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<table>
<thead>
<tr>
<th>Process/Step</th>
<th>Conventional</th>
<th>CastAway System</th>
</tr>
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<tr>
<td>Prepare plates, mix solutions,</td>
<td>120 minutes</td>
<td>&lt; 5 minutes</td>
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<tr>
<td>de-gas, pour, polymerization</td>
<td></td>
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<tr>
<td>and load gel</td>
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<tr>
<td>Electrophoresis</td>
<td>150 minutes</td>
<td>75 minutes</td>
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<tr>
<td>Transfer and Dry</td>
<td>120 minutes</td>
<td>50 minutes</td>
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<tr>
<td>Total</td>
<td>6 hr 30 min.</td>
<td>2 hr 10 min.</td>
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Mutants in complementary chromatic adaptation isolated from the filamentous cyanobacterium *Fremyella disphorophila*. Each of the four mutants shows a lesion in a separate step of the signal transduction pathway controlling complementary chromatic adaptation and shows a different color during growth. The red cells (center, red mutants) are response regulator mutants, and the grayish colonies (upper left, black mutants) are defective in a sensor with similarity to plant phytochromes. See page 1409. [Image: Gregory O. Lam-Niemeier]
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And Then Some.
Gut development
The mammalian intestine plays host to a diverse and exotic flora—the commensal bacteria. What, if anything, do these gut microbes contribute to the host? Bry et al. (p. 1380) show that mice raised under germ-free conditions have abnormal intestinal epithelial glycosylation patterns in comparison to conventionally reared animals. A normal profile can be restored by the introduction of Bacteroides thetaiotaomicron, a single component of the microbiota; furthermore, a mutant strain of the bacterium that is unable to grow on fucose does not restore the normal pattern of glycoconjugates. Thus, the indigenous bacterial flora appears to be essential for the completion of intestinal epithelial cell differentiation.

Reversing tumorigenesis
Tumor development is thought to occur when cells accumulate a series of genetic changes that help maintain the transformed state. Ewald et al. (p. 1384) tested this hypothesis by investigating the reversibility of tumorigenesis in a transgenic mouse model in which expression of the SV40 T antigen gene can be turned on and off. Expression of T antigen in the submandibular gland of the mice produced the characteristic cellular changes that pre-cede tumor development. These changes were reversed when T antigen was silenced after 4 months of expression but not after 7 months of expression. These results support a model of time-dependent tumorigenesis in which cells acquire changes that prohibit reversal of the transformed state, even when the initial transforming stimulus is removed.

Synapse remodeling
Nerves interact with one another at synapses. The strength of synapses can be varied in a process known as synaptic plasticity, thought to play a role in learning and memory. Neurotrophic factors can induce synaptic plasticity. Kang and Schuman (p. 1402) show that the mechanism mediating neurotrophin-induced synaptic plasticity, unlike other forms of plasticity, requires new proteins to be synthesized in the neurons involved, thus remodeling particular synapses.

Seeing with C60
Theoretical studies have predicted that point defects on a graphite surface should exhibit an unusual threefold-symmetric electron-scattering pattern, but studies with conventional metal tips in scanning tunneling microscopy (STM) do not reveal this. Kelly et al. (p. 1371) show that this pattern can be observed when the density of states at the STM tip is modified by adsorbing a single C60 molecule.

Core problem
Some iron meteorites are assumed to be samples of metallic cores from asteroids. Olsen et al. (p. 1365) have studied a relatively rare silica inclusion in a IIIA iron meteorite that provides more details about the origins of this class than from studies of the dominant iron-nickel metal phases alone. The mineral assemblage and isotopic compositions of the inclusion suggest that it is a sample of the lower mantle or that masses of iron may have pooled together in the lower mantle of the asteroid.

Mantle viscosity
The rebound of the Earth’s surface following the last deglaciation depends primarily on the viscosity of Earth’s mantle, which varies with depth, and the thickness of the ice sheets. These two effects must be sepa-rated to infer either. Peltier (p. 1359) presents an analysis based on a numerical model of the deforming Earth and fits to coastal records of uplift or subsidence. The analysis suggests that the increase in viscosity from the upper to lower mantle is less than previously thought.

Cargo receptors
Inside cells, various organelles exchange contents by budding and fusion of transport vesicles. Such transport may occur, for example, from the endoplasmic reticulum to the Golgi complex and back again. The mechanisms controlling what will be packaged in the lumen of these vesicles remains unknown. Fiedler and colleagues (p. 1396) present evidence that cargo receptors in transport vesicle membranes interact with specific coat components to drive transport either forward or backward through the secretory pathway.

Volcanic volatiles
Detecting the distribution of magmatic volatiles in regions of active volcanism has been difficult because in most systems the magmatic fluids are swamped by the large amount of meteoric water in vigorous hydrothermal systems. Rose and Davidson (p. 1367) present an investigation of hydrothermal springs in the southern Cascades using carbon isotopes; because magmatic waters are old, they contain essentially no carbon-14. Analyses near Mount Lassen show a broad region where magmatic carbon dioxide was present in the hydrothermal system.
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Evolving dialogs
An unusually large amount of mail was received about a News & Comment article on education and evolution, including provocative letters about scientific theory, "critical analysis," and the cost of not entering the debate (right, the 1925 Scopes trial). Elsewhere, an author offers to answer charges of anti-Semitism against him that he says are "wrong," but "understandable." One researcher recounts his experience of losing financial support from the Council for Tobacco Research. And analyses of the Chernobyl nuclear power accident are discussed.

Teaching Evolution
In the News & Comment article "Creationists evolve new strategy" by Karen Schmidt (26 July, p. 420), there is reference to the theory of evolution being "fact." As a scientist, my understanding of the scientific method is that one proposes a hypothesis for a given set of observations. Facts are gathered and if the facts support the hypothesis, then it becomes a theory. The facts concerning evolution are the fossils and artifacts painstakingly found over the years. Evolution is the theory developed to explain these facts.

The next step is to continually test the theory. If it proves true in all circumstances, then it becomes a law. There is a Law of Gravity and the Laws of Thermodynamics, but there is not a Law of Evolution of which I am aware. Yet the schools teach evolution as if it is a law, not as the theory it truly is. By teaching evolution in this manner, schools do not convey all the exciting aspects of the evolutionary theory.

While I would not want creationism to be taught in a science classroom, I believe that the current methods for teaching the theory of evolution need to be reexamined and allowed to "evolve" into a more scientific approach to this very emotional topic.

Judy Harvey
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Schmidt reports that the anti-evolution movement's "shrewd new strategy" asks schools "to present evolution as theory, not fact." The tenor of those opposed to this request is that evolution should be presented as fact, and whatever scientific evidence there may be against evolution should not be presented. I disagree. Theories are conceptual frameworks for organizing facts and putative facts. Theories allow prediction of results of proposed experiments. Theories may be so successful that practitioners come to believe in them.

In terms of education, critical analysis is the critical issue. The educational process should explore what scientists mean by evidence and how observations of consistent patterns lead to powerful ways of thinking about the world. The high ground is the concept, fundamental to the scientific method, that no organizing principle is immune to challenge and that progress comes from careful questioning and continuing reassessment of both old and new evidence. If these ideas can be communicated, kids will be able to see for themselves that "creation science" isn't science at all.

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Schmidt's examination of the new creationism is welcome and overdue. It is not only the rise of creationist-inspired school textbook-censorship and legislation that threatens science: the newer forms of anti-science—such as "intelligent design theory"—are making progress on college campuses, as those of us who teach undergraduates know all too well.
The “facts” offered by opponents of evolutionary science are indeed a danger, because they are not facts—radiometric dating grossly in error, no fossil forms intermediate between existing species, "Darwinism" not accounting for complexity, the Grand Canyon formed in the Noachian flood, the Paluxy River "footprints," and the like. And as one commentator has observed, creationists can tell more lies in "debate" than an honest disputer can skewer. Nevertheless, the advice given by Eugenie Scott of the National Center for Science Education—that individual scientists should probably not enter debates—is self-defeating. If not scientists, then who? The claim that to enter such debates is demeaning, or is a lost cause, or might harden the opposition, is an invitation to quietism. It is the same advice as that given, for too long, to opponents of animal rights extremism. It is bad advice.

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The oxymoron of "creation science" is as farcical as are the terms "abrupt appearance theory." It is distressing that creationists' bills use tactics to intimidate teachers and their job security to the point that evolution is not taught, or worse that the teachings provide misinformation. It is also unfortunate that creationists continue to prey on the young and ignorant.

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Charges of Anti-Semitism

Constance Holden's article "Publisher draws censorship charge" (News, 12 July, p. 177) is a concise and accurate synopsis of a protracted and nasty series of events. Although charges of anti-Semitism against me are wrong, they are also understandable. My review (1) of Kevin MacDonald's excellent book, A People That Shall Dwell Alone: Judaism as a Group Evolutionary Strategy (2), made unrealistic assumptions about readers' familiarity with issues at hand, and so drew conclusions based on inadequately supplied information.

Unfortunately, one way to make charges of anti-Semitism stick is to publish a submission that draws such charges, then refuse to publish a rejoinder (3) that apologizes for shortcomings, attempts to clarify misunderstandings, and refers readers to ad hoc sources of relevant information (4). Five editorial board members of Ethology and Sociobiology judged my rejoinder to be such a submission, but the journal's publisher, Elsevier Inc., still refuses to publish it.

I ask interested readers to withhold judgment until they have a fuller explanation of my views—which can be obtained (including a copy of the accepted-but-censored addendum) by forwarding an address label to the address below.

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References
2. K. MacDonald, A People That Shall Dwell Alone: Judaism as a Group Evolutionary Strategy (Praeger (Greenwood), Westport, CT, 1994).

Tobacco Research:
One Researcher's Experience

James F. Glenn's statement (Letters, 12 July, p. 167) that "CTR [the Council for Tobacco Research] has always encouraged

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Investigators to publish results of research, whether favorable or unfavorable to the tobacco industry" contradicts my personal experience when the CTR, through Robert Hocket, then its director of research, and E. Jacob, then its lawyer, came to call on me and threatened that "we would never get another penny from CTR" if we published a paper, submitted for their approval, reporting that inhaling cigarette smoke caused laryngeal cancer in a certain inbred Syrian hamster. This happened in the early 1970s after our research at Tufts University and at the Bio-Research Institute in Cambridge, Massachusetts, had received continuous support since the early 1950s from CTR totaling more than $800,000.

As a witness in the U.S. District Court for the District of New Jersey, I have stated in detail and under oath what happened (1). When I presented our results at a conference in Atlantic City, New Jersey, before our paper appeared, a scheduled press conference to follow my paper was sabotaged (according to a later boast by a CTR public relations person in an internal memorandum of a tobacco company). We never received another penny from CTR after we published our paper in the Journal of the National Cancer Institute in October 1974 (2).

Continued research was made possible by support from a British consortium of the Celanese Company and British tobacco companies, as well as the British Hunter Committee, which found our method useful to evaluate the relative carcinogenicity of cigarette smoke.

Glenn's statement may be true for the more recent phases of CTR activity, but studies implicating cigarette smoke as a health hazard have not been getting support from CTR or are limited to projects with predictably negative outcomes, such as having mice inhale cigarette smoke that kills them because of their sensitivity to nicotine before carcinogenic doses are reached.

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References

I would like to comment on Richard Stone's fine article of 19 April (Special News Report, p. 352). My visits to Chernobyl to conduct the research for and prepare "The Chernobyl 4 Accident Sequence: Update—April 1995" (1) and the work reported on was supported by the Ukrainian Academy of Sciences, foundation grants, and me. The background to the report is contained in the introduction by Academician V. G. Baryakhtar, Vice President of the Ukrainian Academy of Sciences (UNAS). The report (1) provided and discussed estimates of the fuel in the lava. The source of most of the lava information contained in the report was Edward Pazukhin of UNAS's Intersectoral Scientific and Technical Center and the Khlopin Radium Institute. Current estimates of the fuel in the lava range from about 27 tons to more than 130 tons [the referenced paper (2) was presented at "Sarcophagus Safety '94" by C. Gotovchits (head of the Ukrainian Ministry of Chernobyl) and N. Steinberg (chairman of the Ukrainian State Committee for Nuclear and Radiation Safety)]. The wide range of the estimates is cited in the report as a key uncertainty. Although I told Stone...
that in my opinion the amount of fuel in the lava was toward the low end of the estimates rather than the upper end, neither I nor the publication (1) took a hard and fast position on the actual amount. More work needs to be done to map the lava, particularly in the region of the reactor hall floor and in some unexamined rooms.

No new views were expressed about the amount of fuel released from the reactor structure. The issue is the distribution of the fuel in the building. Stone’s article states, “If Purvis is correct, much of the missing fuel would have been ejected in the initial explosion and deposited in the surrounding countryside.” But the forensic analysis, photographs, data, and discussions in the report (1) only provide information about what was found on the roof and the local area immediately around the reactor. My belief is that when examinations are made of the floor of the reactor hall, and the regions immediately under this floor, more lava will be found, leading to a resolution of the current large uncertainties. Gotovchits and Steinberg state that “considerable amounts of fuel are supposedly concentrated in the unit 4 central hall” (2, section 5.1).

A very small percentage of the core would have been fragmented into very small particles and distributed across a wide area. This is what was found. Data were presented concerning this release. A suggestion made is that there be an international effort to analyze “hot particle” data collected by many nations. Such extensive collections exist. There is an extensive technological base for examining such “hot particles” developed during the era of atmospheric nuclear testing. Some of the experts are still available. The data available referred to in the report (1) support the mechanism proposed, that is, that the released steam lifted the entire reactor assembly into the air at least 14.6 meters above the operating floor, where the large reactivity insertion resulting from the water leaving the core resulted in a fuel vapor explosion. A report (3) by the Russian ministry MINATOM set forth a similar mechanism, but had the explosion taking place about 30 meters over the floor of the central hall. [(1) is cited in (3)]. Fuel vapor expansion was the mechanism for providing the destructive energy discussed in detail in the U.S. Department of Energy report on the accident sequence (4) and numerous other papers about the accident.

An analysis, discussed by Stone, concluding that the release of radioactivity to the environment was 150 million curies, has been rebutted, and the U.S. Nuclear Regulatory Commission (4) stated that this was in error and that corrections would halve the estimated total release, making the correct value not too far from the revised Soviet estimate. The report (1) did address problems in the nonmechanistic method of performing this type of analysis, suggesting that the calculations should be mechanistic and consistent with the data.

My hope is that there will be more interest in use of the data collected and that analysts will no longer need to make assumptions and rehash outdated opinions. Why can there not be increased study of the data and information now available?

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10105 Clearspring Road, Damascus, MD 20872, USA

References
3. NIKYET; Russian Scientific Center, Kurchatov Institute, VINIT, Causes of the Accident at the Chernobyl Nuclear Power Plant: Review of Research over 10 Years (Submitted by MINATOM to the International Atomic Energy Agency, Vienna, Austria, 1996).
Focus on Women

M. R. C. Greenwood, in her Editorial “Dancing with wolves” (29 Mar., p. 1787), lists a large number of “notable” scientific societies that “are or have recently been headed by women or minorities.” Without disparaging Greenwood’s choice of the societies worthy of note in this regard, I would like to point out that the American Society for Biochemistry and Molecular Biology could have been safely added to the list. Our current president, Susan Taylor of the University of California at San Diego, is the fifth female scientist in recent years to head the society.

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The cover image of the 5 July issue taken from the painting “Three Ages of Woman” by Gustav Klimt (1905), also shown on page 41 of the same issue, depicts an elderly, naked, despondent woman at the left. Where are the old and decrepit men pictured? Old men are wearing suits and ties (pp. 23 and 24) or are on mountain-tops (p. 26).

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Corrections and Clarifications

In the letter under the title “Tobacco research” by Theodor D. Sterling (12 July, p. 168), the quote on page 168 (near the bottom of the first column) should have read as follows:

does the identification of secondary risk factors for lung cancer play into the hands of the tobacco industry, which grasps at these straws in its relentless efforts to diminish the significance of cigarette smoking as the overwhelming worldwide cause of lung cancer . . . !

Science regrets the error.

In the last paragraph of the report “Late Proterozoic and Paleozoic tides, retreat of the moon, and rotation of the Earth” by C. P. Sonett et al. (5 July, p. 100), the loss of rotation energy of Earth should have been given as 1.19 ± 0.08 × 10^46 ergs, the gain in orbital energy of the moon should have been given as 4.25 ± 0.31 × 10^44 ergs, and the frictional energy loss rate should have been given as 4.03 × 10^44 ergs s^-1. These corrections raise the estimate of frictional loss to about 67% of that given by Munk and MacDonald, but result in no changes to the other parameters reported.

In Anne Simon Moffat’s 21 June Research News article “Form follows function when plants harvest light” (p. 1743), Johann Deisenhofer’s university affiliation was misidentified and his first name was misspelled (p. 1744). Deisenhofer is at the University of Texas Southwest- ern Medical Center in Dallas.

Daniel C. Luk of the Roche Institute of Molecular Biology at Hoffmann-La Roche, Inc., Nutley, NJ 07110, USA, was not included as an author of the report “An enhanced immune response in mice lacking the transcription factor NFATC1” by S. Xanthoudakis et al. (10 May, p. 892). The correct list of authors is as follows: Steven Xanthoudakis, Joao P. B. Viola, Karen T. Y. Shaw, Chun Luo, James D. Wallace, Patricia T. Bozza, Daniel C. Luk, Tom Curran, and Anjana Rao.

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New Manager for Biosphere 2
The controversial Biosphere 2 facility outside Tucson, Arizona, is getting a new boss as Columbia University refocuses the glass-enclosed ecological laboratory on education as well as research. The personnel move is part of a major reorganization of Columbia's geosciences program to include the Arizona site.

The new president and executive director of the 12,750-square-meter Arizona lab will be chemist William Harris, who for the past 4 years has headed the $650 million mathematics and physical sciences (MPS) directorate at the National Science Foundation (NSF). Harris’s departure next month adds to the exodus of top NSF managers (Science, 23 August, p. 1035).

Canadian Scientists Told to Cut the Jargon
Scientists in Canada will soon have to figure out how to explain their work to taxpayers as well as to their peers. New grant applications for the Natural Sciences and Engineering Research Council (NSERC) require a summary “which would explain and justify their research in language that their teenage children or parents would understand,” writes council President Tom Brzustowski in the latest NSERC newsletter. Brzustowski says the $450 million agency, which supported 7300 researchers in 1995, hopes the summaries will help earn Canadians’ support in the face of “pretty tight competition for public funds.”

The catalyst for the policy change, says an NSERC spokesperson, was a press release issued last year by Randy White, a member of parliament from British Columbia. In a move reminiscent of the “Golden Fleece Awards” handed out by U.S. Senator William Proxmire (D-WI) in the 1980s, White listed the titles of grants he viewed as a waste of money.

While it may work for Canada, this plan doesn’t impress Chuck Herz of the U.S. National Science Foundation, which requires only a technical summary. “I would question who really would use” the low-tech summaries, Herz says. But the idea wins plaudits from what might seem an unlikely source: Terry Pearson of the University of Victoria. His research title—Membrane Molecules of African Trypanosomases (the organism that causes African sleeping sickness)—was one of those singled out for ridicule on White’s list. But Pearson says the new, easy-to-read summaries will not only inform taxpayers, but also help him understand projects outside his field. “Real science in straight English,” he says. “I love it.”

Joint Venture to Tackle Cancer Genetics
In what may be a first for a major cancer research center, Memorial Sloan-Kettering Cancer Center in New York City is planning a joint venture with Sequana Therapeutics Inc. to study the genetics of cancerous tumors. The project will focus on the 90% of cancers caused by nonhereditary defects, refining ways of using genetic data from tumors to predict the course of cancer and find new drugs to treat it. Memorial Sloan-Kettering will contribute its clinical expertise and 30 years’ worth of tissue samples and patient data, while Sequana, in La Jolla, California, will bring to the venture its fast DNA sequencing capabilities. “Sequana has the engine; we have the gasoline,” says Memorial Sloan-Kettering spokesperson Avice Meehan. The two partners, each of whom will contribute $5 million for the first 2 years, signed a letter of intent last month.

“The best of my knowledge, no other academic group has teamed up with industry with this sort of project,” says Sequana associate director of investor relations Robert Giargiari. Sequana vice president of molecular genetics Nicholas Dracopoli will be research director of the new venture, which has yet to choose a president. The partners hope to sign an agreement in 50 to 90 days, Giargiari says, and later move into a building on Sequana’s campus.

Dole Targets DOE Civilian R&D
Science and technology issues may not be on the front burner of the presidential campaign, but a proposal by Republican candidate Bob Dole to eliminate the Department of Energy (DOE) and make huge cuts in its programs would drastically reshape everything from high-energy physics to renewable energy research. Dole’s economic plan released last month calls for $32 billion in cuts to the department’s civilian efforts over the next 6 years. That’s about one-third what DOE intends to spend in that period, and virtually all of the money assigned to nondefense programs.

One reason Dole would do away with DOE is to pay for his proposed tax cut. DOE’s defense labs would be transferred “to agencies more appropriate to their mission,” according to the plan. (Dole assured voters in New Mexico last week that the defense labs there—Sandia and Los Alamos—would stay open.) Civilian labs would be moved to the National Science Foundation (NSF). Many civilian efforts, the document says, are outdated and wasteful … such as a program to produce methane gas from ‘tuna sludge.’

DOE Secretary Hazel O’Leary blasted Dole’s proposal last month, noting it would eliminate almost two-thirds of research at Oak Ridge National Laboratory and cripple Pacific Northwest Lab. She added that it would force the closure of Fermilab, Brookhaven National Lab, and other major DOE facilities.

Administration and congressional Democrats are concerned that while the Dole plan shifts facilities to NSF, it doesn’t call for doubling NSF’s budget. Some Republicans sympathetic to DOE civilian research are nervous as well, but they’re taking the document with a grain of salt. Says one Republican congressional staffer: “My guess is no one will take this too seriously.”
Keeping Up With 2000

Crashed computers, failed businesses, the government tied up in knots. That's the picture that many are predicting if the country doesn't get its act together to solve the "2000 problem."

What's the problem? Most computers aren't ready to go into the next century. It seems that back in the dark ages of the 1960s and 1970s, programmers needed to save computer memory, so any programming that related to dates left room for only two digits for the year. After 99 comes 00—which computers will interpret as 1900. At the time, programmers expected their work to be superseded quickly, says an administration official. And it was, but the double-digit habit persisted—indeed, even the calendar in Windows 95 won't go beyond 1999.

Government officials explain that 2000 could play havoc with all the government's date-dependent activities—such as sending out checks, scheduling, forecasting, and calculating benefits. Without a fix, "you get erroneous results or your program stops completely," says Judith Draper of the Social Security Administration. For example, subtracting 12/31/95 from 12/31/05 to get a 10-year-old's age in 2005 would yield —90.

Draper manages a year 2000 project for Social Security, and similar efforts are sprouting at other agencies. But the complexity and cost of solving the problem is turning out to be mind-boggling. Declared a Treasury Department official at a congressional hearing last spring: "Neither the government nor industry has ever tackled a computer-systems problem this massive or pervasive." Millions of lines of computer code have to be scanned for anything related to dates; hardware engineers and software programmers have to decide how to fix the code; then the fixes have to be tested. Computer scientist Kevin Schick of the Gartner Group, international consultants, has estimated that because the task is so labor-intensive, it will end up costing the government between $20 billion and $30 billion.

Schick says getting all of North America's computers ready for 2000 will cost up to $300 billion; the tab for the whole world he pegs at $600 billion. But most people are still behind the curve, he says: "All I see is hand-wringing."

Liquor-Loving Mice

Scientists may have come a wee bit closer in their quest for a gene or genes contributing to alcoholism. Behavioral geneticists in Oregon have demonstrated in so-called knockout mice that the loss of a single gene that affects the neurotransmitter serotonin is enough to turn healthy rodents into heavy drinkers.

"What [we] have now is proof that this gene is important for consumption," at least in mice, says Herman Sampson, a behavioral neuroscientist at the Bowman Gray School of Medicine at Wake Forest University in Winston-Salem, North Carolina.

The gene in question codes for the 5-HT{sub}1B serotonin receptor, a protein that sits on the surfaces of nerve cells and is thought to help control serotonin release, says John Crabbe at the Veteran's Affairs Medical Center in Portland, Oregon. When Crabbe's colleague Rene Hen, now at Columbia University, made these knockout mice 2 years ago (Science, 23 September 1994, p. 1875), the animals were found to be abnormally aggressive. Now the team reports in the September Nature Genetics that the loss of this receptor also causes the mice to prefer liquid containing 20% ethanol over tap water and to consume twice as much alcohol as normal mice. They had suspected this might be the case from mouse studies that have pointed to a number of genes, including this one, possibly linked to alcoholic behaviors.

The yen for alcohol has nothing to do with taste, as the knockout mice show no unusual preferences, says Crabbe. Instead, "it appears they are making this selection on some pharmacological grounds." Drink for drink, the knockout mice get a bit tipsy and are less likely to stumble than are those with the gene.

The work dovetails nicely with findings from human studies showing low levels of serotonin in some alcoholics and in people prone to violent behavior, says Crabbe. "What this [finding] does is allow us to link aggression and alcoholism together," says Denise Tomkins, a behavioral pharmacologist at the Addiction Research Center in Toronto. As such, she adds, the mouse will likely be used "for screening novel agents that have potential for use in the clinic" in treating violent alcoholics.

Endowment for NIH

Although it has some of the elements of a university—a vast campus, regular classes, and a large faculty—the National Institutes of Health (NIH) lacks one thing many great universities have: an endowment. But that may soon change. Last month a handful of biomedical leaders announced that they are creating a private fund, called the National Foundation for Biomedical Research (NFBR), to support special projects at NIH.

The NFBR has been a long (continued on page 1343)
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Vignette: Subsurface Geology

Is there a way of determining how hot Hell is, and how cold it would have to be for it to freeze over? It turns out that there is a venerable calculation for the climate of Hell. It is attributed to a mysterious Mr. Wensel of the U.S. National Bureau of Standards and was reputedly made more than a half-century ago.

He proposed that the searing statement in Revelation 21:8, “But the fearful, and unbelieving . . . shall have their part in the lake which burneth with fire and brimstone,” provided a temperature touchstone. In order for a lake of molten brimstone to exist, the temperature in Hell would have to be below 444.6°C (832.3°F). For, if it were not, this goes his argument, the brimstone and vapor would have become a gas and not a lake. . . .

It seems that every time someone gleefully trots out Mr. Wensel’s numbers, some skeptic points out that an earthly assumption is at work—namely, that the pressure in Hell is the same as the pressure of the Earth’s surface at sea level. And that surely is wrong, if for no other reason than Hades’s placement in the area we euphemistically term “below.” Under intense pressures, brimstone can stay liquid to 1,040°C (1,904°F) . . .

—Stephen Strauss, in The Sizarius (Kodansha)

Phases of Matter


Readers’ reactions to this book might hinge on their interpretation of the title. Those who view condensed matter physics as a generalization of solid state physics incorporating such diverse topics as superconductivity and phase separation in polymer melts will be disappointed; many topics of interest to them will not be found. Those who recognize the authors’ traditional and more circumscribed reference to many-body processes not treated by solid state physics will find a rich and compelling work that fills a void in the library of physics.

Principles of Condensed Matter Physics focuses first and foremost on the phases matter can form into and on the transitions among them. In doing so it provides the first comprehensive overview for many of the forefront topics it covers. Its approach draws on the powerful concept of phases as the physical manifestations of broken continuous symmetries. Phase transitions are the process by which these symmetries are broken and regained. In the process, materials acquire interesting properties such as shear rigidity, which can be calculated and compared with measurements. The authors also address phase transitions involving internal degrees of freedom rather than structural rearrangements, such as the onset of ferromagnetism. This is a remarkably broad and rich range of phenomena. In aiming for a unified presentation, the authors are confronted by the same challenge facing the entire condensed matter community: very few phase transitions have been explained completely. Tremendous progress in recent years, including important contributions by the authors, explains why this work can be written at all. The novelty of the results explains why it is virtually the only graduate-level textbook on the subject.

The solved systems range from the oft-described Ising transition to the more modern isotropic-nematic transition in liquid crystals. The most familiar phase transitions, such as melting and freezing, are treated approximately, by introducing the formalism of mean field theory. For cases where fluctuations are too important to average away, the authors provide a nice overview of the renormalization group, including the requisite discussions of scaling and universality. Since there is not yet a general theory for phase transitions, a sequence of increasingly complex examples, each of which highlights additional features of our still-evolving understanding, is provided. The authors include enough technical detail to provide a dedicated student with a foundation to start doing independent research. Indeed, some of the chapter-ending exercises only recently served as topics for doctoral theses.

Having established a set of theoretical tools for attacking even unsolved problems in the physics of phase transitions, the authors proceed into even more treacherous territory. More than half the book is dedicated to explaining materials’ responses to external forces. These include dynamical responses such as elastic waves, the hydrodynamics of flowing fluids, and even the formation of topological defects during plastic deformation. Once broached, the subject of imperfections in otherwise uniform phases draws the work to its conclusion. The final chapters, dealing with defect-mediated melting, nucleation and growth of one phase in another, and fluctuations at interfaces, provide the reader with a taste of the ongoing research into the detailed mechanisms of phase transitions.

As with any pioneering effort, Principles of Condensed Matter Physics has some rough edges. The theoretical treatment is thorough and reflects nicely the authors’ research interests in complex fluids. Less emphasis is placed on the experimental phenomenology that might invigorate the discussion. Lindemann’s empirical melting criterion, for example, receives only a note in the glossary although it has provided a touchstone for experimental studies of melting for most of a century. Editorial gaffes such as the redating of two 19th-century references into modern times doubtless will be corrected in the next edition and meanwhile will divert students insipid enough to find them. Others, including at least one subtle sign error, might be more troublesome.

Even with these caveats, Principles of Condensed Matter Physics is an excellent introduction to the processes by which atoms and molecules become materials and how materials acquire their properties. It is beautifully organized to form the basis of a lecture course. The authors clearly have taken pains to complement traditional solid state textbooks and have avoided unnecessary overlap with classic texts such as Hansen and MacDonald’s Theory of Simple Liquids. The amount of background required to get the most out of the many and varied examples suggests that Principles of Condensed Matter Physics would best be taken up immediately after a course in solid state physics. For the interested researcher, the self-contained chapters provide succinct overviews of the topics and more than enough information for going it alone into this exciting and evolving field.

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MOLECULAR MODELING SOFTWARE

Tools for 3-D Visualization

Molecular Modeling software focuses on programs that enable researchers to visualize and analyze the structures and interactions of molecules. Computer programs such as these have become important research tools in the fields of combinatorial chemistry and drug design.

Computers have become almost indispensable in the study of the 3-D structure of biological molecules, particularly proteins. Today, with the assistance of sophisticated molecular modeling and computational chemistry software packages, scientists can gain insight into the structures of macromolecules and their interactions. Advances in the field of X-ray crystallography have made it possible to view and analyze the atomic structure of large numbers of proteins, subsequently opening up a wealth of possibilities in the fields of rational and computer-aided drug design. One of the most promising areas in medicinal research these days, explains Michael Cory, a synthetic chemist who manages the Computational Chemistry Group at GlaxoWellcome, is in receptor-based drug design. “When there is a known structure of a receptor protein or nucleic acid that you can crystallize, you’re then able to model that system with any degree of precision you’re willing to dedicate your computing resources to.”

Researchers can take existing structures or protein-homology-built structures, dock libraries of known molecules (or specifically-designed molecules) one at a time into the receptor sites as they are revealed in the crystal structure, and compute approximate energies of interaction. “We can take large databases and order the molecules and say these are the most likely to give you activity,” explains Cory. “And once we get a lead on a new protein, we can then take those docked molecules, get crystal structures of the molecules bound to the receptor, and use them to develop new product molecules.”

Perhaps the most notable development in this field today are HIV protease inhibitors, believed by many to be the most promising approach to the treatment of HIV infection and AIDS. “These drugs were developed with extensive use of computer-assisted drug design,” says Cory.

A protease is an enzyme that hydrolyzes peptide bonds. When the HIV virus genome is replicated in the mammalian cell, the virus infects the DNA. The virus genes get inserted into the mammalian DNA in the human cells, and a protein is made that represents the viral protein. That protein is a polyprotein — a long string of pieces that needs to be broken up into small proteins. The protease enzyme processes the polyprotein at specific sites, giving rise to the other proteins, thus allowing the virus to mature, bud out, and infect the next cell.

“The protease inhibitors are drugs that mimic the peptide sites, the cleavage sites, and bind to the protease better than the polyprotein,” explains Cory. “So the polyprotein doesn’t get processed while these drugs sit in there. By blocking that processing, they block the maturing of the virus.”

LONG BEFORE CHEMISTS ARRIVED AT THE POINT where they could envision, let alone build, such inhibitor drugs, countless researchers have had to contribute insight into the structure and interactions of proteins and enzymes. One of the early steps researchers undertake today in this analytical process is to create 3-D pictures of the molecules in question. Most of the familiar depictions of DNA winding through space, and proteins and enzymes coming together, are created by means of X-ray crystallography. Michael Pique, director of graphics...
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Molecular Modeling Software

development in the department of molecular biology at The Scripps Research Institute, explains that it can take years before a researcher gets hold of the roughly “ten thousand numbers” that describe the shape of a protein molecule. These would be x, y, and z coordinates for a typical protein, which may contain 5,000 atoms.

Of course, the first step in this process is getting enough pure protein for the analysis, says Pique, who has developed a lightweight molecular display program called Flex. Nowadays, this is often done by either making or finding the DNA that gives the sequence of the protein and getting a bacteria or eucaryote, like a yeast, to overexpress that protein. Then the researcher will take a drop and crystallize it. Each of these steps is a worthwhile accomplishment in itself. Once a crystal is formed, the researcher very carefully mounts it in a glass tube containing more of the solution from which it came. X-rays are then beamed through it.

“It’s heartbreaking to go back and read the old papers about this,” explains Pique. “They knew it ought to be possible to do this. They talk about how they take their crystal, and they carefully dry it before putting it in the X-ray machine. You just wish you could have told them, ‘No, no, no, leave that part out. Keep it wet!’”

If all goes well, what results is a piece of film that looks something like a “kaleidoscope view of a snowstorm.” It is a picture comprised of many spots of different sizes and densities, with an overall symmetry. After merging scores of different images of the snowstorm — collected by rotating the crystal to create a certain redundancy — the researcher might be able to begin to make out the crystal structure.

Because the spots are not in color — they show intensity but not the phase — the analyst often has to retrieve information lost during the X-ray procedure through the use of different techniques. One method is to make use of crystals soaked in heavy atoms, such as mercury or gold, which act as landmarks within the structure. Another is a technique called molecular replacement.

This can be done if the protein in question is similar to a known structure. In this case, hoping to find something similar, the analyst will search for the protein whose structure is known within the unknown crystal. “It’s like passing around a little template to find ‘Waldo,’” explains Pique. “Of course, it’s a six-dimensional search because there’s translation and rotation.” So, by moving this template around, if ‘Waldo’ hasn’t moved his arms too much, the researcher may be able to pick him up in the crystal. “It’s not guaranteed but it’s become fairly routine.”

All this work, if successful, culminates in an electron density map of the molecule in question: a cube of numbers, often 64 x 64 x 64, with the numbers ranging from, say, 0 to 100. This map can be imagined as a cloud in space with clumps where the big numbers are. That’s where the electrons are, and, by extension, the atoms. “You get a picture that looks like a piece of coral sitting in space, with high spots and low spots and curves and branches going out,” says Pique, “and the challenge is to try and fit what we know about the molecule into this electron density map.”

This used to be done by hand in the 1960s and 1970s. Modelers would trace the density map onto clear plastic sheets and put them together. (It could have been like looking through a fish tank with many lines running through it.) By eye, these modelers would try to identify the clusters and strands and turns.

With the electron density map, it’s possible to filter the image in such a way that only density spots within or above a given tolerance will be displayed. With protein and DNA the density inside the protein is higher than the density of the substance outside, which is typically water. This technique may produce a basket weave or wire frame picture of the molecule.

At this point, “getting an overview is hard,” explains Pique. “Usually people are lost for a while.” Initially, they look for landmarks — a helix, say, or a big, heavy residue that stands out — or better still, a metal like copper or zinc. A pair of sulfurs can act as a lighthouse to get a fitting started. Following along the chain, the modeler tries to piece together the chains of amino acids, while maintaining a good 3-D geometry.

Explains Pique: “Computer software helps with the rules, but it’s still up to the scientist to say, for example, ‘I see a
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lump here. It’s attached to a metal. According to the sequence, there’s a histidine. We know from chemical studies that the histidine is bound to the metal, so I think that’s probably histidine 43. And then maybe next to it we’ll see something that has a ring on it, and we’ll look at the sequence and see that 42 is a glycine and 44 is a phenylalanine, so we’ll decide that that’s the direction the chain goes.”

Of course, by the time the scientist has gotten to the point where he’s fitting the protein, he’s often been living with it for two or three years. “He’s on intimate terms with all of its residues and chains,” says Pique.

The proliferation of protein information through these techniques has made structure visualization and prediction and homology modeling accessible to experts in computational chemistry as well as bench chemists, educators, and students interested in gaining a basic understanding of molecular structure and interactions. Examples of companies that have developed broad-based molecular modeling and combinatorial software packages for a wide range of applications are HyperCube, Molecular Applications Group, and Chemical Design.

“There’s not much question in my mind that every chemist could use modeling or visualization in some fashion. It’s not the purview of the professional molecular modeler. It’s a universal kind of tool for chemists.”

That’s Neil Ostlund, a computational chemist-cum-computer architect and founder of HyperCube, which produces HyperChem, a Unix- or Windows-based modular program that integrates molecular mechanics, semi-empirical and ab initio quantum mechanics, and molecular dynamics simulations with a set of visualization and manipulation tools. “HyperChem allows you to draw or build any molecular system interactively on the screen, visualize that molecular system in various ways, and perform a variety of computational chemistry calculations on the block molecules that are part of that system,” explains Ostlund.

HyperChem’s “open architecture” allows users to extend the program with other modules for specific applications including HyperNMR, which is used for the prediction of one-dimensional NMR spectra, and ChemPlus, which handles RMS fit, molecular presentation, sequence editing, crystal and sugar building, QSAR (quantitative structure-activity relationships), and conformational searching. An upcoming release of HyperChem will include a chemist’s developer’s kit to make it easier for users to interface with any Windows package or with custom-designed software.

Ostlund sees HyperChem as a generic program best suited for teaching purposes. “Our top application is educational use,” he explains. “Even in the drug companies that have our software, it is mainly used by people who want to teach themselves about modeling. It’s so easy to use — we get high school students using it who sit down and say, ‘This is fantastic!’”

In fact, HyperCube has released an inexpensive version of its software called HyperChem Lite, designed specifically for researchers, educators, and students.

Molecular Applications Group (MAG) was founded in 1990 by Stanford University Professor Michael Levitt. Levitt had developed MACIMDAD (Interactive Molecular Design and Display for the MAC), an easy-to-use molecular visualization program, as a teaching tool at a time when much of the visualization software was command line-driven or needed to be run on powerful workstations. For many without access to these resources, or without programming backgrounds, MACIMDAD offered an opportunity to be able to sit down and visualize and dissect protein structure. Before long, Levitt’s colleagues at Stanford were asking for copies of MACIMDAD for use in their classes.

In 1994, MAG released LOOK, a second-generation product, which has at its core two algorithms to allow bench biologists to model protein structures themselves: Levitt’s homology modeling algorithm SegMod and a site-directed mutant modeling algorithm developed by Chris Lee. LOOK, which runs on Silicon Graphics workstations and supports client-server environments for PC and MAC front ends, integrates molecular visualization and modeling on the protein structure side with protein sequence analysis functionality. It includes an electronic notebook that can be cross-referenced and hyperlinked to structure data.

“Our focus is on ease of use and interrelating information,” explains Charlene Son, director of marketing for MAG. “For example, we have made homology
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modeling as simple as pressing a button. As a user, all I need to do is build a sequence alignment containing a template structure."

Scientists can model the structure of a protein based on another known structure, for example, a Protein Data Bank structure. Based on a user's sequence alignment, LOOK automatically builds the structure through a matching method, applying the folding information from the known structure to the new model. This approach produces accurate results in five to fifteen minutes, explains Son.

"If you want to model a protein structure or build a homology model," she adds, "with many programs you'll spend a lot of time altering parameters and making manual manipulations to the structure as it's being built. It's incredibly time consuming and often requires someone who is an expert modeler or computational chemist."

With LOOK, explains Son, "a molecular biologist or a bench chemist can handle many of their modeling and molecular visualization needs by themselves, without having to look over the shoulder of an expert modeler. Molecular biologists and bench chemists can take advantage of structural information to drive their experiments."

LOOK allows scientists to easily interrelate sequence and structure depictions of data. A protein structure and the sequence for that structure can be displayed simultaneously, providing representations that complement each other. "If you click on one part of the structure you can immediately see where you are in your sequence and vice versa. That direct connection can be very powerful."

If a user clicks on a central residue in a protein image, the corresponding sequence data will be highlighted as well as the structural neighbors. "A lot of times you'll see structural contacts that are 50 or 100 residues downstream if you look at the linear sequence," explains Son, "but they're actually right on top of each other."

Finally, by creating a hyperlink to the electronic notebook, the scientist can move down the line from structure to sequence to notes. "Say you have your structure, and you've highlighted the critical binding site and have it in a certain orientation," explains Son. "You can then highlight notebook text relating to that image, and it will connect to that depiction. You can build a historical lab notebook to use for later reference and to share with your colleagues."

Earlier this year, Chem-X, a modular software system developed by Chemical Design for use by specialists and general users in new product research, won Scientific Computing's Automation Magazine's Readers' Choice Award for chemistry software. Chem-X was initially developed in the 1980s as a molecular modeling tool. In the 1990s, chemical database software which was fully integrated with the computational tools was added. Recent developments for combinatorial chemistry enable Chem-X to integrate library registration, diversity analysis and library design, lead generation and optimization, robotics programming, and biological data management.

Chemical Design offers a range of entry-level systems, including Chem-X/Draw, Chem-X/Model, Chem-X/Base, and, more recently, Chem-X/Diverse, any of which can be enhanced by further standard modules, such as ChemProtein, ChemStat, or ChemQM. "Chem-X can grow by adding new functionality as you need it," explains Judith Bandy, technical writer at Chemical Design. "From simply drawing molecules on the screen and analyzing their properties, you can build an integrated software system for drug discovery that uses databases for selecting molecules to test, allows you to screen by a particular receptor site, and can use combinatorial chemistry to design new libraries."

Chem-X is available under a common user interface on a range of hardware platforms including PC, Macintosh, and UNIX workstations. Recently, the focus at Chemical Design has been modified to providing software for combinatorial chemistry that is aimed at pharmaceutical organizations interested in accelerating drug discovery. "With the need to increase dramatically the number of new molecules that can be considered for activity testing, Chemical Design has been working with leading pharmaceutical organizations to develop software for combinatorial chemistry," says Bandy. "The result is an integrated information management system for exploiting, and not simply archiving, chemical and biological data."

Last summer, two of the largest computer-aided molecular design companies, BIOSYM and Molecular Simulations Inc. (MSI), merged to form a new company, known simply as MSI, which is today the largest vendor of computational chemistry software, supporting 3,500 commercial, academic, and government research and development sites in numerous industries, including pharmaceuticals, chemicals and biotechnology. MSI offers a wide range of software pack-
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ages for molecular modeling and computational chemistry, including Cerius2, Insight II, Quanta, and Catalyst.

Cerius2, for example, combines tools for building and visualizing models of molecular structure with a wide range of computational algorithms. "Cerius2 provides a set of modules, each of which has a specific application focus," explains Michael Stapleton, a chemist and MSI’s vice president of product marketing. "If I wanted to correlate the activities of a range of drugs and predict activities of new drugs, there’s a whole suite of tools in the QSAR module to do that. If I wanted to predict the bulk particle shape of a drug molecule or a pigment or a dye, I’d use the morphology module. To determine the structure of a small molecule or an inorganic catalyst, I would use the X-ray diffraction module. If I wanted to predict the crystal structure of a drug, ab initio, without any experimental data, I would use the polymorph predictor."

MSI has a focus on molecular modeling to the "downstream end" of the pharmaceutical industry — the formulation and development end — explains Stapleton. "Typically these chemical engineers and chemists have already been delivered the drug molecule, and they’ve got to prepare the most effective way of delivering it to people as rapidly as possible."

"Right now, it’s driven experimentally," he adds, "but more pharmaceutical companies are starting to use our sort of software to speed up knowledge acquisition in that area."

Pascal Toma, a crystallographer and senior research chemist in the analytical research department of Merck & Co., explains that where modeling software helps him most is in analyzing the morphology of drugs. "We grow crystals, load them into the computer, and calculate the powder patterns to confirm whether this drug is the same form in the bulk product as the crystals that are grown," he explains.

Ken Morris, a principal scientist in the chemistry department at Bristol Myers Products, says he relies on molecular modeling software principally to "make sure that the material that we have is what we think we have," and to solve problems in the determination of drug dosage forms.

"You want to control the shape so that they flow better, compact better, and allow for better mixing and content uniformity," he adds.

Morris uses software for morphology prediction, simulation of powder X-ray patterns from crystal structures, refining of powder X-ray defraction patterns to compare the purity of phases, and powder indexing. "We’re trying to bring the level of our powder diffraction program up to the state-of-the-art where we’ll be able to index and really know the cell dimensions without actually having to solve the crystal structure each time. That would be really nice."

"There are people who can do this stuff without the software," he adds. "But I’m not one of them. I wouldn’t be able to do the more theoretical and resource-intensive calculations that I do now and carry out my other experimental functions without these programs."

Many of today’s modeling programs are extremely easy to use, explains Morris. "Whether you understand the concepts or not you can use the software," he says. "But they’re not a substitute for understanding the concepts. On the other hand, if you understand the concepts, [using the software means] you don’t have to grind through all the calculations every time you want to do them."

John Holland, senior product manager at Oxford Molecular, identifies two distinct types of users of molecular modeling software: the computational chemist who works mostly with a computer; and the bench chemist working in a wet lab who needs to do some modeling to generate ideas. For the latter, Oxford Molecular offers a line of software tools under the name CAChe (the capital letters stand for computer-aided chemistry).

"CAChe is designed to allow the bench chemist to ask detailed questions of high-end scientific products without having to understand the technical details of what those scientific products are," says Holland. CAChe, which runs on Macintosh, Power Macintosh, and Windows platforms and can access high-end computational tools mounted on a Silicon Graphics or IBM RS6000 server, may be used to predict and visualize many molecular properties.

"The chemist can enter a structure and ask of the program, 'Show me the UV or IR spectra, or the NMR (nuclear magnetic resonance) shifts,'" explains Holland. "The chemist doesn’t care whether he needs to perform ab initio quantum mechanics or semi-empirical quantum mechanics or run a force field program. The software has a built-in database of intelligence, so the parameters that the program needs to generate that information have been entered by a specialist who knows the best values."

Where the big changes are occurring today, explains Holland, are in combinatorial chemistry with the introduction of synthetic robots capable of building large numbers of compounds. One of the traditional goals of molecular modeling has been to investigate molecular properties to try to predict the most useful drugs to build. Historically, a problem affecting the interaction of modelers and chemists was that the modelers were able to predict many more compounds than the chemists could build.

Today, "synthetic robots can now probably make as many compounds as
modelers can model, if not more," says Holland. "The technology of modeling has been turned around from looking at individual molecules and making accurate detailed descriptions of them to the study of libraries, in the same way that chemistry is changing to look at libraries of compounds."

The upshot of this is that it is becoming just as important, or perhaps more important, to be able to study molecules as a set and make predictions about the set than it is about individual molecules. "The problem that the molecular modeler faces," adds Holland, "is not so much trying to design new drugs from individual compounds; it's perhaps now more to guide the synthesis people to help them decide which subset of their 'virtual library' they're actually going to build."

Typically when researchers want to build a library to screen against all possible targets, they usually begin by trying to make the library as diverse as possible within a manageable size. How to measure molecular diversity is, itself, a complex task. Recently, Oxford Molecular redesigned its QSAR software, called TSAR, which was formerly aimed at studying problems involving up to about a thousand molecules where all these molecules could be investigated in detail. "We're transforming it into a program capable of dealing with hundreds of thousands or millions of molecules, a program that is limited only by your machine," explains Holland. "And we're building up a spreadsheet interface that will allow you to look at the subsetting problem on a number of levels."

EVerY PHARMACEUTICAL company has as one of its main assets a proprietary database of the chemicals they have made and tested over time. The leading company providing database software and information management software to these companies is MDL Information Systems. "Molecular modeling tools are design tools," explains Steven Goldby, MDL's chief executive officer. "We represent the information feed into that design process."

"If you look at the HIV protease inhibitors," he adds, "that was a project that was tailor-made for the application of computational chemistry. Part of the protease enzyme had been isolated, and its structure was known. So people could use software and databases to design and select compounds that would preferentially interact with the enzyme."

People came up with hypotheses as to what sort of structures would bind with the protease. "They did searches of 3-D databases using MDL software," explains Goldby, "and defined chemicals they already had which would have that structure. They tested those chemicals and then began a process of refinement that involved molecular modeling tools as well as the traditional techniques of medicinal chemistry."

MDL's client-server system for database management, ISIS (which stands for Integrated Scientific Information System), incorporates a series of packages for creating chemical graphics; managing project data consisting of molecules and reactions; and accessing relational, chemical, reaction, and 2-D and 3-D structure databases. ISIS clients are available on Macintosh and Windows and Silicon Graphics workstations; servers run on Digital Open VMS, IBM Research Systems 6000, and Silicon Graphics workstations.

Using ISIS, explains Goldby, a researcher who believes that a particular portion of a chemical structure is responsible for a given activity would be able to do a search for all chemicals that the company had made and tested in the past or had been reported in the literature which had that substructure as part of it. A new package called Project Library, which runs on Macintosh and Windows desktop computers, is designed to help researchers manage project chemical and biological data generated by combinatorial chemical processes.

In the coming years, pharmaceutical and biotechnology companies will continue to develop new techniques for searching through structure databases, looking for candidate molecules with a given shape and set of properties to act as possible receptors for particular targets. An important task will be to develop better representational storage and search techniques. One of the great challenges in representing 3-D properties with numbers is coming up with mathematical representations that are efficient to use. "If you need so many numbers to represent your 3-D situation that you can't handle them, it doesn't help very much," explains Michael Cory. "Now, if we can develop improved methodologies for representing molecules in 3-D and better visual patternning techniques for multiple molecules, we would be very much further ahead. The challenge is really that the volume of numbers to manage is so much greater than ever before."

-David Bornstein

DAVID BORNSTEIN IS A JOURNALIST WHO SPECIALIZES IN TECHNOLOGY, FINANCE, AND ECONOMIC DEVELOPMENT REPORTING.
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Pathologist
Manage all aspects of clinical pathology for projects using biotherapeutics and gene therapy to control small animal diseases. Will also analyze complex biological pathways and disease pathogenesis to develop assays, reagents and tools for evaluating new vaccine candidates. Requires a D.V.M., Board Certification and two years of experience in pathology or veterinary internal medicine.

Clinical Research Investigator
Develop animal disease models, participate in the design and implementation of experiments, and conduct and interpret clinical evaluations. Requires a D.V.M., post graduate training and related experience in academia or commercial research.

Senior Research Scientists (4)
Four leaders are needed to provide supervision and hands-on expertise in each respective area as listed below. Successful candidates will have experience working with multi-disciplinary research teams, excellent communication skills and a strong publication record.

- Design and develop purification and characterization processes for native and recombinant proteins and develop appropriate analytical techniques to monitor the processes. Requires a Ph.D. in Biochemistry with directly related experience in protein isolation and analytical methodologies. Experience in purification of glycoproteins and carbohydrate biochemistry is desired.
- Design, conduct, and evaluate experiments in parasite immunology, T-cell cytokines and molecular parasitology. Requires a Ph.D. in Immunology or related discipline with post doctoral training using molecular and cellular biological skills for studying host parasite interactions. Additional experience in parasitic protozoan animal models and molecular manipulation of parasites is desired.
- Conduct research designed to identify and characterize protective antigens for veterinary diseases induced by Mycoplasma spp. Requires a Ph.D. in Microbiology or related discipline with post doctoral training in molecular pathogenesis of Mycoplasma spp. Work with M. hyopneumoniae employing molecular genetic techniques is desired.
- Conduct research designed to identify and characterize protective antigens for veterinary diseases induced by pathogenic spirochetes. Requires a Ph.D. in Microbiology or related discipline with post doctoral experience in molecular pathogenesis of spirochetes. Work with Leptospira spp. employing molecular biological techniques is desired.

Research Scientists (7)
Seven scientists are needed to provide guidance and expertise to project teams in each of the respective research areas listed below.

- Design and conduct experiments in B-cell biology with particular emphasis in mucosal immunity and protective memory responses. Requires Ph.D. in cell biology or related discipline with post doctoral training in molecular manipulation of B-cell genomes. Training in antibody therapies and protective memory responses desired.
- Utilize molecular and general virological methodologies to elucidate the function of viral genes appropriate for virus vaccines for use in animals. Requires a Ph.D. in Virology or related discipline and post doctoral training in molecular virology. Understanding of animal virus diseases to include pathogenesis, immunology and epidemiology is desirable.
- Conduct research on the molecular biology of gene identification, cloning and expression, develop new expression technologies, and evaluate immunogenicity of potential vaccine candidates. Requires a Ph.D. in either Virology/Molecular Biology/Cell Biology or Microbiology with post doctoral experience in developing expression systems and applying the systems to solve the research problems.
- Develop animal disease models and provide support to discovery projects in veterinary biologicals for livestock or companion animals. Will initiate the design and implementation of animal experiments, conduct clinical evaluations and interpret results, and generate appropriate reports. Requires a D.V.M. with graduate training in clinical veterinary medicine and experience in livestock or companion animal research. (Two opportunities exist, one for livestock, the other for companion animals.)
- Design and conduct experiments to elucidate protective immune responses and disease pathogenesis in response to viral pathogens. Requires a Ph.D. in Virology or directly related discipline with post doctoral experience in molecular manipulation.
- Develop expression systems for use in virus vectors, eukaryote cells and DNA vaccines using contemporary molecular biological approaches. Requires a Ph.D. in Virology/Molecular Biology/Cell Biology or Microbiology with experience in expression systems desired.

Scientist
Optimize cell lines necessary for maximum virus or protein yields. Requires a B.S. in Biology or related life science with experience in culturing and optimizing of mammalian cells. Production and optimization of modified cell lines is desirable.

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