming in science and technology that will also generate new problems to solve. Chemistry must learn how to swim in these turbulent waters, or run the risk of being swept under. One particularly interesting issue is the development of different forms of science in different geographical regions. Europe, the U.S., and Japan have been accustomed to having little competition in advanced science and technology from the rest of the world. That protection is disappearing, as different geographical regions develop different scientific strengths, cultures, ambitions, and objectives. In chemistry, the U.S. still dominates in biochemistry and related fields; a resurgent China is beginning to take over significant areas of synthesis; one focus of India is "frugal innovation"; Europe is especially strong now in the emerging field of "systems chemistry." What will this competition—a competition that did not exist in much of the era now over—lead to? What will be added as Africa and South America develop their own styles of science? And how will regional industries respond (with new technologies and products, and by creation or elimination of jobs) to the different opportunities created by regional strengths and weaknesses? The development of the Internet also will be a major force for disruption. Everyone's information—proprietary or not—will probably be available to everyone. Will this (sometimes unwanted) sharing stimulate original chemical research, or make it more attractive to be a fast follower, and depress originality?

24. Combinations with adjacent fields. Some of the opportunities for chemistry lie with new intellectual partners (some obvious, some not). For example, most efforts in medicinal chemistry now devoted to the subject of "lung cancer" focus on high-technology medical intervention—surgery, chemotherapy, radiation, immunotherapy—in treating established disease. Their success is at best spotty. The most effective way of dealing with lung cancer is clearly to avoid it: cleaning polluted urban air, reducing specific environmental exposures, stopping smoking, and perhaps recognizing genetic and environmental interactions that lead to high risk. This problem is not exclusively a chemical problem: it is a problem at the unfamiliar boundaries between chemistry, sociology, psychology, public health, and city management, but the "chemical" aspect is essential. Similarly, understanding "fracking" must involve the interaction of chemistry, geology, climate instability, public health, and geochemistry. Developing hypotheses about the origin of life must involve chemistry, biology, and planetary astronomy. Arguably, since chemistry is typically the science (among the physical sciences) that deals most fundamentally with the perceptible world, it has the greatest to gain by forming new alliances with other fields—especially in the social sciences—where molecular interactions and human behaviors overlap—but more expansively wherever there are combinations of difficult problems (technically, economically, and ethically) that would benefit from complementary technical strengths.

Setting Priorities for The Future

Political and financial imperatives. Many factors beyond academic preference determine what areas of academic science flourish: intellectual inertia tends to prevent universities from changing rapidly, and governments and societies have their own agendas that are not necessarily aligned with those of professors. For the foreseeable future, many of the most important problems for society (and perhaps for government) will require chemistry, although not necessarily the kind of chemistry now popular in the research universities. Stabilizing the environment, managing energy, providing affordable healthcare, generating jobs, protecting societies in unsettled times: all are extraordinary challenges, opportunities (and obligations), but they are also evanescent: if chemistry does not accept them, other fields will. For large chemical companies, short-term financial return will continue to dominate strategy. Will it be possible to combine the academic enthusiasm for obligation-free funding, government's need to solve problems, and industry's focus on profitability?

Academic strategy: curiosity, solving problems, or both? A problem among scientists—especially those who think of themselves as doing creative, curiosity-driven work—is the perception that pure science and applications are somehow incompatible. Don Stokes developed a useful formulation of this problem—now called "Pasteur's Quadrant." (Figure 7)[20]

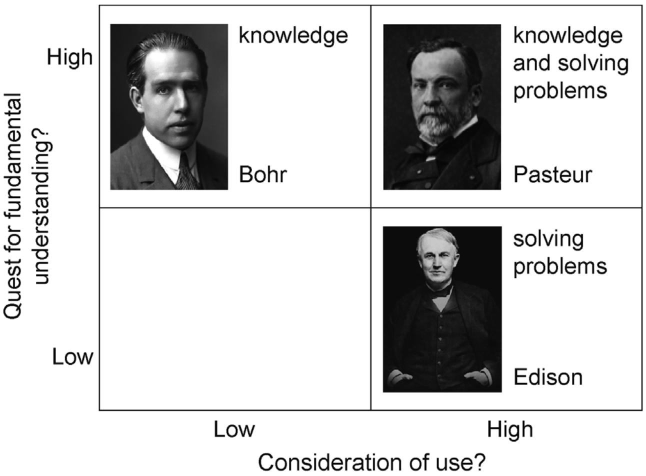

Figure 7. The quad diagram proposed by Don Stokes to summarize his arguments about different styles of research, modified slightly in terminology in this Essay by replacing the terms "pure research" and "applied research" with "knowledge" and "solutions". The justification for this modification is that the "pure"/"applied" distinction is artificially sharp; there is no bright line separating research intended to generate knowledge (which will ultimately, ideally, be used to solve problems) and research directed toward solutions of problems (which, for big, non-routine problems, will require generating new knowledge and understanding).

In this formulation, science is partitioned (artificially) into problems motivated by curiosity and understanding, and problems motivated by practical ends. The names "Bohr" and "Edison" are associated with these two styles. The interesting quadrant is given the name "Pasteur" (to whom is attributed early work in vaccination– that is, now, applied immunology—and in heat sterilization—now microbiology). Pasteur is given credit for an approach that starts by identifying important societal problems with practical implications (death from rabies; illness from spoiled milk) for which there were no solutions and no relevant science, and then *invents* the new fields of science necessary to solve them. Pasteur did not apply known science; he invented new science to apply. The Pasteur's quadrant approach implies that it is possible to couple, simultaneously, the development of fundamental science to the solution of problems important to society. It *uses* very difficult problems to stimulate scientific discovery. Working in the Pasteur's quadrant is not—as it is sometimes called—"just applications."[20b]

The unproductive debates over "pure" versus "applied" also form one basis for the problems with the peer review system. Populist review of proposals very successfully filters out proposals with the worst ideas, and also, sometimes, the most unfamiliar, ambitious, and original ones. Pasteur's quadrant research, ideally, is stimulated simultaneously by curiosity and problem solving, and is ambitious and uncertain along both axes. (And, hence, probably inappropriate for peer review: Pasteur himself would probably have a difficult time making it through the modern peer review system.) Embracing research in Pasteur's quadrant will require modifying peer review.

Change

> *"A new scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die, and a new generation grows up that is familiar with it."*
>
> Max Planck (Translation by T. S. Kuhn in *The Structure of Scientific Revolutions*).

If chemistry needs to change—from the style developed in the period post-WW II to that needed to solve very different types of problems—who should lead the change?

Research universities: in principle, the organizations with the greatest flexibility. Universities should, ideally, lead in changing the structure of chemistry, not because they are more competent than industry or government, but because they are less constrained, and because one of their jobs is education, and education *is* the future. Many useful types of change would be (in principle) easily accomplished: combining different departments (chemistry, biochemistry, chemical engineering, materials science), broadening education, and changing the criteria for tenure to give credit for collaborative research are among them. Others may be more difficult. For example, there is growing agreement (at least in the U.S.), that graduate research groups in many areas of science (including chemistry) need some form of restructuring).[21] Liebig would recognize most current research groups: a professor, a student, a project, a thesis, a paper (Figure 8). This structure is basically that of master and apprentice, and it is, arguably, exactly what is *not* appropriate for students who will face problems in their careers that their professors cannot solve.

And what about teaching? The impact of the web and social networking on students has been profound; it is just

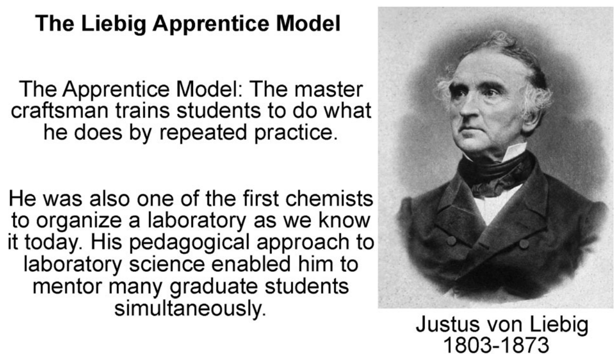

Figure 8. Liebig invented an organization with which to carry out academic research with students (the apprentice model). In many areas of chemical research, over a period of 150 years, this model has not changed much. Since, in their careers, current students will be facing problems that do not now exist, the Liebig model and the apprentice system are no longer appropriate. (Text in Figure: modified from Wikipedia.)

beginning to influence teaching. Although there are wonderful, wise textbooks, textbooks will almost certainly disappear. Since anything can be put on the web now, for free, instructors will have the ability to pick and choose what they need, and students will largely be freed of paying for it. MOOCs, web-based tools, active learning, inverted classes, interactive classrooms—all are important current experiments, but Google Glass may be just a step toward the disappearance of a "university" as a place with real estate, buildings, and food services, and with professors and students interacting in the same room through courses. I am not imaginative enough to see how to replace physical laboratories completely with virtual ones, but many shared instruments are now operated virtually.

The chemical industry: retirement, or evolution and disruption? The big chemical companies are essential to the production of chemical products and hydrocarbon fuels that require handling large amounts of materials, energy, and capital. They have settled into a strategy of technically sophisticated improvements to existing processes and products. Industries that do not change when technology shifts dramatically sometimes disappear—companies that produced steam engines, film for silver halide photography, and adding machines are examples—but Society will continue to need sulfuric acid, concrete, and polyethylene film. The largest chemical companies will not disappear, but a future producing commodities at declining margins is not exciting. More importantly, these enormous, technically sophisticated companies have unique skills in managing technically demanding and dangerous processes on very large scales, in controlling flows of heat and materials, and managing capital: it would be a great loss if those skills were not applied to managing water resources, atmospheres, and megacities (Figure 5). Society (and their own stockholders) would be much better for it if they were to choose to explore avenues for growth, rather than to settle into a retirement that is irrelevant to channeling the streams of technology that will shape the future world.

Government. Government agencies everywhere could improve the effectiveness of the funds they spend by minimizing the bureaucracy associated with those funds. The amount of effort that goes into writing proposals, reports, and program reviews—worldwide—is now extraordinary, and actively damaging to the research being supported, and ultimately irresponsible in its supervision of the money taxpayers provide. Young investigators—those who will build new fields—learn quickly where the bureaucracy is and if possible, go elsewhere. Bureaucracy repels innovation; bureaucracy also attracts bureaucrats.

That said, government agencies still contribute—aside from the money—problems and priorities in areas too long-term for industry to address, and too unconventional or too far in the future for the university to have thought about; they can initiate fields that take 50 years to mature, and introduce new and sometimes unwelcome ideas into science and technology. Some agencies are better at it; some are worse. Money and a good program manager can be much more valuable than just money.

Chemistry, Public Understanding, and a Sense of Style.

One final point: Chemistry is relentlessly utilitarian in the way it presents itself to the non-scientific public. The now-abandoned DuPont slogan "Better things for better living through chemistry" was an example. This phrase may have pleased chemists, but most people thought of "better things" as "glue" and "paint." Useful, yes, but ordinary. Not much poetry about them.

If there is little public appreciation of a field, there is little public support for it, and ultimately little money. At the end of each year, the popular scientific press publishes various roundups: "The 100 most exciting inventions of 20XX!" chemistry is seldom mentioned. Nobel prizes in chemistry are largely ignored in the public press. Society will support chemistry only to the extent that it is excited by what it does; and that part of society that does love science loves it—not for better glue—but for intellectual astonishment, and mysterious ideas, and glamour, and promises of the extraordinary.

Other fields manage to be exciting, each in its own way. Although biology is a field with as many incomprehensible details as chemistry, "Biology cures cancer," and "Life" seems mysterious and endlessly wonderful. Physics contemplates the mysteries of space and time. Astronomy brings wonderful images of exploding stars, and whispers of the Big Bang and black holes. Computer science and social engineering rewires the minds of our children. Even statistics now keeps watch over "Big Data" (whatever that might be). What does chemistry do? "Better glue" is not an arresting answer.

Let me sketch a conversation I have had on various occasions—in one form or another—at dinner parties and on airplanes. The person next to me says, "What do you do?" I answer "I'm a chemist." S/he responds: "Chemistry was the one course in high school I flunked. What is it that chemists do, anyway?" I have tried two types of answers.

One is: "Well, we make drugs. Like statins. Very useful. They are inhibitors of a protein called HMGA-CoA reductase, and they help to control cholesterol biosynthesis and limit cardiovascular disease." (This answer usually ends the conversation.)

The second is: "We change the way you live and die."

The second works better.

Acknowledgment

I thank my long-time friend and colleague, Professor John Deutch (M.I.T), for his often excellent and sometimes alarming comments on the subject of this Essay. Chris Flowers contributed to the independence of opinion. My wife, Barbara, and my colleagues in the research group, helped to make it clearer.

Received: November 19, 2014
Published online: February 12, 2015

[1] F. Aftalion, *A History of the International Chemical Industry*, 2nd ed., Chemical Heritage Press, Philadelphia, **2001**.

[2] Fundamental research means basic and applied research in science and engineering, the results of which ordinarily are published and shared broadly within the scientific community, as distinguished from proprietary research and from industrial development, design, production, and product utilization, the results of which ordinarily are restricted for proprietary or national security reasons.“ (National Security Decision Directive (NSDD) 189, National Policy on the Transfer of Scientific, Technical, and Engineering Information), **1985**.

[3] a) M. J. Nye, *Before Big Science: The Pursuit of Modern Chemistry and Physics, 1800–1940*, Twayne, Prentice Hall, New York, London, **1996**; b) C. M. Vest, *The American Research University from World War II to World Wide Web: Governments, the Private Sector, and the Emerging Meta-University*, University of California Press, Berkeley, **2007**.

[4] N. Davies, *Europe at War, 1939–1945: No Simple Victory*, Macmillan, London, **2006**.

[5] a) V. Bush, *Science the Endless Frontier. A Report to the President*, United States Government Printing Office, Washington, DC, **1945**, Available: https://www.nsf.gov/od/lpa/nsf50/vbush1945.htm; b) G. P. Zachary, *Endless Frontier: Vannevar Bush, Engineer of the American Century*, MIT Press, Cambridge, **1999**.

[6] L. Stout, *The Shareholder Value Myth*, Berrett-Koehler, San Francisco, **2012**.

[7] a) C. M. Christensen, *The Innovator's Dilemma: When New Technologies Cause Great Firms to Fail*, Harvard Business School Press, Boston, **1997**; b) J. Lepore, *The Disruption Machine: What the gospel of innovation gets wrong*, The New Yorker, June 23, 2014, 1–14; c) J. S. Francisco (Chair), Innovation, Chemistry, and Jobs, Meeting the Challenges of Tomorrow, American Chemical Society, Washington, DC, **2011**.

[8] a) G. M. Whitesides, *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1209–1218; *Angew. Chem.* **1990**, *102*, 1247–1257; b) G. M. Whitesides, *Angew. Chem. Int. Ed.* **2004**, *43*, 3632–3641; *Angew. Chem.* **2004**, *116*, 3716–3727.

[9] a) F. J. Dyson, *Origins of Life*, Cambridge University Press, Cambridge, **1985**; b) C. De Duve, *Blueprint for a Cell: The Nature and Origin of Life*, Neil Patterson Publishers, Carolina Biological Supply Company, Burlington, **1991**; c) E. Schrödinger, *What is Life? And Other Scientific Essays*, Cambridge University Press, Cambridge, **1944**.

[10] a) U. Weiss, *Quantum Dissipative Systems*, 4th ed., World Scientific, New Jersey, **2012**; b) J. K. Hale, *Asymptotic Behavior of Dissipative Systems*, American Mathematical Society, Providence, **1988**; c) J. C. Willems, *Arch. Ration. Mech. Anal.* **1972**, *45*, 321–351; d) J. C. Willems, *Arch. Ration. Mech. Anal.* **1972**, *45*, 352–393.

[11] a) P. W. Snyder, M. R. Lockett, D. T. Moustakas, G. M. Whitesides, *Eur. Phys. J. Spec. Top.* **2014**, *223*, 853–891; b) P. Ball, *H_2O: A Biography of Water*, Weidenfeld & Nicolson, London, **1999**.

[12] T. S. Kuhn, *The Structure of Scientific Revolutions*, University of Chicago Press, Chicago, **1962**.

[13] R. P. Feynman, *Feynman Lectures on Computation*, Westview Press, **1996**.

[14] S. H. Woolf, L. Aron, *US Health in International Perspective: Shorter Lives, Poorer Health*, National Academies Press, **2013**.

[15] a) P. J. Turnbaugh, M. Hamady, T. Yatsunenko, B. L. Cantarel, A. Duncan, R. E. Ley, M. L. Sogin, W. J. Jones, B. A. Roe, J. P. Affourtit, *Nature* **2009**, *457*, 480–484; b) I. Cho, M. J. Blaser, *Nat. Rev. Genet.* **2012**, *13*, 260–270.

[16] a) D. MacKay, *Sustainable Energy – Without the Hot Air*, UIT Cambridge, **2008**; b) The original of Figure 6 is available on the Lawrence Livermore National Laboratory website: https://flowcharts.llnl.gov/.

[17] a) F. J. Dyson, *The Sun, the Genome & the Internet: Tools of Scientific Revolutions*, Oxford University Press, New York, **1999**; b) P. Galison, *Image and Logic: A Material Culture of Microphysics*, University of Chicago Press, Chicago, **1997**; c) F. Dyson, *Science* **2012**, *338*, 1426–1427.

[18] a) G. M. Whitesides, The Frugal Way, *The Economist*, November **2011**, 154; b) C. K. Prahalad, *The Fortune at the Bottom of the Pyramid*, Pearson Education India, **2006**; c) M. Yunus, *Creating a World Without Poverty: Social Business and the Future of Capitalism*, Public Affairs, **2007**.

[19] a) P. R. Ehrlich, J. P. Holdren, *Science* **1971**, *171*, 1212–1217; b) S. D. Lane, *Soc. Sci. Med.* **1994**, *39*, 1303–1314.

[20] a) D. E. Stokes, *Pasteur's quadrant: Basic science and technological innovation*, Brookings Institution Press, **1997**; b) The blank, unnamed quadrant in Figure 7 is sometimes, perhaps unkindly, called “the university quadrant.”

[21] a) S. Tilghman (Chair), Biomedical Research Workforce Working Group Report: a Working Group of the Advisory Committee to the Director, National Institutes of Health, Washington, DC, **2012**; b) L. Faulkner (Chair), *Advancing Graduate Education in the United States*, American Chemical Society, Washington, DC, **2012**.