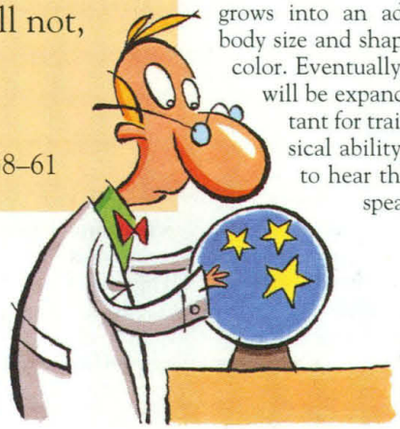
Through the Glass Lightly

A collection of scientists at the frontier were asked what they see in the future for science.* Here are their views....

If you can look into the seeds of time,
And say which grain will grow and which will not,
Speak then to me, who neither beg nor fear
Your favors nor your hate.

Shakespeare, *Macbeth*, 1.3.58–61



ILLUSTRATIONS BY TERRY E. SMITH

THERE WILL BE ENORMOUS INROADS INTO human biology and human disease via genomics, gene therapy, and mouse knockout models; a revolution in drug design by combinatorial chemistry; an understanding of the specificity of nerve connections and cognition; and the basic logic of development will be solved (if it is not solved already). New technologies will be developed for studying the structure, function, and dynamics of multiprotein ensembles—for example, the eukaryotic transcription complexes. New methodologies will be developed for studying the behavior of single, live cells in isolation or in the context of an embryo. This includes studying the activity of the cell itself as well as various subcellular structures.

Hal Weintraub
Fred Hutchinson Cancer Research Center
Seattle, Washington

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BY THE YEAR 2000 OR SO, THE COMPLETE genomic sequences of at least five model eukaryotic organisms will be known—*S. cerevisiae*, *S. pombe*, *D. melanogaster*, *A. thaliana*, and *C. elegans*—with substantial information from mouse and humans. Novel sequencing methods will increase the speed of DNA sequencing by a factor of at least 1000. We will also have a complete database of all living organisms, including not only taxonomic data, but also morphological, ecological, biogeographical, and biological data. A complete census of the living organisms in selected habitats will be made.

Michael Ashburner
Department of Genetics
University of Cambridge

BY THE END OF THE DECADE, ALL THE GENES contributing to genetically complex diseases of humans will be known. Population screening will allow identification of individuals at risk for diabetes, schizophrenia, obesity, and many other diseases. In many cases, disease will be either avoidable by modification of behavior or ameliorated by therapeutic intervention. For societies with socialized health care programs, the economic cost of screening will need to be balanced by the overall savings in disease reduction. If individuals refuse preventive treatment, screening is not cost-effective. For societies with private health care systems, the rich will become healthier and the poor sicker. In both systems, balancing the rights of individuals against the needs of society is going to be difficult.

Peter N. Goodfellow
Department of Genetics
University of Cambridge

BY USING TECHNIQUES INVOLVING IN VITRO fertilization, it is already possible to remove one cell from the developing embryo and characterize any desired region of DNA. Genetic screening of embryos, before implantation, may soon become routine. It will be possible, by sequencing important regions of the mother's DNA, to infer important properties of the egg from which the person develops. This assumes that predictions of protein structure and function will be accurate enough so that one can deduce, automatically, the relevant properties of many important proteins, as well as the regulation of their expression (for example, how much will be made at a particular stage in development in a particular tissue or cell type) from the sequence of genomic DNA alone. All of this information will be transferred to a supercomputer, together with information about the environment—including likely nutrition, environmental toxins, sunlight, and so forth. The output will be a color movie in which the embryo develops into a fetus, is born, and then grows into an adult, explicitly depicting body size and shape and hair, skin, and eye color. Eventually the DNA sequence base will be expanded to cover genes important for traits such as speech and musical ability; the mother will be able to hear the embryo—as an adult—speak or sing.

Harvey F. Lodish
Whitehead Institute for Biomedical Research
Cambridge, Massachusetts

THE OLD PHRASE "YOU can't get blood from a turnip" may be proven incorrect, at least partially. Transgenic plants hold promise as biomanufacturing systems for a wide variety of human proteins, including those found in blood plasma. Serum albumin, for instance, has been shown to be expressed and processed correctly when the gene encoding it was introduced into plants. The missing element in this scenario is process technology, which will make it possible to do large-scale protein purification from plant tissues. Advances in high-level protein expression in specialized plant tissues (such as seeds, fruits, or tubers) coupled to engineering improvements in protein isolation may make this technology feasible in the coming decade.

Charles J. Arntzen
Institute of Biosciences and Technology
Texas A&M University

IN THE LATTER HALF OF THE 1990S THERE will be an increasing realization that nature has been constructing transgenic organisms for millions of years. The natural mechanisms of horizontal gene transfer will be discovered and the consequences will have major impact on the public perception of transgenic organisms and their release into the environment.

For many years the control of insects has stressed eradication. A far better long-term strategy would be to replace a population with one that can do no harm—for example, to replace a population of *Anopheles gambiae*, a major vector of malaria, with one that is unable to transmit the parasite. Three developments are required, all foreseeable with an extension of current technologies: (i) a robust method to transform

*See also Editorial, p. 1575.

nondrosophilid insects, (ii) the identification of genes with the required characteristics (for example, that confer on their carriers the inability to transmit a parasite or alter host plant preference of an insect pest), and (iii) the discovery of ways to drive these genes into natural populations (for example, by using transposable elements or symbiotic microorganisms).

Michael Ashburner
Department of Genetics
University of Cambridge

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THERE IS AND WILL BE NO TRULY COMPREhensive theory of a single mechanism of superconductivity. The basic physics of the phenomenology has been under control for nearly 40 years and is the paradigmatic example of broken symmetry: gauge symmetry broken by condensation of Fermion pairs. It is clear that there are about four (or five if one includes ^{3}He) distinct mechanisms giving pair condensation, of which at least one (the mechanism in ultra–low temperature heavy electron metals such as UBe_{13}) is totally unknown. As for the high critical-temperature cuprates (T_c), a solution is evident, although some minor details remain to be filled in. Five years will certainly be enough for the more general dissemination of that realization and for the more formal working out of the theory's consequences. More difficult is guessing when or whether the log-jam in the theory of metals, which is blocking our understanding of the other cases and many other puzzling phenomena in related fields, will give, if ever.

The question of room-temperature superconductivity is very much a layman's question, since it is the one question no theory of superconductivity will ever answer (just as no theory of liquids can tell you the boiling point of water). The cuprates seem to be going to peak under 200 K. The cuprate mechanism could possibly give a higher T_c if there were some (possibly chemically unstable) way in which CuO_2 planes could become even more closely coupled. All of the other hypothetical mechanisms proposed for higher T_c's over the years (bipolarons, excitons, antiferromagnetic spin fluctuations, and so on) are, for one fundamental reason or another, unworkable.

We will come in 20 years to wonder why we cared so much. It is not clear why or whether a room-temperature superconductor would be more useful for most purposes (although it could be a godsend for biological instrumentation). For most uses, advances in cryogenics will make 77 K so easy to manage that little flexibility is lost.

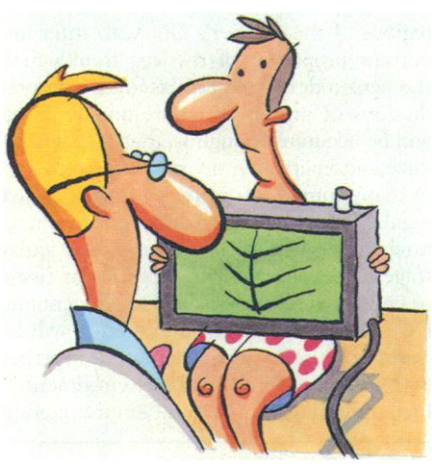
In 20 years a 100-Tesla magnet for scientific uses will exist using currently known materials. By that time power transmission on superconducting wires will occupy some special niches, and experimental fusion reactors will use superconducting magnets with at least partially cuprate windings. Experimental superconducting Maglev trains will exist. SQUID (superconducting quantum interference device) magnetoencephalograms will be a major diagnostic technique. But the real major use of superconductivity will turn out to be something we haven't yet thought of.

P. W. Anderson
Joseph Henry Laboratories of Physics
Princeton University

THE UNEXPECTED DISCOVERY OF THE CUPrate family of superconductors which can carry substantial supercurrents at liquid air temperatures (–196°C) has made a room-temperature superconductor conceivable. This new form of superconductivity has an electronic origin, and this makes it more similar to other electronic states such as magnetism, which often set in well above room temperature. A useful room-temperature superconductor, able to support a large supercurrent, will need to have an even higher transition temperature. It is clear that the conditions to realize this new form of superconductivity are restrictive, and considerable ingenuity or luck (or both) will be necessary to synthesize a useful room-temperature superconductor.

T. M. Rice
AT&T Bell Laboratories
Murray Hill, New Jersey

MAJOR BENEFITS FOR MEDICINE, TELECOMmunications, and electrical power systems will be realized in the near future, based on the high-temperature superconducting cuprates. We expect new medical systems with more powerful, less harmful, and cheaper diagnostics for noninvasive probing of the heart, brain, and body. Clinical tests with arrays of SQUIDs, which are by far the most sensitive detectors of magnetic signals,



will replace less informative, riskier, and more costly catheter procedures used to locate the excess electrical currents associated with arrhythmia and other heart malfunctions. In magnetic resonance imaging (MRI) systems, the great improvement in signal-to-noise ratio that superconducting coils in liquid nitrogen have over the copper detector coils will lead to faster and cheaper diagnoses. Similar improvements will occur in nuclear resonance spectroscopy. MRI will be extended to inexpensive, low magnetic field systems in doctors' offices rather than in hospitals. MRI mammograms, which can replace x-ray scans, will be much more reliable and safer. The development of passive radio-frequency circuits that can handle large amounts of microwave power will result in transmitters and receivers for microwave telecommunications that will double the effectiveness of the limited frequency band that has been allocated by the Federal Communications Commission for such purposes. New strategies such as ion beam–assisted vapor deposition will lead to the manufacture of the long lengths of wire and cable needed for the higher temperature, higher field systems. Coaxial superconducting underground power transmission cables, which offer high capacity, no visual pollution, and are relatively inexpensive, will be used to bring more electrical power into our cities.

Theodore H. Geballe
Department of Applied Physics
Stanford University

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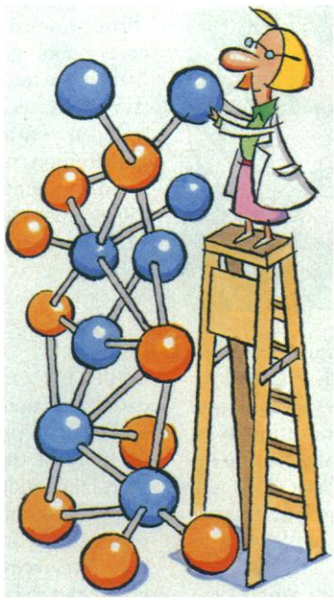
RATIONAL DRUG DESIGN BASED ON STRUCtural information is often discussed but seldom realized. The discovery that many important enzymes such as protein kinases, protein phosphatases, and steroid hormone receptors are held inactive by intrasteric inhibition may stimulate rethinking. Frequently the intrasteric inhibition, defined as a segment of the protein that blocks its active site, is of the pseudosubstrate type. For example, in protein kinases the inhibitory region can have a primary amino acid sequence similar to that of the substrate, but lacks a residue that can be phosphorylated. Synthetic peptide analogs of these autoinhibitory domains can have affinities for the enzyme that are three orders of magnitude greater than those demonstrated by physiologically relevant substrates. Such proteins are activated by a regulatory protein or by phosphorylation in a signal transduction cascade, leading to removal of the autoinhibitory sequence and providing ready access to the active site. Solving the three-dimensional structure of such proteins in the autoinhibited and active state should allow rational design of peptides or

organics that would mimic the pseudosubstrate. Such synthetics should reveal a reasonable degree of specificity and thus could prove to be useful drugs.

Anthony R. Means
Department of Pharmacology
Duke University
Medical Center



RATIONAL DRUG DESIGN will be possible in the near term for only a few disorders. While modern technologies make possible the tailoring of compounds to block enzymatic actions, or put defective ligands in unoccupied receptors, the intricacies, interdependencies, and redundancies of human physiology will continue to defy simple pharmaceutical solutions to most diseases. Occasionally the rational drug designers will be lucky, but more often our lack of knowledge of the details, particularly the details of the integration of functions, will lead to ineffective compounds or unacceptable side effects. Rational drug design will be generally successful in the future, but not yet!

The rapid emergence of drug-resistant microbial agents will lead to renewed searches for antibiotics. Common antibiotics were identified by screening natural products—for example, soils and molds. Renewed searches of other natural products will identify one or more "new" classes of agents with new modes of action. Rational drug design may play a role in this search, but whether synthetic or natural products will be identified first is far from clear.

Helen M. Ranney
Alliance Pharmaceutical Corporation
San Diego, California

RATIONAL DRUG DESIGN INVOLVES DETERmination of the detailed three-dimensional structure of a target protein, such as an enzyme or a cell surface receptor. Molecular modeling is then used to design a small molecule that is expected to bind tightly to the recognition surface of the protein and thereby perturb its biological function. Now, however, in vitro selection techniques coupled with DNA amplification by the polymerase chain reaction allow RNA or DNA ligands to be identified that bind tightly to virtually any protein, without any knowledge of its structure. These methods allow libraries of 10^{14} random nucleic acid sequences to be screened for activity and specificity by a single student in a few weeks or months, a far cry from the 10^5 compounds that can be screened by a large pharmaceutical company in a year. Because it is so fast and dependable, irrational drug design may overshadow rational drug design as the basis for discovering new pharmaceutical leads. Similar principles can be applied to organic synthesis. Miniature biochips allow multiple random reactions to be carried out in a large matrix, which can then be screened for activity and the active compounds identified.

Thomas R. Cech
Howard Hughes
Medical Institute
Boulder, Colorado

COMBINATORIAL CHEMICAL libraries will be a major source of new leads for drug development. Not only will the range of libraries be greatly extended, but new automated screening procedures will be developed. Combinatorial algorithms will influence the genetic engineering of microbes for the production of antibiotics and other chemicals. Biologists will screen commercially available libraries for ligands. Combinatorial chemistry will influence the design of proteins with novel catalytic and biological properties. Novel DNA-binding proteins will be designed at will.

Michael Ashburner
Department of Genetics
University of Cambridge

THE MARINE ENVIRONMENT HAS ONLY RECently been explored as a source of new drugs, such as antibiotics and anticancer drugs. Promising drugs, such as curacin-A and bryostatin-1, are undergoing clinical trials. Bryostatin-1, which stimulates the immune system to promote growth of normal bone marrow cells, has been somewhat effective against melanoma, ovarian cancer, and leukemia. Other marine-based drugs should provide a rich complement of new pharmaceuticals. What is not yet clear is whether there are fundamental principles underlying the uniqueness of marine organisms that will permit predictive pathways leading to the development of new anticancer agents and antibiotics.

Rita R. Colwell
Maryland Biotechnology Institute
University of Maryland

INVESTIGATORS OF CANCER, INFLAMMATION, and other diseases continue to discover rate-limiting biochemical events as targets for useful drugs. Often the ideal drug would block an interaction between two proteins or between a protein and DNA or RNA. The complexity of macromolecular interactions greatly exceeds that of interactions between small ligands or substrates and an allosteric regulatory protein or enzyme. Because peptides or other macromolecules that compete effectively for a targeted binding site are usually poorly suited for oral absorption and penetration across the cell membrane, small molecules are usually more suitable for development as drugs. Recent advances make it possible to produce the relevant macromolecules and to devise large-scale assays of their interactions. Such screening assays could efficiently identify the necessary small molecules. Alternatively, three-dimensional mapping of binding interfaces between macromolecules could reveal how to design small molecules that can block the interaction with affinities suitable for developing useful drugs.

Henry R. Bourne
Department of Pharmacology
University of California, San Francisco

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THE 70-YEAR-OLD PHILOSOPHICAL DEBATE about the meaning of measurement in the quantum theory is steadily being overtaken by the skills of experimentalists. Within a decade or two some experimental breakthroughs will have occurred and we will understand a great deal more about this problem, though it will never be declared solved to everyone's satisfaction.

P. W. Anderson
Joseph Henry Laboratories of Physics
Princeton University

OVER THE LAST TWO DECADES A THEORY known as the "standard model" has developed that successfully accounts for the structure of matter and the interaction between the elementary entities. The recent evidence for the existence of the top quark is another confirmation of the theory. Yet the model is known to be incomplete, for when it is extrapolated to teraelectron volt energies, it predicts that the scattering of certain particles (W bosons) exceeds the bound imposed by unitary. Because probabilities greater than unity are not allowed, we know that something must happen but don't know what. I expect that within the next decade, experiments at electron-positron colliders will give the clue.

One of the peculiarities of matter according to the standard model is the electric charge of the fundamental building blocks of nature. These blocks are the quarks and leptons that come in three families. Within each family the charges of the constituents in units of the magnitude of the electron's charge are +2/3 and −1/3 for the quarks and 0 and −1 for the leptons. The leptons (the neutrino and electron, for example) can be observed directly, but the quarks are always

bound together by a force that continually increases with distance and can be observed only in combinations that have integral charge. To the theorists there is no problem, but it has always seemed strange that a universe whose observable constituents are all integrally charged really has some fractionally charged components down deep.

A similar situation seems to exist in condensed matter physics, where the fractional quantum Hall effect appears to require entities of fractional charge. This Hall effect is a two-dimensional problem (the system is planar), and theory has shown how "quasiparticles" of apparent fractional charge can appear from the interaction of electrons and flux quanta. Perhaps a similar situation exists in the three-dimensional world of quarks, and the elementary constituents are all really integrally charged after all and matter is built from things that are observable.

Burton Richter
Stanford Linear Accelerator Center
Stanford, California

IN THE LAST DECADE, IDEAS FROM QUANTUM field theory have produced startling results in geometries of two, three, and four dimensions. Using mostly formal path integrals, physicists have obtained new formulas and relationships in mathematical fields far removed from traditional mathematical physics. Geometers are trying to incorporate these novel methods into mathematics. I expect that the mathematical structure underlying geometric quantum field theories will soon be clarified and give an even more powerful tool for studying low-dimensional geometries. As a result, within a decade the classification of all compact smooth three- and four-dimensional manifolds will be completed. In particular, we will be able to answer Poincaré's almost century old question: Is every bounded three-dimensional manifold without holes an ordinary three sphere? We may be as naïve about four dimensions today as scientists and philosophers were about two dimensions in 1820 just prior to the discovery of hyperbolic geometry. What we now call exotic or fake four-dimensional spaces could give revolutionary new models in cosmology. And surely a complete understanding of how strands link in three-dimensional space will illuminate DNA unraveling and DNA recombination.

I. M. Singer
Department of Mathematics
Massachusetts Institute of Technology

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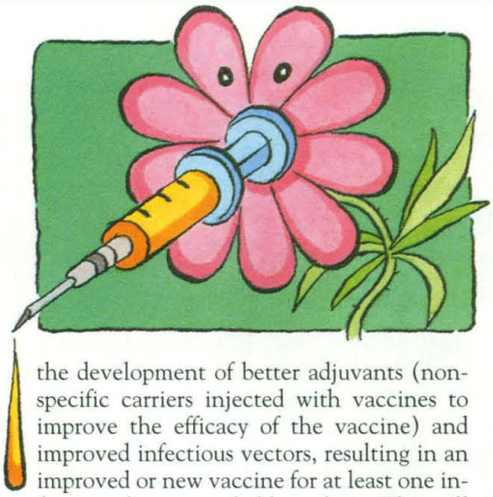
THE RESPONSE OF LYMPHOCYTES TO SPECIFIC antigens, for example, HIV gp120, is greatly helped by nonspecific inflammatory processes, such as those triggered by endotoxins. Realization of this fact will lead to



the development of better adjuvants (nonspecific carriers injected with vaccines to improve the efficacy of the vaccine) and improved infectious vectors, resulting in an improved or new vaccine for at least one infectious disease, probably malaria. This will be a slow and difficult development because no government or company will want to pay for the process.

Scientists will discover that a single peptide from a protein found in human joints is the target of the autoreactive T cells that initiate rheumatoid arthritis in more than half of the cases of this disease. Clinical trials in which the peptide is given in various forms to prevent the disease will be started in the year 2005 and ended in 2050 for lack of patient enrollment.

Philippa Marrack
Howard Hughes Medical Institute
Denver, Colorado

ALLERGIES ACCOUNT NOT ONLY FOR COMmon ailments such as hay fever, but also for life-threatening sensitivities to insect venom, foods, and certain drugs. These allergic responses are all mediated by immunoglobulin E antibodies, the production of which is caused by a bias toward a T helper cell 2 (T_H2) instead of a T_H1-type immune response. The type of response that is initiated depends on the particular cytokines that are present at the time of antigen-dependent differentiation of T cells into T_H1 or T_H2 types. It should be possible to vaccinate against allergies by linking the allergen peptide to the appropriate cytokine that promotes T_H1 development and down-regulates T_H2 development. This vaccination could be done with naked DNA constructs encoding the allergen peptide and cytokine.

Douglas T. Fearon
School of Clinical Medicine
University of Cambridge

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MUCH OF TODAY'S ECONOMIC PROGRESS hinges upon the continued increase in cost and performance of silicon integrated circuits, made available by steady improvements in lithography over the past quarter century. While we still have some way to go, the end seems in sight. As line widths shrink toward 0.1 micrometers and factory costs zoom past 1 billion dollars apiece, little more improvement in conventional lithography technology seems likely. Hopefully, an entirely new way of fabricating multibillion transistor circuits will be devised. One atom at a time seems a bit tedious, but who knows how fast microfabrication techniques might work?

Arno Penzias
AT&T Bell Laboratories
Murray Hill, New Jersey

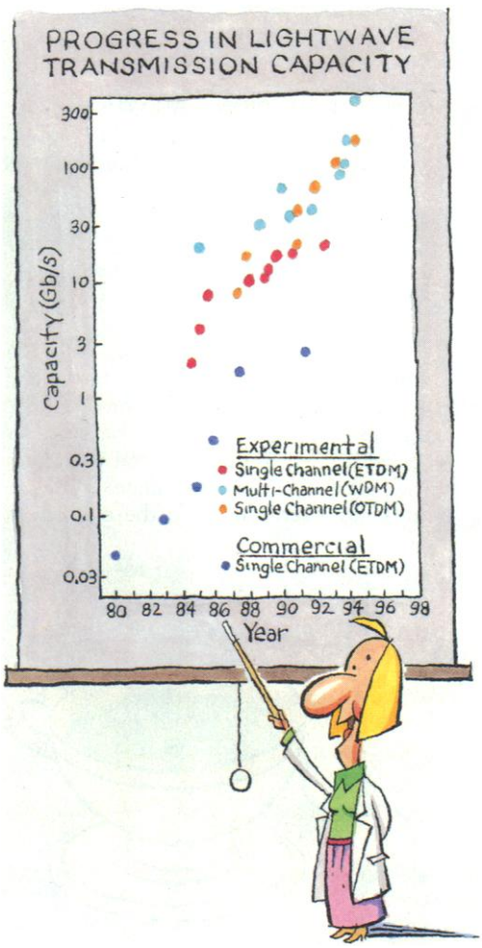
WHILE BIOLOGICAL SYNTHESES OF COMPLIcated and useful molecules are carried out within small (micrometer) size cells, the overall scale of these syntheses dwarf those of man-made industrial chemicals that are used to produce our food, as well as many of our fibers, drugs, and other materials. An advantage of carrying out reactions at small size, compared to large laboratory flasks and even larger pilot plant and industrial reactors, is that experimental conditions can be closely controlled and sequences of reactions precisely timed. One can envision computer-controlled integrated chemical synthesizers consisting of small (millimeter to micrometer) reactors along with associated devices for analysis and separation. These could incorporate principles currently used in polypeptide and DNA synthesis, where the growing molecule is immobilized on the appropriate support, but could also use microversions of conventional liquid- or gas-phase reactors. Scaling up to produce useful amounts of products would require a means for running many of these reactors in parallel and, hence, a need for mass production and assembly techniques as in integrated circuit technology in the fabrication of microreactors. Such systems, compared to larger conventional ones, should allow better yields, improved heat transfer, and the possibility of working at high temperature and pressure.

Conventional inorganic semiconductor materials, especially silicon and gallium arsenide, have been used in a remarkable array of electronic devices. Improvements in performance have been accomplished by decreasing the size of elements and control of material properties and purity. Much less effort has been expended on organic and organometallic materials for electronic and optoelectronic applications, except, perhaps for use in liquid crystal and electrochromic displays. Organic materials could find a role in active displays (organic light-emitters), transistor-like devices, memory, and bulk storage media. Organic materials might also allow new operational modes, for example, multilevel logic. Few experiments have been carried out with electronically conductive polymers, charge-transfer salts (organic metals), and porphyrin and phthalocyanine crystals. Advances in this area will require a bet-

ter understanding of structural effects on optical and electrical properties and improvements in controlling purity. Analogous applications of ultrathin films (for example, self-assembled monolayers) are also possible, if these film structures can be controlled and stabilized for long periods of time.

Allen J. Bard
Department of Chemistry and Biochemistry
University of Texas, Austin

A REVOLUTION IS OCCURRING IN TELECOMmunications. Transmission of a terabit per second over a single fiber will be accomplished before the end of this century. Only 12 years ago fibers could carry 45 megabits per second, while today systems are becoming available that can carry 10 to 20 gigabits per second over distances as far as 2000 or 3000 kilometers. Laboratory experiments have shown that through wavelength-division multiplexing (WDM) a single fiber can carry 17 wavelengths each at 20 gigabits per second for a total of 340 gigabits per second—only a factor of 3 from the goal of a terabit per second. Transmission of larger numbers of bits at a single wavelength is limited by the speed that electronic circuits can create light pulses, so scientists are now developing optical means of multiplexing either at different wavelengths (WDM) or by interleaving the pulses optically in time (optical time-division multiplexing, OTDM). The practicality of these two approaches has been greatly enhanced by the realization of an optical amplifier based on Erbium-doped fiber where excited Er atoms act to amplify pulses of light at wavelengths around 1.5 micrometers. With such amplifiers an entire group of pulse streams (17 in the experiment mentioned above) can be amplified at once without optically separating them or converting them to electrical pulses before amplification. It appears that the combination of distances and bit rates attainable are on the order of 100 terabit-kilometers per second. More exciting uses of multiple wavelengths are also in store. Simple adds or drops of a single wavelength are possible, and passive optical switches where wavelength selection determines destination have been demonstrated. Thus, in the future we will have backbone optical networks that can transmit and switch an enormous capacity of information.



William F. Brinkman
AT&T Bell Laboratories
Murray Hill, New Jersey

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WE ARE IN THE MIDST OF A PRODUCTIVE search for genes that place an individual at increased risk for cancer. Over the next few years, for every major cancer—breast, prostate, colon, lung, and ovarian, as well as many of the rarer forms of neoplasm—a gene or genes will be identified whose presence increases the risk for the specific cancer or cancers. These discoveries are providing the basis for diagnostic tests in the presymptomatic stage of cancers.

Further, these developments bring to the fore the possibility of the chemoprevention of clinical cancers. The real payoff in improving our ability to control and cure cancers will most likely come from discovery of effective, nontoxic agents that can prevent the progression of transformed cells to clinical cancer. The target can be agents that modulate the factors controlling cell cycle progression in a selective manner.

Paul A. Marks
Memorial Sloan-Kettering Cancer Center
New York, New York

ONE OF THE BEST WAYS TO REDUCE MORbidity and mortality from cancer is through early detection. In normal tissues, there is a characteristic equilibrium, with cell death precisely equaling cell birth. A slight alteration in this balance, over years, results in tumor development. Detection of such a small imbalance is currently not practical, but the extremely accurate and sensitive physical methods now used to examine the far reaches of the universe and subatomic structure might be employed for this purpose. Two probes could be used, one that detects cell birth (for example, mitosis or DNA synthesis) and one that detects cell death (for example, apoptosis or disintegration). In any small volume of tissue wherein birth equals death, the normalized signals will be equal. In tumors, a positive signal will be recorded, with its amplitude directly proportional to the net rate of growth. The signals from these probes will be detected with sensitive tomographic instruments (like magnetic resonance imaging) that will allow the determination of signal ratio with high resolution. The abnormally growing regions can then be removed with fiberoptic surgical techniques or eradicated with radiation stereotactically targeted with the aid of the instrument used for detection.

Bert Vogelstein and Kenneth W. Kinzler
Oncology Center, Johns Hopkins University

THE APPLICATION OF MOLECULAR GENETICS may soon greatly refine our ability to deduce the specific causes of cancer. This prospect stems from the identification of protooncogenes and tumor suppressor genes, whose malfunction lies at the heart of tumorigenesis. By determining the nature of the physical or chemical damage inflicted on these genes in cancer cells, it should often be possible to infer the nature of the mutagen or mutagenic event responsible for the damage. This strategy has been validated retrospectively by the use of both animal models and those human malignancies with established causes, so there is good reason to believe that it can be used in a prospective manner.

J. Michael Bishop
The George Williams Hooper Foundation
University of California, San Francisco

CERTAIN TUMORS ARE CAUSED BY, OR ARE dependent on, the mutation of both alleles of tumor suppressor genes. Normal copies of these genes could be restored to tumor cells with retroviral vectors that are targeted to tumor-specific cell surface antigens. Targeting could be accomplished by replacing the retrovirally encoded protein that mediates cellular binding with the Fv regions of antibodies (or smaller loops of hypervariable regions of such antibodies) that have been selected by phage display systems. This method of targeting could be expanded to include the expression of other proteins that might interrupt signaling within the tumor cells.

Douglas T. Fearon
School of Clinical Medicine
University of Cambridge

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IT SHOULD BE POSSIBLE IN THE FUTURE TO study the chemistry (the energetics and kinetics of electron transfer, proton transfer,

and bond formation) of individual molecules. Techniques such as scanning tunneling and atomic force microscopy have permitted the observation of individual atoms and molecules on surfaces. In a few cases it has been possible to move these around on the surface or cause controlled removal or deposition of small numbers of atoms or molecules. Advances in scanning probe microscopy would make possible actual observation of complexation between a metal and ligand, host-guest interactions, and bioconjugation. It should be possible to extend these techniques to measure bond strengths and intermolecular forces, to study the effect of structural changes on the rates of enzyme reactions, to observe hybridization and replication of DNA, or to follow an antibody-antigen reaction. The application of spectroscopic methods via near-field optical microscopy should allow one to determine the spectra of individual molecules in solution and to watch changes caused by complexation or other interactions. Similarly, electrochemical microscopy should permit measurement of electrode potentials and diffusion coefficients of single molecules, as well as changes brought about by chemical effects.

Allen J. Bard
Department of Chemistry and Biochemistry
University of Texas, Austin

THE UNDERSTANDING OF LIFE PROCESSES requires knowledge of complex cascades of chemical events at the molecular level. A limiting step in acquiring such knowledge is the ability to carry out analyses in microenvironments or with microsamples. Meeting this challenge often requires analyses to be performed with high spatial and temporal resolution (1 to 100 nanometers and 1 to 1000 microseconds), with high sensitivity (femtomoles or less), and with high specificity. A number of related developments in instrumentation, when taken together, will allow dazzling advances that integrate the study of chemistry and biology. Recent breathtaking advances in microscopy offer resolution at the molecular level; electrophoretic and chromatographic microcolumn separation techniques can now resolve complex biomixtures found in small volumes; and detector advances, particularly the development biosensors, can respond specifically to selected ligands to provide biofunctional assays with a sensitivity approaching single-molecule detection. These instrumentation breakthroughs put us on the threshold of understanding many of the remaining mysteries of life, such as the chemical basis of learning and conditioned response.

Richard N. Zare
Department of Chemistry
Stanford University

MOST OF OUR INFORMATION ON CELLULAR metabolism is uncertain, as it comes from the study of disrupted cells or their constituents. Advances in magnetic resonance imaging may change this limitation. Current imaging technology allows the study of metabolic pathways in intact organisms and organs; however, it lacks the resolving power to "see" biochemical reactions within cells or subcellular compartments. Rapid advances in microelectronics, computer technology, and in our understanding of superconductivity will allow us to breach this barrier and should provide detailed and reliable information on the metabolism of normal and diseased living cells.

Gottfried Schatz
Biozentrum
Der Universität Basel

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ENZYMES HAVE BECOME INCREASINGLY ADmired for their catalytic prowess, substrate specificity, and their ability to operate at ambient temperatures and pressures in an aqueous environment. These properties make them particularly desirable as environmentally sparing catalysts. De novo catalyst design has become more attractive as an achievable goal with the development of novel methods to create vast chemical arrays through combinatorial synthesis and to fabricate selective genetic screens for the desired catalytic properties. The unsolved issue is how to rapidly evolve these synthetic candidates so that their catalytic properties approach those of enzymes.

Stephen J. Benkovic
Department of Chemistry
Pennsylvania State University

MUCH EFFORT IS DEVOTED TO THE DESIGN of catalysts that mimic enzyme action; an alternative strategy is the design of artificial enzymes. We know a great deal about the relation between protein conformation and biological activity, but our ability to construct a protein so as to achieve a desired conformation is still extremely limited. Better understanding of the intra- and intermolecular forces and the mechanism of protein folding that determine stable three-dimensional protein structures, coupled with advances in calculational methodology and in synthesis of peptide chains (including nonnatural amino acids), should allow the design of artificial enzymes that could be optimized for catalysis of virtually any desired reaction.

Efficient transformation of alkanes, especially methane, to more valuable chemicals and fuels is a particularly challenging problem in catalysis, because the C–H bonds that must be activated to initiate alkane functionalization are usually far less reactive than those of the desired products. Despite significant advances in C–H activation methods over the last 10 years, various hurdles (including activity, selectivity, catalyst stability, and economics) have so far precluded practical application, except for special cases where product reactivity is not so high (for example, butane to maleic anhydride). The ability to functionalize alkanes at a desired position in good yield would provide major advantages in managing energy resources.

Harry B. Gray
Beckman Institute
California Institute of Technology

SEVERAL HIGHLY USEFUL CATALYSTS HAVE been developed in recent years for regio- and stereospecific oxygenation of organic substrates. However, the sources of oxygen atoms used with these catalysts are usually expensive reagents that are already activated relative to O_2—for example, single oxygen atom donors or peroxides. These will be replaced by oxygenase enzymes that contain heme cofactors, nonheme metal ion cofactors, or organic cofactors. Significant advances in our understanding of the mechanisms of activation of O_2 by these enzymes will lead to the development of synthetic catalysts capable of using O_2 directly from air.

Joan Selverstone Valentine
Department of Chemistry and Biochemistry
University of California, Los Angeles

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THE ROLE OF THE TROPICS AND THE IMPACT of growing human activities in this part of the world will be central, and training and active participation of scientists from these regions will be essential.

Paul J. Crutzen
Max-Planck-Institut für Chemie
Mainz, Germany

IN A WORLD BEYOND OUR IMAGININGS, children going to school for the first time will, like now, return with sore throats, running noses, muscle pains, and headaches. They will be left to suffer, as viral infection is the best way to train the immune system. Adults, however, will have the option of

taking a cup of tea, an infusion of the moss *Sphagnum antivirans*. This moss, discovered just before the felling of the last stand of the world's rain forest, is a potent source of small molecules that block viral adhesion to epithelial cells. The only side effect of this natural drug is that it produces a mild euphoria. The rain forests of the world will have been saved, in order to provide sufficient quantities of tea for those of us fed up with the autumnal ritual of suffering brought about by the new school year.

Peter N. Goodfellow
Department of Genetics
University of Cambridge

THE AMERICAN PUBLIC WILL BE TOLD BY the popular press that bacterial products help the immune response to infections such as the common cold. Consequently, health clubs will set up programs to put "muscle into lymphocytes," in which yuppie individuals in leotards swallow capsules containing Gram-positive bacterial cell walls mixed with bee pollen.

Philippa Marrack
Howard Hughes Medical Institute
Denver, Colorado

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DAMAGE TO THE BRAIN OR SPINAL CORD, caused by acute insults such as stroke or trauma, or neurodegenerative diseases such as Alzheimer's disease or amyotrophic lateral sclerosis, can destroy the quality of life, or life itself. The first neuroprotective treatments, capable of slowing or limiting neuronal loss, have now entered clinical practice—methylprednisolone for spinal cord trauma, deprenyl for Parkinson's disease. Presumptive identification of the mechanisms responsible for neurodegeneration in certain diseases, including overactivation of neurotransmitter signaling systems or inappropriate triggering of genetically programmed apoptosis, has led to the development of therapeutic countermeasures, many of which should move to clinical trials over the next 5 to 10 years.

Understanding the principles governing axonal outgrowth and correct synaptic connectivity during ontogeny, together with appreciation of the specific hurdles posed by tissue responses to injury, should lead to practical methods for promoting human nervous system regeneration. Approaches to replacing lost tissue with transplanted cells derived from fetal brains, or cell lines transfected with useful genes, also have considerable momentum in the animal laboratory.

Disability resulting from the selective disruption of major central or peripheral nerve pathways will find remedy in "silicon shunts." Microdetectors placed proximal to a lesion in nerve stumps, sensory organs, or higher order cortical centers could guide electrical effector arrays placed downstream in brain or muscle targets.

Dennis W. Choi
Department of Neurology
Washington University School of Medicine

OUR UNDERSTANDING OF BRAIN FUNCTIONS will be steadily advanced, but it is difficult to predict whether we will have any big discoveries during the coming decade. Instead, we may be able to enjoy big developments in diagnostic technology and therapeutic treatments in brain disorders on the basis of our understanding of molecules (receptors and secretory vesicular molecules) essential for brain functions.

Shigetada Nakanishi
Institute for Immunology
Kyoto University

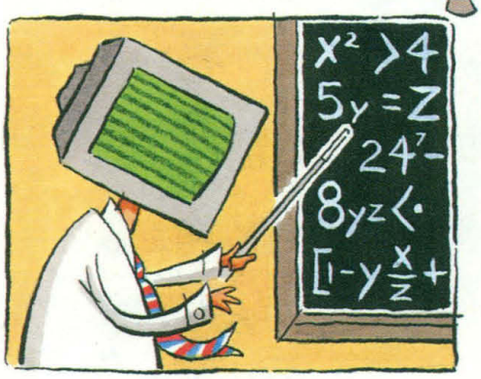
WITHIN THE NEXT SEVERAL YEARS, THE etiology and pathogenesis of many common diseases of the nervous system including degenerative diseases will be established with greater or less degrees of certainty. Knowledge about the etiology of diseases like Alzheimer's dementia, schizophrenia, and manic-depressive states will be reflected in improved management, but curative therapy for many of them will elude scientists for at least two more decades.

Helen M. Ranney
Alliance Pharmaceutical Corporation
San Diego, California

EACH STUDENT HAS SPECIFIC STRENGTHS and weaknesses, and effective education will respect such individual differences. Recent advances in human brain imaging allow researchers to characterize which parts of the brain are activated during specific types of processing. It is now possible to design tasks that selectively activate different areas of the brain, including those that play a key role in different types of cognitive strategies—for example, visual-spatial, analogical, and deductive. These tasks can then be administered and scored by a computer, allowing it to assess an individual's "information processing profile." The computer could then "tune" its presentation style to take advantage of the student's effective processing and avoid taxing his or her cognitive weaknesses.

It should soon be possible to diagnose which cognitive functions have been destroyed by stroke or other kinds of brain damage, and design rehabilitation programs that selectively encourage growth and reorganization of intact tissue.

The means by which central nervous system activity affects the body (via the endocrine, immune, and autonomic systems) are now coming to be understood. In due



course we will understand the mechanisms that underlie placebo effects (which are often very large). We will understand not only the mechanisms that promote healing, but also the psychological factors that engage these mechanisms. The technology that emerges will replace some drug therapies and will produce a healthier population while reducing health costs.

Some forms of psychotherapy have been shown to change brain metabolism. Measures of such effects could be used to determine the most effective form of therapy for a given individual. Indeed, therapies may be developed that make use of "hill climbing" techniques, with brain scanning results being used to direct the course of therapy.

Recent advances in brain imaging (for example, functional magnetic resonance and magnetoencephalography) and local brain stimulation (via focused magnetic fields) could open a whole new era of "virtual reality." Such a development would be useful not only for remote control of mechanical devices (using on-line brain imaging to provide instructions to computers), but also for communication, psychotherapy, and entertainment. However, given the subtlety and complexity of the nueral code and the possibility of great individual differences in the coding of high-level cognitive processes, such rich sensory-motor direct interface is probably unattainable. Nevertheless, even modest progress would be useful for people with impaired sensory organs or motor control.

Stephen M. Kosslyn
Department of Psychology
Harvard University

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THE DEEPEST AND MOST INTERESTING UNsolved problem in solid state theory is probably the theory of the nature of glass and the glass transition. This could be the next breakthrough in the coming decade. The solution of the problem of spin glass in the late 1970s had broad implications in unexpected fields like neural networks, computer algorithms, evolution, and computational complexity. The solution of the more

important and puzzling glass problem may also have a substantial intellectual spin-off. Whether it will help make better glass is questionable.

P. W. Anderson
Joseph Henry Laboratories of Physics
Princeton University

PHOTON SOURCES THAT PROVIDE COHERENT radiation in the x-ray region do not yet exist, but there is good reason to believe that they can be constructed. These sources would have a major impact on x-ray diffraction studies, especially those of large molecules such as proteins. Effectively such sources would obviate the phase problem and should make structure determination significantly easier and faster.

John I. Brauman
Department of Chemistry
Stanford University

THE PROTEIN "SEQUENCE-STRUCTURE" problem will be solved based on homology comparisons to known structures (but the solution of the ab initio folding problem will not be). New approaches will be developed for bioremediation and environmental cleanup. Novel metabolic pathways will be identified to carry out the biosynthesis of various compounds. Biomaterials with novel mechanical and catalytic properties will be discovered, such as biomineral, spider silk, and hyperthermostable proteins. There will be a computational solution of the crystallographic phase problem for macromolecules and substantial progress in determining the structures of single molecules by various scanning probe microscopies.

Douglas C. Rees
Division of Chemistry and Chemical Engineering
California Institute of Technology

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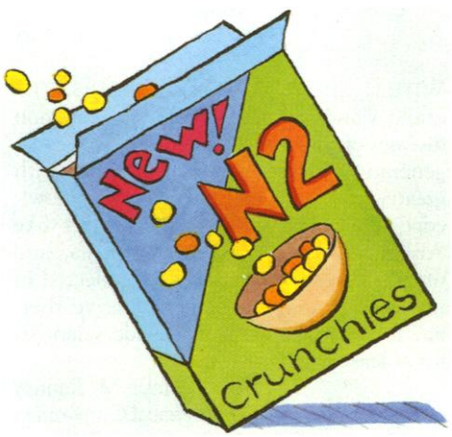
THE COMMERCIAL EXTINCTION OF MANY species of fish in previously rich fishing areas, such as the Grand Banks of the North Atlantic, has placed enormous pressure on aquaculture as a source of food. The maximum sustainable catch has been estimated at approximately 100 million metric tons, whereas demand for fish and fish products predicted for early in the next century is in the range of 135 to 165 million metric tons. Major advances in hormonal regulation of spawning and egg production should allow most commercially important species to be raised in closed systems. A major breakthrough will be the development of tissue culture procedures for maximum production of fish protein in a controlled, pathogen-free system.

Rita R. Colwell
Maryland Biotechnology Institute
University of Maryland

IF WHEAT, CORN, OR RICE COULD OBTAIN a substantial amount of nitrogen (N) through biological reduction of N_2, the economic and environmental benefits would be enormous. Because of the extreme biochemical complexity of nitrogenase, it is unlikely that an N_2-fixing cereal will result from transforming bacterial nitrogen fixation genes into the plant. However, bacteria that normally fix N_2 might be selected to produce excess N as they grow on cereal roots. This would involve identifying potential strains and optimizing both bacterium and plant genomes to generate an effective association.

Winston J. Brill
R&D Innovator
Madison, Wisconsin



CONTROLLING THE RATE OF RIPENING OF fruits and vegetables is a target of much activity. Technical and regulatory success in this arena led to the 1994 market introduction of a tomato with extended shelf life. Many related products are now being planned, from bananas to papaya. New sources of income will be possible when post-harvest stability of tropical crops is improved, thus increasing the amount and diversity available for export. With the reduction of post-harvest losses due to spoilage, the increased delivery may represent the margin needed to allow poor countries to become self-sufficient in food production.

Charles J. Arntzen
Institute of Biosciences and Technology
Texas A&M University

PLANT MOLECULAR AND CELLULAR BIOLOGY and related biotechnologies, when combined with traditional breeding, will contribute significantly to the development of agriculture in the next decades. Isolated genes, independent of their evolutionary origin, can be reconstructed, introduced into the genome of most if not all crops, and expressed in a regulated manner in various organs of transgenic plants. It already is, or will be, possible to target gene products to specific subcellular compartments, such as plastids, vacuoles, and membranes. Research based on molecular genetics should be able to identify genes that confer increased resistance to both biotic (for example, fungal, bacterial, and viral diseases; attack by insects; and competition by weeds) and abiotic (climatic) stresses. Judicious introduction of other types of genes will enable plants to synthesize useful lipids, carbohydrates, and biodegradable plastics, or even pharmaceutical products. Detailed chromosomal maps will enable plant breeders to accelerate as well as refine their programs.

Rapid reactions in plants to environmental signals can result from rapid changes in the activity of some cellular proteins or from differential RNA stability. Understanding the underlying biochemical mechanisms could lead to the breeding of crops with yields less affected by changing environmental influences. Knowledge of the mechanisms that control cytoplasmic streaming and modifications of the structure and properties of the cytoskeleton in response to various endogenous or environmental signals could also contribute to the improvement of plants. Elucidation of the biochemistry and the genes underlying the synthesis of lignin in trees, as well as the structural role played by these polymers, should help to produce trees with properties that allow a cleaner and more economical production of paper.

We will understand and be able to make use of the phenomenon of totipotency—that is, the ability of some plant tissues to regenerate whole, fertile plants from differentiated somatic cells. However, it is unlikely that the signal transduction mechanisms that control plant growth will turn out to be fundamentally different from those in yeast and animal cells. Totipotency, therefore, might be the result of the action of the same signals throughout the whole process of plant development.

Jeff Schell
Max-Planck-Institut für Züchtungsforschung
Köln, Germany

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UNDERSTANDING THE MECHANISM OF PRE–messenger RNA (mRNA) splicing will require a detailed picture of secondary and tertiary interactions among chemically reactive groups within the spliceosome. The recent crystallization of the ribosome has fueled speculation that other complex ribonucleoprotein structures could be subjected to analysis at the atomic level. The crystallization of the spliceosome and the solving of its structure would provide invaluable information concerning the catalytic mechanisms whereby nuclear pre-

mRNA is spliced. Since the interactions of the functionally important components of the spliceosome are dynamic in nature, ultrastructural investigations of specific conformational states (for example, prior to the first or second transesterification reaction) would provide a detailed picture of subtle structural changes occurring during the splicing process.

Reinhard Lührmann and Cindy L. Will
Institute for Molecular Biology and Tumor Research
Philipps-Universität Marburg

A SIGNIFICANT LANGUAGE BARRIER SEPARATES chemistry and molecular biology. The disappearance of this barrier will in and of itself cause many biological processes to be perceived as complex chemical systems that can be understood in chemical terms. This is happening in gene regulation where molecular biologists frequently are able to define systems in a manner that permits the chemical nature of the processes to be recognized. In the future, detailed understanding of the chemical reactions involved in O_2 metabolism and toxicity and the associated shifts in the redox potentials inside living cells and organelles will improve our understanding of fundamental life processes and will advance research in many areas, including aging, carcinogenesis, and neurodegeneration.

Joan Selverstone Valentine
Department of Chemistry and Biochemistry
University of California, Los Angeles

UNDERSTANDING THE MOLECULAR CIRcuitry that mediates signaling among and within cells may require computer modeling. What at first appeared as simple linear arrays of switches has now emerged as an elaborate network with hundreds (if not thousands) of nodal points. Attempts to trace a signal through the circuitry soon become lost in a welter of crosstalk and feedback. The circuitry may be complicated by the existence of quantitative thresholds for transmission at the nodal points. Components of the circuitry have become targets for drug screening and rational drug design in the search for therapeutic agents against cancer and inflammatory and infectious diseases. It seems unlikely that these efforts will be fully effective unless a global view of the molecular circuitry can be achieved.

J. Michael Bishop
The George Williams Hooper Foundation
University of California, San Francisco

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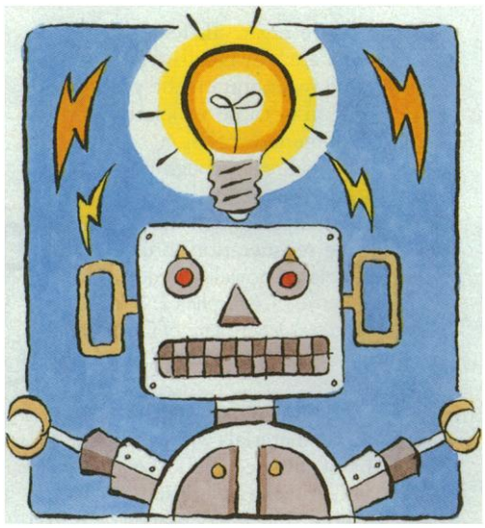
ANYONE WHO EXPECTS ANY HUMAN-LIKE intelligence from a machine in the next 50 years is doomed to disappointment. But by



that time we will at least have given up the meaningless "Turing Test" as the criterion of success.

P. W. Anderson
Joseph Henry Laboratories of Physics
Princeton University

WE WILL SEE LARGE ADVANCES IN UNDERstanding complexity in computation, with profound practical as well as mathematical and philosophical consequences, and in managing intellectual complexity, the central issue of software. If we "discover" how to manage that sort of complexity, we win. If you subtract all the hype about virtual reality, there remains the single most fundamental barrier to greater application of intelligence—us! We need ways to utilize the senses and motor systems that were developed to hunt and to understand and control far stranger beasts. With regard to the impact of computer technology on science, the collaboratory concept and the exploitation of the National Information Infrastructure (NII) in general will yield fundamental changes. It is really hard to overstate the impact that the Internet has already had, and the NII is so much more! Finally, the ability to put microinstruments in situ brims with possibilities.

William Wulf
Department of Computer Science
University of Virginia

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OUR UNDERSTANDING OF THE CAUSES AND consequences of extinction will increase as knowledge about the organisms and environments increases, and as chronological precision improves. The production of the incremental data falls in the category of hard labor in the vineyards, but it is absolutely crucial to the major advances in the field. It will become widely recognized that significant evolution is a temporarily discontinuous phenomenon that occurs only under rather restricted conditions and at widely separated intervals of time. This will affect the way we think about the conservation and maintenance of species.

With the popularization of large databases and enhanced capabilities of remote sensing, ecologists and evolutionary biologists will be able to free themselves of the pervasive small-scale approach to one in which phenomena can be studied on large spatial and long temporal scales. In this way, the current gap between paleontological and ecological studies will be bridged. The result will be that present-day and future conditions will be seen to depend on history as well as on processes observable today (such as dispersal, competition, and predation). Environmental change and habitat destruction are global, yet most of our understanding of them has up to now been local. I believe this will change as large-scale ecology will be integrated with the historical record as revealed through paleoceanography, paleontology, and more sophisticated climate modeling.

The net effect of these incremental improvements will be to increase our ability to understand the consequences of environmental change and our role in these changes. This will force humans to take the consequences into account in our future economic and political decisions.

Although evolutionary and economic principles have for years been justifiably accorded a place of great importance and generality, this central role will be strengthened by future developments. From microeconomics and microevolution at the local level to macroeconomics and large-scale evolution at the regional to global scales, we shall appreciate more than ever that a few fundamental economic and evolutionary principles related to selection, markets, and competition will apply.

Geerat J. Vermeij
Department of Geology
University of California, Davis

THEORETICAL ECONOMICS WILL HAVE VIRtually abandoned classical equilibrium theory in the next decade; the metaphor in the short-term future will be evolution, not equilibrium.

P. W. Anderson
Joseph Henry Laboratories of Physics
Princeton University

THE FOUNDATIONS OF ECONOMIC ANALYsis since the 1870s have been the rationality of individual behavior and the coordination of individual decisions through prices and the markets. There has already been a steady erosion of these viewpoints, particularly with regard to the coordination function. Now the rationality of individual behavior is also coming under attack. What is still lacking is an overall coherent point of view in which

individual analysis can be embedded and which can serve as a basis for new studies.

What I foresee is a gradual systematization of dynamic adjustment patterns both at the level of individual behavior and at the level of interactions and transactions among economic agents. Indeed, the distinction between these levels may well be blurred and reclassified. In the course of this development, the very notion of what constitutes an economic theory may well change. For a century, some economists have maintained that biological evolution is a more appropriate paradigm for economics than equilibrium models analogous to mechanics. Evolutionary theory is a point of view rather than a complete theory such as has been the desideratum of economists, and economic theory may well take an analogous course.

Methodology will also change. Formal theory-building, with assumptions and logical inferences, will never disappear, but it will be increasingly supplemented by simulation approaches. These need, of course, to be guided by deductive reasoning, but they will acquire independent significance.

Kenneth J. Arrow
Department of Economics
Stanford University

THE SCIENTIFIC WORLD IS RIPE FOR THE INvention of a new field of inquiry: "bio-psycho-social." It will synthesize ingredients from molecular biology, genetics, and neurosciences on the one hand and from the behavioral and social sciences on the other. Spectacular strides have been made on the biological substrates of behavior, and equally compelling knowledge is accumulating on the effects of culture, social structure, and behavior on both normal and pathological functioning of the organism. The new field will involve a full synthesis with new paradigmatic structures. Its impact may ultimately be comparable to that of biochemistry in the life sciences.

Neil J. Smelser
Center for Advanced Study in the Behavioral Sciences
Stanford, California

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THE LONG-DESIRED GOAL OF ORGAN REgeneration may come to fruition through discoveries in genome mapping and of the controls for cellular development. The outcome of this effort would be the ability to clone from a small collection of cells the entire organ. If, for example, beginning with one's own cells an individual's liver may be regenerated, the problems of organ rejection or those associated with the required immunosuppression would be avoided. Such a breakthrough would allow treatment of a number of diseases including pancreas replacement in diabetes and intestine regeneration in ulcerated colitis and related bowel disorders.

Stephen J. Benkovic
Department of Chemistry
Pennsylvania State University

THE DEVELOPMENT OF INERT NONthrombogenic materials will permit the replacement of diseased blood vessels of the heart or brain, or the aorta itself, with a synthetic material. The use of cloned cells from the patient (or from a compatible donor, depending on the nature of the disease) in organ transplants may be developed sooner (islet cells of the pancreas) for some organs than for others, depending in part on organ architecture. It is hard to visualize application to kidney or heart.

Helen M. Ranney
Alliance Pharmaceutical Corporation
San Diego, California

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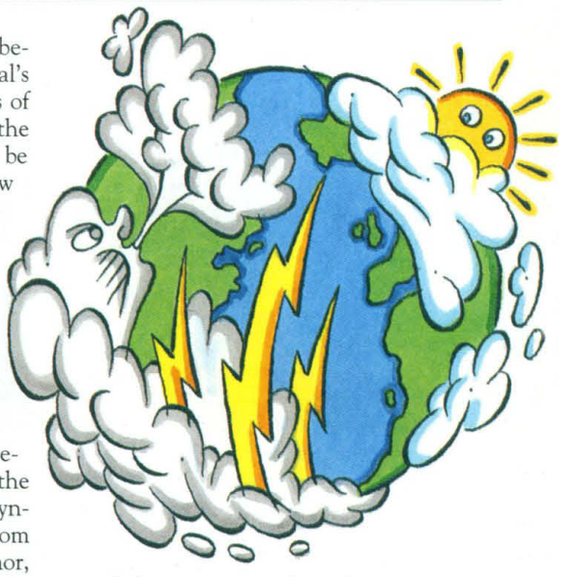
IN ABOUT 10 YEARS WE SHOULD HAVE three-dimensional maps of the structure of Earth's interior, from surface to center, with a resolution of a few hundred kilometers, including anisotropy and anelasticity. We will see convection currents and shadows of past continental positions. This prediction is based on extrapolations of global instrumentation, computers, and visualization techniques. With new techniques (global positioning system and satellite altimetry) we will be monitoring and modeling deformation of Earth's surface, continental drift, pre-earthquake deformation, and so forth. We will also have accurate equations of state under extreme conditions of temperature and pressure to model elastic and thermodynamic properties throughout Earth's interior in order to interpret seismic data in terms of chemistry, crystal structure, temperature, and dislocation density.

Don L. Anderson
Seismological Laboratory
California Institute of Technology

INTERACTIONS BETWEEN THE BIOSPHERE and climate will be at the center of much research. We will see a steady and still much



needed progress in technical means to measure the chemical composition of the atmosphere. Miniaturation and automation will provide exciting new opportunities to make measurements in remote parts of the atmosphere—for example, through remotely piloted aircraft and kites. Models will play an increasingly important role in future national and international environmental policy, putting considerable requirements on keeping science and politics apart.

Paul J. Crutzen
Max-Planck-Institut für Chemie
Mainz, Germany

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IN THE FUTURE, RESEARCH POLICY WILL BE increasingly in the hands of politicians and, hence, subject to change in a few weeks when some crisis suddenly erupts. Current trends in trade deficits, oil importation, and a weakening dollar will lead to unprecedented events with resultant impact on science and technology. We are neglecting some areas because they are not producing spectacular results—for example, energy. Within another decade the situation in East Asia will be drastically changed. They will be competing in high technology and in other ways. In the physical sciences, increasing emphasis will be placed on applied research. Easy, low-cost experiments have been conducted. Costly ones remain.

Another guess is that within 10 years, the United States is likely to experience a terrorist nuclear explosion.

Philip H. Abelson
AAAS
Washington, DC