What Will Chemistry Do in the Next Twenty Years?

By George Whitesides*

The path of chemistry in the future will be determined both by its participation in solving large-scale societal problems and by its generation of new ideas through basic research. This article sketches four of the areas of societal "pull" in which chemistry will play a role in solving applied problems—national security, health care, the environment, and energy—and four areas in which basic research will be especially fruitful—materials chemistry, biological chemistry, computational chemistry, and chemistry exploring the limits of size and speed in chemical phenomena.

1. Introduction

Chemistry advances on two feet: one is utility, one curiosity. A prediction of its future path can only be a guess, based on its past progress and its present position. The *most* interesting and important directions to come—those that represent radical departures from the present—I cannot predict. What I *can* identify are societal concerns that seem certain to require solutions that are (at least in part) technical, and scientific ideas that seem equally certain to drive basic research for at least some time. What are these societal problems and scientific ideas?

I propose to organize this discussion in terms of the "pull" of societal concerns and the "push" of science and technology. I suggest four topics in each category (Table 1). A fifth topic under "pull"—globalization— is probably equally important as a determinant of societal concerns. The technical aspects of globalization (as opposed to its political or commercial aspects) are, however, largely subsumed in the other topics. I start with a discussion of the four current societal issues, not because they are more important than the four scientific themes driving basic research, but because they provide the context for discussions of applications of the basic research.

Table 1. The "pull" of societal concerns and the "push" of basic research set the direction of chemistry.

Pull	Push
National Security	*Materials Chemistry*
Economic competition as the equivalent of war	Polymers
	Surfaces and interfaces
	Functional and "smart" materials
Health Care	Materials for manufacturing
An aging population	Environmentally compatible materials
Global epidemics	
Cost containment	*Biological Chemistry*
Drugs	Molecular recognition
	Evolution and self-assembly
The Environment	Bioenergetics
Global change	
Waste management	*Computational Chemistry*
Toxicology	Increasing power
	New architectures: massively parallel machines and neural nets
Energy	
Alternatives to fossil fuels	
Electricity	*Small Basic Science*
	Exploring the limits: very small; very fast; very large
Globalization	

2. Societal Concerns That Will "Pull" Chemistry

2.1. National Security

Concern for national security is a major determinant of the allocation of resources. ("National" will, undoubtedly, be replaced by "regional" as globalization proceeds, but the concern remains the same.) National security concerns (largely meaning, in the past, military concerns) have been a major source of motivation, developmental capital, and markets for new technology. Development of nuclear power, high-octane gasoline, penicillin, computers, the jet airplane, and satellite communications, for example, all had roots in military problems.

For an interval (and perhaps permanently), we can hope that the probability of large-scale war between major powers will be small. What, if anything, will take the place of war as the ultimate expression of national and regional competition? As concerns with military technology decline, what will the consequences be for the development of new technology?

One form of competition that seems certain to intensify is economic. The future success or failure of nations—as judged by their ability to pay for essential public services for their citizens—may be based largely on their ability to compete in global markets. This competition will, I believe, emphasize an ability to produce and sell products with very high quality and acceptable cost for consumer markets. Chemistry will certainly play a key role in manufacturing and economic competitiveness, because it supplies key materials to virtually all manufacturing sectors of the economy.[1] Further, as the manufacturing process becomes more highly integrated—with, for example, designers of plastic automobile body parts ultimately specifying the detailed molecular weight distribution of the polymers from which these parts are made, to ensure the quality and reproducibility of their injection-molding processes—chemistry will necessarily be more heavily involved in materials, design, and manufacturing issues. *Simply making chemical compounds will not suffice for economic success.*

The shift in focus of national security from national defense to economic competitiveness will probably foster a

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shift in emphasis from very high performance materials to materials for manufacturing. At the same time, national subsidies for materials-related research will decline, and an increasing share of these research and development expenses will fall upon corporations. In effect, until or unless there are changes in national policies that will make manufacturing a government priority (unlikely, in most countries, in a world in which capitalism has emerged triumphant), the shift from military to economic defense will represent a form of privatization of national security.

One other, smaller, area of national competition (and, perhaps, cooperation) seems likely to influence the allocation of resources in technology and science—namely, "big science" projects. The motivations for these projects are complex, but a decision to pursue the manned exploration of the planets, the superconducting supercollider (SSC), or the human genome project would represent a major choice in setting national priorities in science and technology. Each of these projects has a specific molecular component, but this component can range from moderately large (for the genome project) to insignificantly small (for the SSC).

2.2. Health Care

Health care remains a central societal concern (Table 2). Four issues in health care will be important in the next years: all have implications for chemistry.

Table 2. Prevalence in USA of selected conditions [prevalence in millions]. The list of human infirmities is, depending on one's viewpoint, a sorrow or a shopping list of opportunities for biomedical research. (Adapted from *In Vivo*, January 1990; Source: Mattson Jack).

Condition	Prevalence	Condition	Prevalence
Periodontal disease	45.0	Polyps (colon/rectum)	7.0
Obesity	34.0	Diabetes sequelae	6.0
Chronic sinusitis	28.1	Insomnia	6.0
Arthritis	25.9	Cancer	4.8
Hypertension	23.7	Congestive heart failure	4.0
Osteoporosis	18.0	Ulcers	3.8
High cholesterol	17.8	Stroke	2.2
Heart conditions	16.4	Alzheimer's disease	2.0
Allergy	15.6	Emphysema	2.0
Lower back pain	15.0	Psoriasis	2.0
Depression	11.1	Benign prostatic hypertrophy	1.0
Migraine	7.7	AIDS and AIDS-related conditions (ARC)	0.7

One is an aging population. The great majority of health care costs pay for treatment of the diseases of old age—heart disease, cancer, stroke, diabetes, arthritis, and others. As the population ages, the number of individuals subject to and concerned with these diseases increases. In addition, new concerns arise—most recently, Alzheimer's disease and related neurological conditions. The importance of chemistry in developing drugs to treat these conditions, and the importance for chemistry (and for society) of forming effective interactions with biology and medicine in order to solve these medical problems, increases. The majority of drugs will continue to be chemical entities, made by chemical syntheses.

A second health-care issue is the emergence of global epidemics. Rapid, large-scale movement of people and materials between countries makes it likely that new diseases will emerge and spread rapidly: AIDS, antibiotic-resistant bacterial disease, and new strains of influenza represent current examples. There will be an increased need to respond rapidly to these epidemics with analytical and clinical tests, drugs, and vaccines.

A third health-care issue is cost. Although no one will argue that health care is not an essential component of a high standard of living, many will argue that even now health care costs too much. There will be intense pressure from both government and insurers, and as a result of competition among companies, to decrease the cost of developing and producing new drugs. The fact that many of these costs are mandated by regulatory requirements will not decrease these pressures and will, in fact, provide competitive advantage to the companies able to meet them. To meet these challenges will require the fusion of chemical and biological sciences to improve all phases of the process of drug development: screening, targeted drug design, optimization, demonstration of safety and efficacity, manufacturing, formulation, and distribution.

A fourth issue related to health care is drug abuse. The direct impact of drug use on the standard of living, especially in large cities, is large and increasing. The indirect impact—through spread of disease, damage to children born to women using drugs, loss of individuals from the work force—is perhaps even larger. Curiously, chemistry has, so far, played a relatively modest part in dealing with drug abuse: it has contributed primarily through development of clinical assays and a small number of drugs used in treating addiction. As neuropharmacology advances, chemistry may have a more active role in this area.

2.3. The Environment

The environment promises to be a major societal concern for many years (Table 3). It is based simultaneously on heartfelt popular concern and interest, inadequate scientific evidence, and exceptionally difficult matters of public policy requiring international cooperation and agreement.[2, 3] Both analysis of the problem and the technical component of its solution will require essential contributions from chemistry and active cooperation between chemistry and other fields.

Global warming is of intense current interest and will remain so until the implications of large-scale climatic change caused by human activities—especially combustion of fossil fuels and farming—have been resolved (Fig. 1). If, in fact, it is possible to establish that human activities are responsible for global warming and that this warming is undesirable, it may then be possible (or necessary) to ameliorate the climatic change by modifying these activities or by supplying corrective solutions. The role of chemistry in these activities will be crucial. The analytical methods necessary to establish the stable and reactive chemical entities in oceans and atmospheres are still incomplete; understanding the kinetics of the reactions of these chemical entities is a necessary part of global modeling; development of alternative methods of

Table 3. Public concern with environmental problems corresponds only approximately to the seriousness of these problems, as characterized by the US Environmental Protection Agency (EPA). (From L. Roberts, *Science (Washington, D.C.) 249* (1990) 616.)

EPA's top environmental problems (not in rank order)	Public concerns (in rank order)
Ecological risks	1. Active hazardous waste sites (67%)
Global climate change	2. Abandoned hazardous waste sites (65%)
Stratospheric ozone depletion	3. Water pollution from industrial wastes (63%)
Habitat alteration	4. Occupational exposure to toxic chemicals (63%)
Species extinction and biodiversity loss	5. Oil spills (60%)
	6. Destruction of the ozone layer (60%)
Health risks	7. Nuclear power plant accidents (60%)
Criteria air pollutants (e.g., smog, O_3, SO_2, NO_x)	8. Industrial accidents releasing pollutants (58%)
	9. Radiation from radioactive wastes (58%)
Toxic air pollutants (e.g., benzene)	10. Air pollution from factories (56%)
Radon	11. Leaking underground storage tanks (55%)
Indoor air pollution	12. Coastal water contamination (54%)
Drinking water contamination	13. Solid waste and litter (53%)
Occupational exposure to chemicals	14. Pesticide risks to farm workers (52%)
Application of pesticides	15. Water pollution from agricultural runoff (51%)
Stratospheric ozone depletion	16. Water pollution from sewage plants (50%)
	17. Air pollution from vehicles (50%)
	18. Pesticide residues in foods (49%)
	19. Greenhouse effect (48%)
	20. Drinking water contamination (46%)
	21. Destruction of wetlands (42%)
	22. Acid rain (40%)
	23. Water pollution from city runoff (35%)
	24. Nonhazardous waste sites (31%)
	25. Biotechnology (30%)
	26. Indoor air pollution (22%)
	27. Radiation from X-rays (21%)
	28. Radon in homes (17%)
	29. Radiation from microwave ovens (13%)

producing energy or fuels that do not generate CO_2—electricity from nuclear-, solar-, or wind-powered generators, dihydrogen from nuclear thermal cycles—will require the development of relevant materials technologies. The biochemistry of CO_2 consumption and methane generation is incompletely understood. Dramatic large-scale ideas—promoting CO_2 fixation by marine algae by adding iron to the polar seas—would require detailed modeling. We may yet be called on to produce a chemical consumer of CO_2 that is the equivalent of the Amazonian rain forest!

The management of industrial and urban waste is a second economically and technically demanding environmental problem. Cleanup of existing waste will require innovative technology, particularly if some value is to be recovered from this waste by the separation of its components. Minimization of future industrial waste will be a key part of the development of new processes, of redesigning or replacing old ones, and of integrating production of basic starting materials with manufactured products. The cost of waste management will make "yield" an increasingly important parameter and may require the large-scale modification of catalysts and processes for the largest-volume chemicals. The minimization of the quantity, environmental impact, and unfavorable public reception of industrial waste (including byproducts of chemical production such as scrap and solvents/materials used in manufacturing, packaging, use, and disposal—that is, overall production and life-cycle waste) will increasingly determine the cost of products. Minimization of costs—especially costs of waste management—is not as exciting as generating new materials and products, but will be an essential (and probably heavily regulated) part of any business that uses chemicals or materials.

The impact of requirements for waste management will, in due course, probably also strongly influence the course of basic research. University laboratories are even less well equipped to handle the costs of disposal of chemicals and treatment of effluents than are industrial laboratories—there are no customers to whom to pass on the cost! The environmental costs of a university laboratory involved in biochemistry, for example, are intrinsically less than those of a laboratory doing exploratory synthesis in organoselenium chemistry. The difference will inevitably encourage some types of research relative to others, influence the rates at which new ideas are generated in different fields, and determine the numbers of trained professionals that are produced in these fields.

A final, constant theme in concern about the environment is understanding the toxicology of chemicals and materials, both products and waste (Fig. 2). Developing truly rational

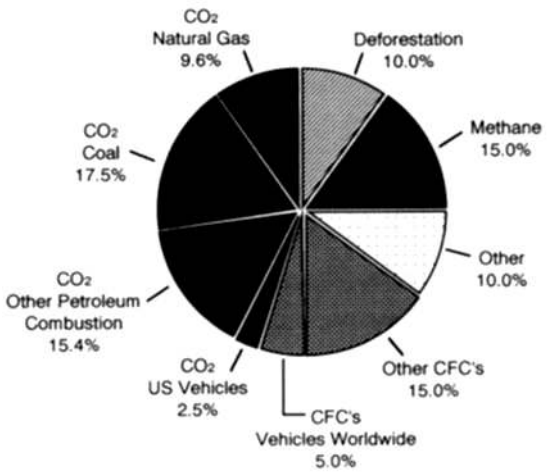

Fig. 1. Currently identified, major worldwide contributors to global warming include combustion of fossil fuels, agricultural practices, and release of chlorofluorocarbons. The contribution associated with each is uncertain.

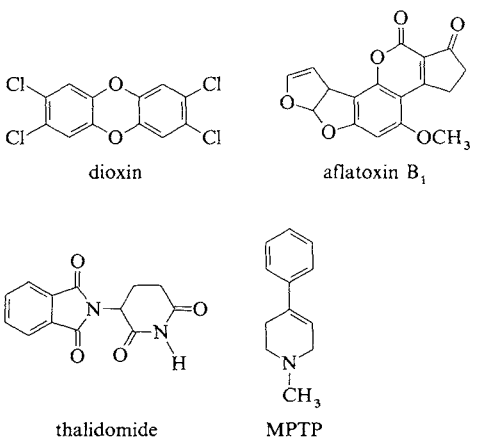

Fig. 2. The hazard associated with many prominent chemical substances (dioxin, aflatoxin, thalidomide, MPTP) was discovered only retrospectively: in most cases, this hazard could not have been predicted based on knowledge of metabolism. Accurate *prediction* of toxicity for new compounds requires much deeper understanding of metabolism and molecular biology.

bases for regulating release of chemicals into the environment or the workplace during manufacture, use, disposal, or accident may be too much to hope for, but wildly *irrational* bases for regulation are guaranteed unless we acquire a firm understanding of metabolism and toxicology of chemicals and materials and of their transformations during processing and in the environment.

2.4. Energy

The fourth major societal concern will continue to be energy. In the next 20 years the cost of energy will rise as the most readily available of the world's petroleum reserves are depleted. Whether significant new opportunities will arise for application of chemistry in enhanced oil production and exploitation of other fossil fuels, in developing technologies that promote conservation or increase fuel efficiency, or in rationally or irrationally mandated alternative fuels such as methanol and ethanol, remains to be seen.

The only technology capable of replacing fossil fuel combustion in very large-scale power generation is, of course, nuclear. If nuclear generation does reemerge as a politically acceptable source of power, the replacement of liquid hydrocarbons by electricity as an energy source for vehicles will create a myriad of opportunities in batteries and electrically functional materials (such as conductors, insulators, and dielectrics) (Fig. 3). Even if the transition from fossil-fuel-based to nuclear power is slow, regulations designed to control urban air pollution now seem certain to force the development of electric and hybrid-combustion electric automobiles. This process of regulation is most clear and most advanced in southern California. In this matter, with high probability, "As goes Los Angeles, so goes the world!"

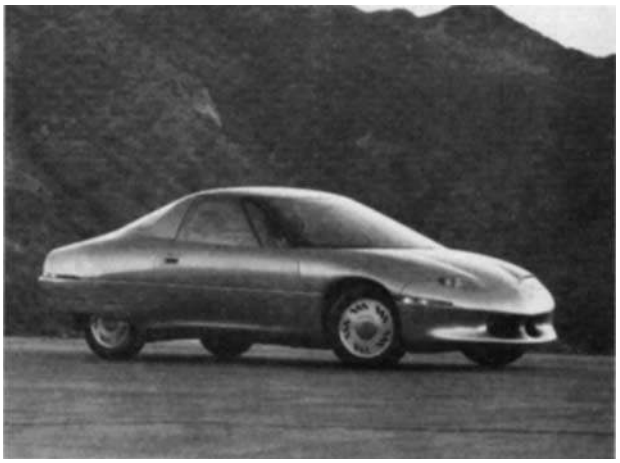

Fig. 3. The General Motors "Impact" prototype electric vehicle. Environmental issues and a declining availability of petroleum are forcing serious consideration of electric and hybrid automobiles. These vehicles will require new materials and technologies for electrical storage and use, for lightweight, aerodynamic construction, and for safe operation.

The development of small, safe nuclear reactors might, in the longer term, make electrochemistry and high-temperature chemistry attractive for new chemical processes.

3. Four Scientific Themes That Will Push Chemistry

One reason for pursuing scientific research is to solve problems; another is to understand how nature functions. Three scientific themes in chemistry—materials chemistry, biochemistry, and computational chemistry—have captured the interest and imagination of many chemists, because these areas offer important problems in basic science, rapidly advancing analytical technology to use in addressing these problems, and opportunities for applications. Each of these three themes will remain strong for years to come.

A broad range of other areas in basic research are also being explored on smaller scale. From these many exploratory efforts, I have arbitrarily selected one representative theme that seems certain to produce important new science: research involving phenomena occurring at scales of size, time, or intensity that have historically defined the limits or boundaries of interest of chemistry—that is, phenomena occurring at scales of fractions of atomic dimensions, or faster than bond vibrations.

3.1. The Chemistry of Materials

The chemistry of materials is the first of the major scientific themes that will unite broad areas of research in the future.[4] Chemistry has moved from the study of atoms and small molecules to the study of large molecules and collections of molecules. One focus of this study is the chemistry of materials (an area of ill-defined boundaries, sharing many concerns with polymer and solid-state chemistry, condensed matter physics, and materials science and engineering). Two of the broad objectives of this area are understanding the macroscopic properties of matter based on a knowledge of its microscopic (atomic-scale) structure, and preparing new materials having new properties. Questions representing these objectives would be: "How can one predict the structure and moduli of a organic polymer knowing only the structure of its monomeric units?" and "How can one synthesize a solid that is superconducting at 400 K?" The chemistry of materials is an exceptionally broad field, and I will only touch on a few themes here.

3.1.1. Man-made Polymers

Man-made polymers have historically been the most important of the contributions of chemistry to materials science. It seems unlikely that there will be many new commodity polymers introduced in the future. A new polymer would have to provide fundamentally new properties or significantly lowered cost for existing properties to justify its introduction; neither possibility seems likely. New *processes* for existing monomers and polymers will, however, be important, to minimize byproduct streams and environmental costs and to adapt to changing raw materials. These process improvements for manufacture of large-volume chemicals (and production of hydrocarbon fuels), and development of new processes to produce specialty polymers, will continue to provide important and deeply challenging problems in catalysis.

Heterogeneous systems based on polymers—phase-separated copolymers, alloys, fiber-reinforced composites—provide a field of great interest and utility.[5] The development of fundamental understanding of all aspects of these systems is still at an early stage. Fiber-reinforced composites represent a particularly interesting example. In principle, these systems offer very attractive properties; in practice, their application has been limited by incomplete fundamental understanding of almost every aspect of their behavior: What is the atomic basis of fracture in composites? How are composite properties related to the bulk properties of the matrix, the fiber, and the matrix–fiber interface? How is energy dissipated in the solid at the molecular level? Answering these questions will require a deep understanding of the atomic/molecular behavior of solids under stress.

3.1.2. *Surfaces and Interfaces*

Surfaces and interfaces are ubiquitous in systems from microelectronic devices through heterogeneous catalysts to living tissue.[6] One trend in materials is toward the use of nanostructured materials—that is, materials having components with dimensions of 0.2–100 nm. In nanostructured materials, interfaces may be major determinants of properties and may constitute a significant fraction of the total volume of the system. The interface can be considered, in a certain sense, as a separate phase of matter. Interfaces are regions where gradients in properties can be very steep, and where structure, properties, and reactivity can be very different from those in bulk matter (Fig. 4).

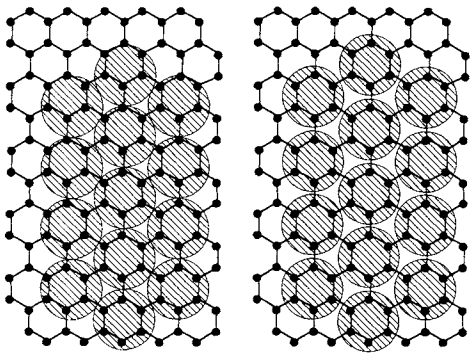

Fig. 4. Monolayers of matter can show behavior distinct from that of bulk matter. For example, krypton on graphite shows two distinct crystalline phases, one commensurate with the underlying graphite lattice, one incommensurate. (Adapted from work of R. Birgenau, *Science (Washington D.C.) 232* (1986) 329.)

New analytical techniques—from X-ray photoelectron spectroscopy (XPS) to scanning tunneling microscopy (STM)—have revolutionized the study of interfaces.[7] Synthetic techniques such as chemical vapor deposition (CVD)[8] and molecular self-assembly make possible a high level of control over the structures of interfaces. Combination of these analytical and synthetic techniques makes interfacial chemistry as tractable now as solution chemistry has been in the past.

Developing structure–property relationships for interfaces will be an extremely rewarding area of condensed matter science and invaluable in the design and applications of materials whose properties are based on phase-separated systems.

3.1.3. *Functional and "Smart" Materials*

A current challenge to materials synthesis is the design and preparation of materials with exceptional properties. Three recent examples are metal oxide high-temperature superconductors,[9] polyaniline-derived organic conductors,[10] and vapor-deposited diamond thin films.[11] The list of candidates for new ideas in design is enough to engage the creativity of those interested in the solid state for the foreseeable future: examples include "room temperature" ($T_c \approx 400$ K) superconductors, materials with very large nonlinear optical coefficients,[12] organic ferromagnets,[13] solids having negative Poisson's ratios,[14] thermally conducting organic solids, and high-temperature elastomers.

The availability of materials with unusual properties leads naturally to what promises to be a major area of materials science in the next years: namely, the development of so-called smart materials and structures—materials and structures that respond to their environment with large changes in one or several of their properties. Examples of smart materials are photochromic glasses (which change color in response to light),[15] ferromagnetic fluids (which change shape in response to magnetic field gradients),[16] and electrorheological fluids (which change viscosity in response to electric fields).[17] These materials often exhibit their interesting properties as reflections of cooperative behaviors—phase changes and aggregation—of central interest in pure chemistry. They offer the basis for new classes of devices (in the examples given, sunglasses, rotary magnetic seals, and clutches).

3.1.4. *Materials for Manufacturing*

The increased emphasis on understanding and controlling manufacturing has highlighted a broad series of problems offering both basic and applied components. For example, understanding the wetting of solids by polymers and the flow of polymers in high shear is central to understanding the manufacturing of composites, injection molding of polymers, and a host of other technologies. These areas have also provided a stimulus to try to rationalize the motion of fluids (especially polymeric fluids) near interfaces.[18] Designing packages for integrated circuits has focused attention on understanding the influence of strain on thin films and on controlling adhesion and the coefficient of thermal expansion in these systems.

Virtually every manufacturing process—molding, machining, welding, coating—contains elements of basic science that have seemed in the past too complicated and too applied to address at the level of basic science (Fig. 5). The combination of new analytical techniques, advanced computational techniques, and practical necessity now makes many of these problems tractable. In the same way that much of the basic research in biochemistry has been supported under the banner of "health care," "manufacturing" (as opposed

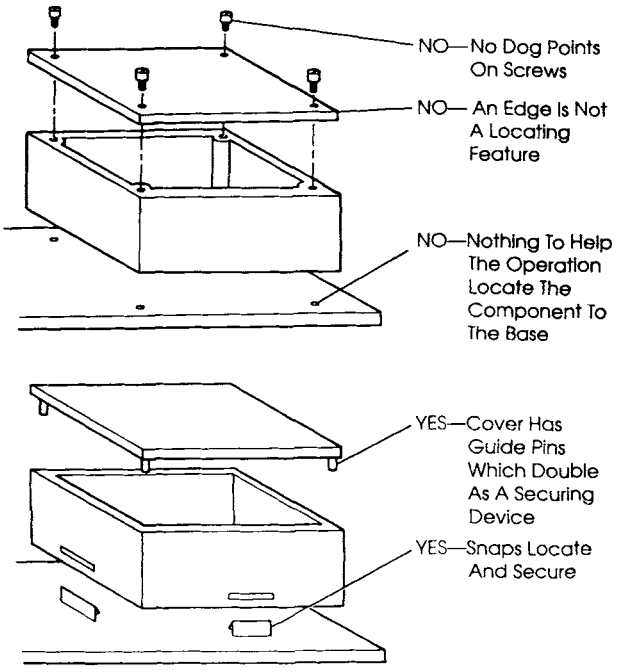

Fig. 5. Design for manufacturing (DFM) introduces complex shapes into molded parts. Successful application of DFM requires close control over materials and process variables. (Adapted with permission from a drawing by Munro and Associates, Inc.)

to "high-performance materials for defense") may provide both the justification and the focus for a broad group of neglected but very interesting problems in the chemistry of materials.

3.1.5. *Environmentally Compatible Materials and Processes*

The concern of society for the environment has been slow to sink into the chemical consciousness and slower still to be converted into programs leading to new classes of materials *designed* for compatibility with the environment. At least two themes have, however, emerged from this concern to receive increased (although still small) effort in materials science: materials that can be recycled[19] and materials that will biodegrade.[20] Both of these themes are, of course, well recognized, but their ultimate impact in terms of new materials and processes in not yet defined.

3.2. Biological Chemistry

The second major scientific theme dominating current basic chemistry and certain to push chemistry in the future is the study of the substances and reactions relevant to life. Biology has been the center of one of the great intellectual revolutions of the century, and its excitement will continue for many years. Reducing the broad descriptions provided by biology to molecular detail, exploiting the knowledge from these molecular descriptions in pharmacological and agricultural chemistry, and extracting new principles of organization and reaction for development in nonbiological systems are a central occupation of chemistry.

The scope and speed of development of biology and biological chemistry are so broad as to make any short description trivial, but some of the areas of opportunitiy for chemistry are already well established.

3.2.1. *Molecular Recognition*

A very large number of biological processes share a common event: the selective recognition of one molecule or molecular fragment by another in the very complex mixture present in the cell or organism, as well as the association of these two entities.[21] Although this sort of recognition—of an enzyme for its substrate (and perhaps transition state) or of a receptor for its ligand—is ubiquitous, understanding the basis for molecular recognition in sufficient detail to make successful predictions has proved astonishingly difficult.[22, 23] Chemistry has been very successful in dealing with systems involving single strong bonds—the covalent bond, the hydrogen bond. Biological systems seem to utilize large numbers of relatively weak interactions, occurring over large areas of molecular surface, together with poorly understood contributions from solvent, to achieve selectivity in recognition. A range of techniques—from site-specific mutagenesis through two-dimensional NMR spectroscopy and X-ray analysis to computation—is now being focused on understanding molecular recognition in biological systems. There is every reason to expect rapid progress in this area, but no reason to expect that there will be a single solution to it, or that molecular recognition will ultimately prove to be simple.

An application and extension of molecular recognition is the problem of "rational drug design".[24] The process of drug development is presently slow and expensive, with much time spent in random trial and error. In principle, it should be possible to make this process much more efficient by taking advantage of techniques from molecular biology. The proposed paradigm (much oversimplified) would have three steps: first, through studies of biology, identify a key enzyme or receptor involved in a disease; second, clone the gene for this protein, obtain substantial quantities of it, and determine its structure by X-ray crystallography; third, design and synthesize molecules that bind tightly to its active site (Fig. 6). This process would, of course, only generate tight-binding inhibitors of key target proteins and would

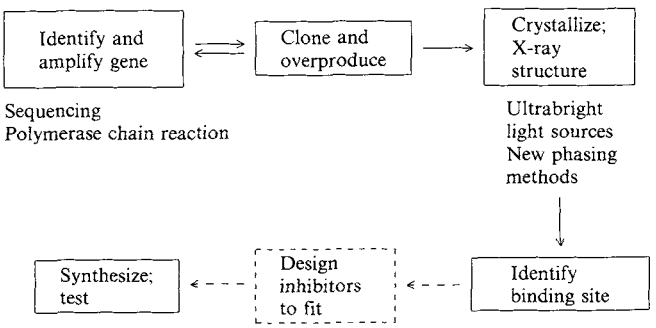

Fig. 6. All phases of the paradigm for rational design of candidate drugs work well, except for that part requiring the design of organic molecules to fit specific sites on proteins.

leave the other parts of the cycle of drug discovery—testing for safety and efficacity, manufacturing—unchanged. It would, nonetheless, shorten and simplify the overall process.

All elements of this process work well except that of designing molecules to fit an active site. This problem in molecular recognition has proved difficult, and, although certain specific systems have yielded impressive results, the difficulty and labor involved in achieving these successes have remained large.[25]

A third aspect of studies of molecular recognition that has increasingly attracted attention focuses on "biodiversity". Nature, so the teleological argument goes, achieves tight binding by randomly generating many structures (for example, polypeptides) and selects from among these, using various strategies, those having biological activity. Can chemistry use the same strategy? Can it generate compounds randomly, and efficiently select desirable activities from this random collection?

It is clear that this approach can sometimes work brilliantly, especially when chemical and biological approaches are coupled. One example is the development of catalytic monoclonal antibodies, by raising antibodies to analogues of transition states.[26] There are, so far, no purely chemical analogues to this type of process, since it is difficult to achieve the type of selection and amplification that characterizes life in nonbiological systems. The challenge of developing practical tactics for generating large numbers of compounds, and for selecting desirable activities from them is, however, being actively studied.

A final theme in molecular recognition is that of binding "simple" molecules to one another[22, 23] and to relatively ordered biological targets such as nucleic acids.[27] Starting from the discovery of crown ethers and proceeding to recognition based on hydrogen-bonding networks, it has been possible to generate satisfyingly specific interactions, often by incorporating and adapting naturally occurring recognition elements. The extension of these systems to self-replicating structures, complex self-assembled molecules, and related topics promises to offer substantial understanding of recognition, to provide guidelines for synthesizing structures based on noncovalent interactions, and to generate new reagents for biochemistry.

3.2.2. *Evolution and Self-assembly*

The origin of life and the nature of evolution are among the great questions in natural science. Early studies showed that it was possible to form simple molecules under plausible prebiotic conditions, but gave no hint of the route from these simple species to complex ones, or to living organisms.[28] Demonstrations of plausible pathways from α-amino nitriles to porphyrins and from glycolaldehyde phosphate to ribose have established a new paradigm for examining this type of problem and offer evidence that the path from simple to complex molecules may be remarkably direct.[29] These studies suggest that a broad range of processes in the early molecular stages of evolution should be reconsidered and perhaps used as the basis for new types of chemical reactions.

These studies open one new door along the corridor leading (perhaps) from an undifferentiated, primordial soup to life; they leave others still closed, or only slightly ajar. The spontaneous assembly of certain classes of molecules into assemblies or structures held together by noncovalent bonds is also central to understanding the procession from molecules to life. "Self-assembly" is clearly relevant to the formation of lipid membranes, to the folding of polypeptides into globular proteins, and to a wide variety of other processes leading to organized assemblies in biological systems.[30 - 32] Self-assembly has also stimulated interest in uncovering the rules for these systems and in using them in nonbiological or quasi-biological systems to form new types of structures (such as ordered monolayer films, liquid crystals, and liposomes).

These advances in a number of separate areas have suggested sections of a pathway from molecules to life. A key part of the path—that dealing with self-replication of the organized ensemble representing a primitive cell—still remains hidden.[33] A major step in understanding self-replicating systems might enable chemistry to begin to make serious proposals concerning the origin of life.

3.2.3. *Bioenergetics*

One of the most interesting unresolved puzzles in biological systems is that surrounding "vectorial" chemistry (Fig. 7). Energy is stored in all organisms (to some extent) in

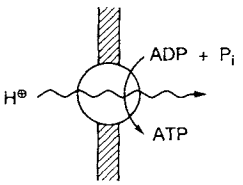

Fig. 7. In biological systems, energy is stored, in part, in concentration gradients across membranes. The discharge of a concentration gradient coupled with the formation of a chemical bond is a ubiquitous process in biology, but poorly understood at the molecular level.

the form of concentration gradients of ions across membranes.[34] Despite its enormous importance, this idea—*Mitchell*'s famous chemiosmotic hypothesis—has virtually no nonbiological model. How is the discharge of the concentration gradient coupled to the formation of ATP from ADP?[35]

The structures of the proteins involved in these vectorial processes are now emerging and will help to solve the puzzle.[36] As with molecular recognition, however, until good models that have predictive power have been developed, the puzzle of how energy is stored in and regenerated from concentration gradients across cell membranes remains unsolved.

3.3. Computation

The use of computation is the third major scientific theme that will push chemistry in the future. Computational power is one of the few items in chemistry that is rapidly becoming more available. Large-scale computation has traditionally

been the province of the "quantum mechanician". Computation (especially in semiempirical forms such as molecular mechanics,[37] molecular dynamics,[38] and large-scale simulation) is now rapidly becoming an indispensable component of experimental programs as well, particularly those concerned with complex systems. The power of computation is such that calculated results may exceed experimental results in their ability to identify trends and to distinguish contributions of individual factors. It is, for example, straightforward by simulation to "mutate" an NH group in a protein into a CH_2 group while leaving other elements of the structure unchanged, or to change the dielectric constant of water.[39,40] Accomplishing these transformations experimentally is, obviously, more difficult (or impossible!).

Identifying some of the pending changes in the technology of computation is relatively straightforward: chemistry is, in general, a follower rather than a leader in applying computers, and one has only to look at computationally more advanced areas—electrical engineering, fluid dynamics, or computer science—to see what will be available. In addition to an ever lower "price per bit" and "price per flop", the next years will see exploration and application to chemistry of two important new architectures in computers: massively parallel machines and neural networks (Fig. 8). The former

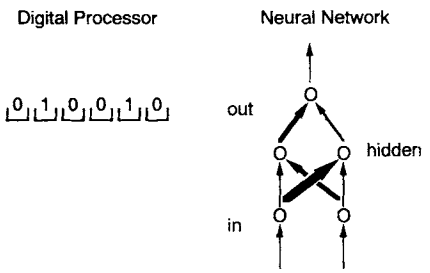

Fig. 8. The information in a digital processor (a conventional computer) is stored in bits (0 or 1) in specified locations. The information in a neural network is stored in connections of different strengths between nodes. Neural networks are particularly useful for analyzing complex nonlinear problems where high numerical precision is not required and for problems in pattern recognition. The fact that chemistry has many such problems suggests that neural networks may be useful here.

should make it possible to handle problems involving very large numbers of atoms (or other components); the latter is presently poor for problems requiring high numerical precision, but may be excellent for certain types of problems involving pattern recognition, highly nonlinear relationships, or relationships in which the functional form connecting input and output is unknown.[41,42]

To what problems will these new methods of computation be applied? To calculations in molecular and supramolecular structure and reactivity, of course, but also to a range of problems that have historically been outside the realm of chemistry: fracture, complex coupled systems of many reactions in the atmosphere or in a cell, flow of a non-Newtonian polymer, and protein folding. The routine incorporation of large-scale computation into experimental programs has as much potential as any other technique to change the way in which chemistry is practiced.

3.4. Exploring the Limits: Very Small, Very Fast, Very Large

This fourth theme that will push chemistry is one of many that could be identified in basic research. The new capabilities and ideas emerging constantly in chemistry and in related areas of physics and biology are an astonishing testimonial to the vitality of these fields. Chemistry has begun, in certain areas, to push to the limits of what is usually defined as "chemistry". It is, for example, now possible to visualize atoms directly and to study processes occurring more rapidly than a bond vibrates. There is an enormous amount to be learned now, and in the future, by studying phenomena occurring at these boundaries of the intellectual territory named chemistry. Whether chemistry will respond to reaching these boundaries by pushing further (for example, to studies of inner-shell electrons) or whether, more probably, it will turn toward other frontiers (for example, very complex systems and the chemistry of cognition, perception, and memory[43]) remains to be seen. Some of the activities in basic research at the present limits are discussed below.

3.4.1. Very Small

The scanning tunneling microscope (STM) and its many progeny have started a revolution in the visualization of structure.[44] Subatomic-scale resolution—the limit of interest in almost all chemical problems—of nonperiodic structures is routine in many systems, although interpretation of STM images remains a challenge. STM will clearly be a key instrument for high-resolution structure determination in conducting materials; atomic force microscopy provides complementary information, including information concerning insulators.

The phrase "very small" applies to quantity as well as size. The polymerase chain reaction (PCR) has made routine the manipulation of very small numbers of copies of a gene.[45] As chemistry incorporates techniques from biology, the PCR and yet-to-be-discovered techniques for gene identification, amplification, and modification will be indispensable.

3.4.2. Very Fast

Femtosecond IR spectroscopy also reaches the practical limit of interest in chemistry.[46] The ability to follow a characteristic infrared chromophore on scales of time short compared to vibrations is clearly not a general technique, but it makes possible the analysis of bond-forming and bond-breaking processes and of energy transfer with exquisite detail (Fig. 9).

Femtosecond spectroscopy depends on the laser to generate very short pulses of light. A related application of intense photon sources is flash X-ray diffraction—using a synchrotron as a source of X-rays and an array detector to collect diffraction data, it is possible to obtain the information needed to solve the structure of a protein (in favorable cases) in very short intervals.[47]

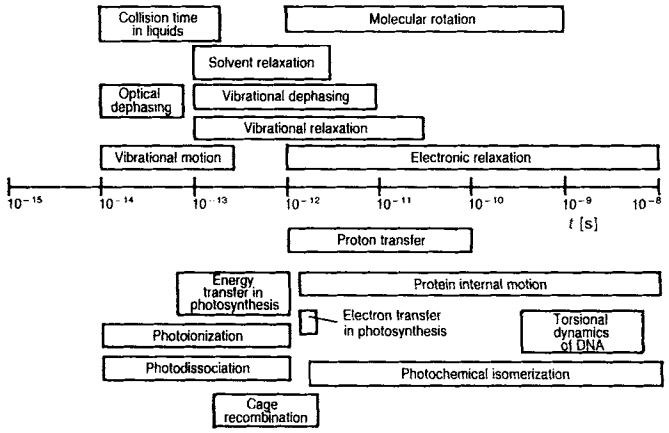

Fig. 9. Fast forms of spectroscopy have opened for investigation areas that encompass the fastest processes that concern chemistry. (From G. R. Fleming, P. G. Wolynes, *Phys. Today 43* (1990) No. 5, p. 36.)

3.4.3. Very Large

The very large electromagnetic fields generated by focused lasers make possible the ordering of particles in new ways ("light matter")[48] and even the trapping and observation of single atoms (in light traps).[49] The synthesis of isotopically pure ^{12}C diamond[50] has confirmed the theoretical prediction that this material has the largest thermal conductivity known and illustrates the coupling of theory and synthesis in materials science.

4. Conclusion

Although the subjects of interest in chemistry have changed dramatically in the last 20 years and will probably change even more in the next 20, its fundamental character remains the same. *Chemistry is the most fundamental of the sciences concerned with perceptible reality*. The affairs of nucleons and of galaxies are extraordinarily interesting, but are removed from everyday experience. Biology ultimately reduces to chemistry. Chemistry combines understanding of the molecules and processes that underlie reality as we experience it directly—from inanimate structures and fire through life—with tools to shape this reality—polymers, fuels, and drugs. It combines curiosity and utility in the direct service of man.

The details of recent changes in chemistry suggest its future. In the commercial sphere, the era of large-scale "simple" chemistry is over as an area of innovation. Discovering processes to new compounds has largely been replaced by the effort to discover sophisticated processes to existing compounds, while meeting increasingly complex boundary conditions: low cost, low capital cost, safety, environmental acceptability. Although new reactions or new catalysts always offer the opportunity to develop new processes, the emphasis has shifted to strategies for adding value to bulk chemicals—by blending or compounding them or by moving downstream to production of complex systems (coatings, multilayer films, components of composites) to meet complex needs. More carefully specified raw materials compatible with high-quality manufacturing will either be offered by chemical producers in the future or be demanded of them by users.

The chemical industry seems determined to move to materials to increase its margins and perhaps to the manufacture of engineered components. Catalysis will remain centrally important in providing economical routes to the precursors and to the final materials (Fig. 10). Although materials and components offer great opportunities, they also require a degree of sophistication in design, manufacturing, and contact with customers that is unfamiliar to many chemical companies.

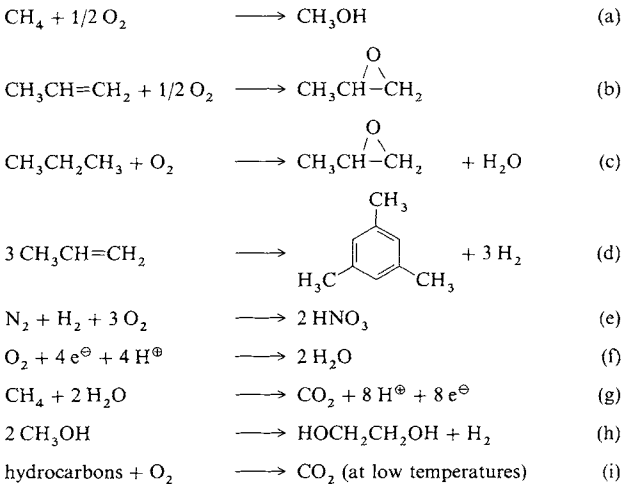

Fig. 10. Catalysis, one of the central disciplines in chemistry, offers a continuing range of challenges. All of these reactions are presently unknown or impractical, and the development of efficient reactions and catalysts to accomplish them would be useful in areas such as commodity synthesis (b, c, d, e, h), fuel transportation (a), fuel cell operation (f, g), and automobile emissions control (i).

The pharmaceutical companies expect, doubtless correctly, a stream of opportunities from biochemistry, biology, and research medicine. Organic synthesis will remain the most important technology in manufacturing drugs.

In basic science also, the focus has shifted from simple chemistry—synthesis of new organic and inorganic compounds (albeit of very great structural complexity), study of the dynamics of basic reactions—to studies of much more complex molecules, molecular ensembles, and processes. The physical-organic chemistry of 20 years ago (solvolysis of norbornyl tosylate) has become the study of factors influencing binding of oligopeptides to proteins using site-specific mutagenesis. Studies of intermolecular potentials using molecular-beam scattering has evolved into studies of two-dimensional phase separation of lipids in supported bilayers.

The problems posed by biology and by the behavior of condensed phases—solids and solutions—offer a host of opportunities for those attracted by complexity. Computers, advanced light sources, and new classes of analytical instruments capable of dealing with very small objects and very fast processes provide new tools for studying these problems. The first hints of answers to certain big questions—the origin of life, the molecular basis of memory—are beginning to appear.

What the unexpected developments will be in the next years is, of course, impossible to predict. The rate of change in chemistry and in the fields surrounding it is, however, sufficiently rapid that there is, fortunately, no doubt but that there *will* be unexpected developments. I will be lucky if the

predictions I have offered here are good for ten years; beyond that, all is conjecture.

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