MARCH 1991
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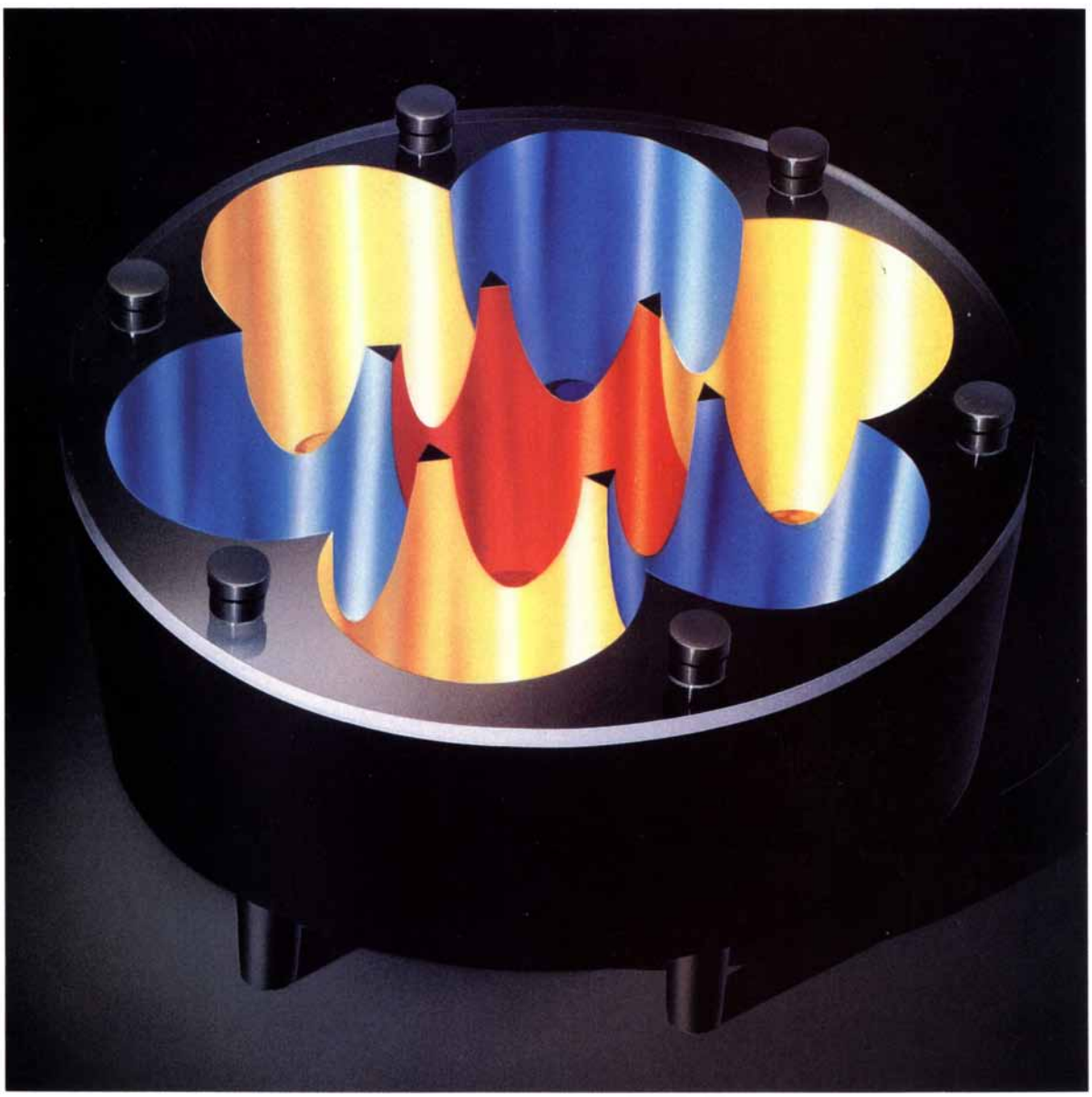
SCIENTIFIC AMERICAN

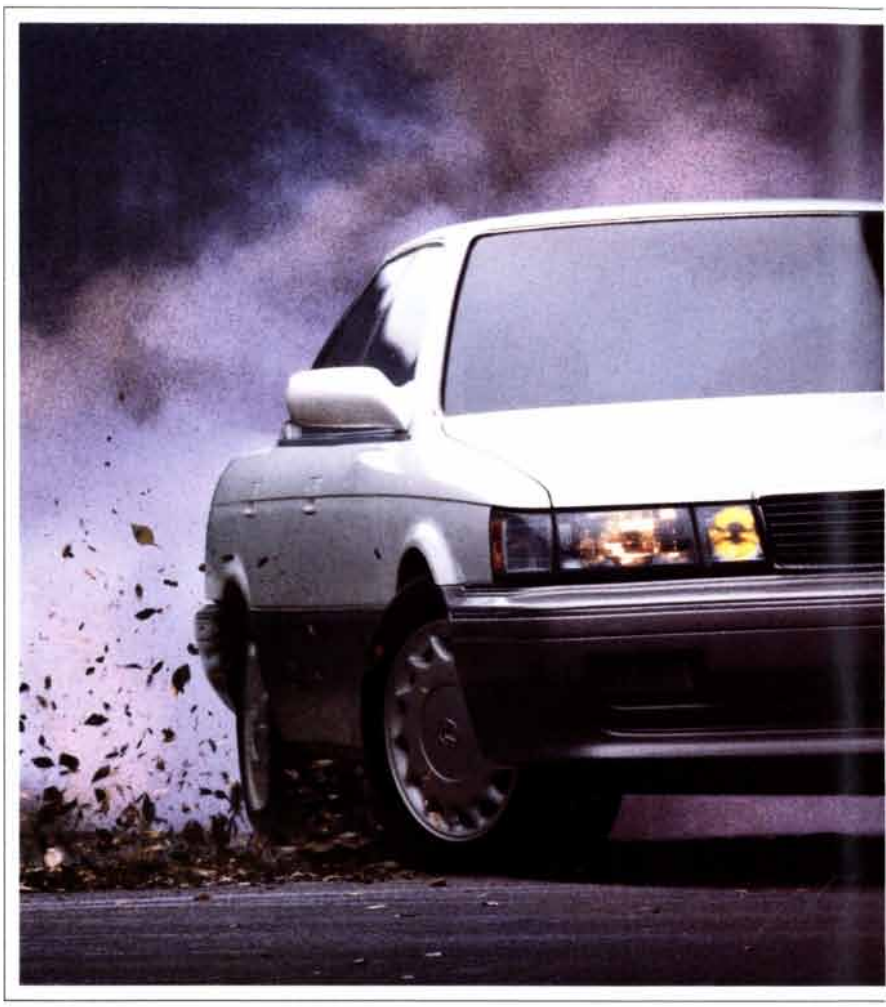
How rising continents cooled the earth.

Will drugs ever cure drug addiction?

The Russian weed that won the West.



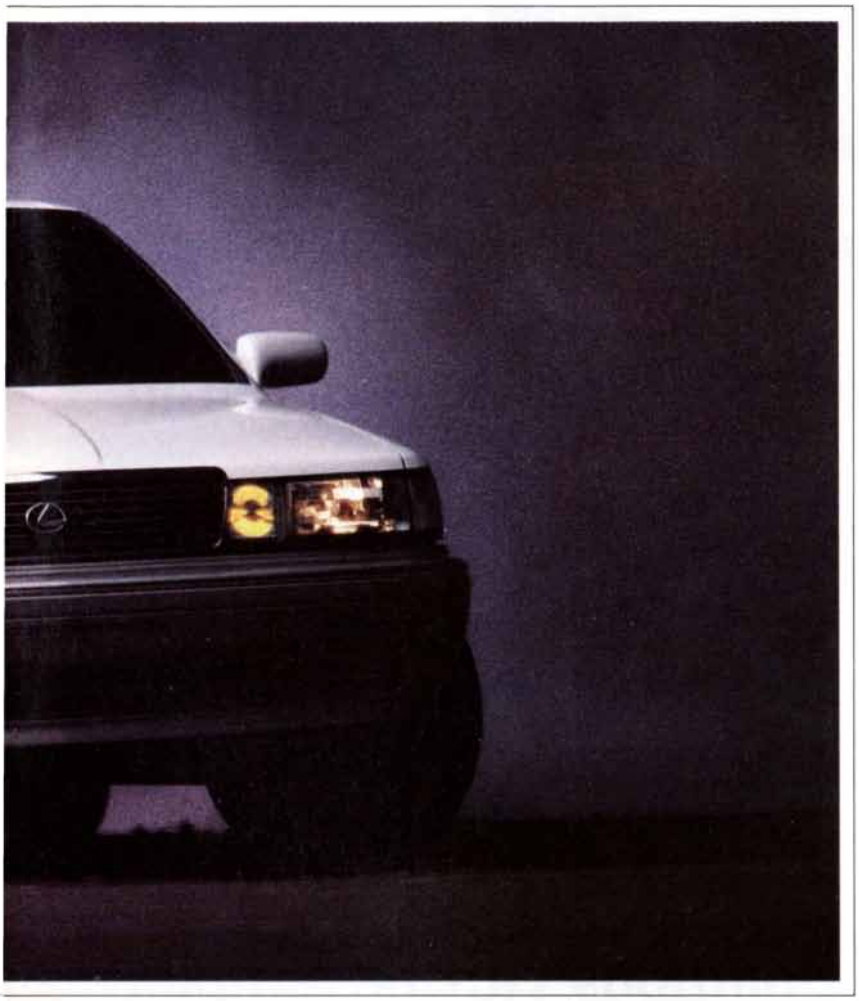
Funnels for light *can concentrate solar energy to supersolar intensity.*



Submerse Yourself Without Drowning In

Luxury is often defined in terms of rich, supple leather. That's fine if you're designing sofas. But try negotiating

**The driver's-side Supplemental Restraint System (SRS) will inflate only in a severe frontal impact. In a moderate collision, the three-point seat belt provides primary protection; the airbag will not inflate.*



In Luxury Boredom.

a hairpin turn on your living room divan. The Lexus ES250, on the other hand, offers luxuries that go far deeper than the padding in the seats. A simple depression of the accelerator will demonstrate our point.

The responsive Four-Cam V6, coupled with a Vorlauf-inspired suspension, can turn the anguish of everyday driving into an act of anticipation. Of course, this type of power requires restraint. To that end, we appointed the ES250 with one of the most advanced anti-lock braking systems available.

Yet, given its bent for performance, this sports sedan is not without its share of creature comforts. Like an ultraquiet cabin with optional leather trim package. High-output, six-speaker audio system. Even the comfort of a driver's-side airbag Supplemental Restraint System.*

And, oh yes, perhaps the most luxurious feature of all. Standard with every ES250 comes the pure thrill of driving it.

LEXUS

The Relentless Pursuit Of Perfection.

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THE POWER OF BELIEF: #5 in a series

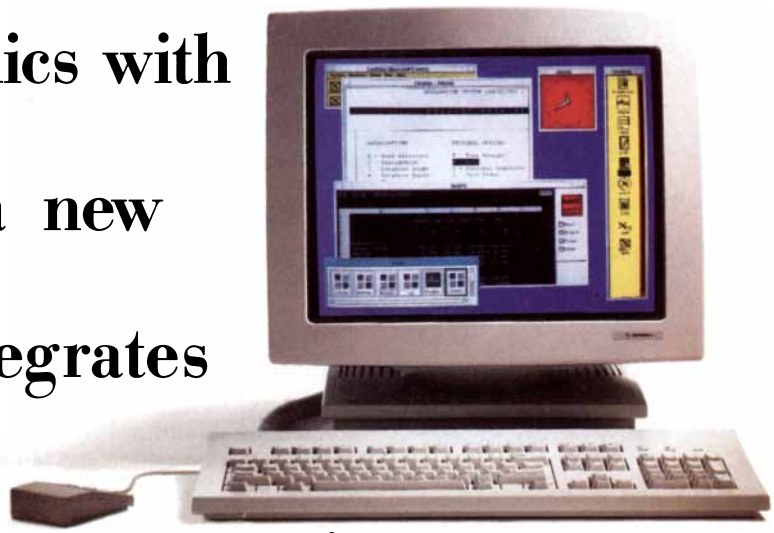
New ideas are everywhere. All they need is the environment to make them happen.

Creativity isn't limited to special people, places or times. ■ Given shared goals and an enabling environment, everyone can contribute. Not just at Motorola, but also among our suppliers, customers and end users. ■ Solutions can be simple, like redesigning a product so it snaps together

Product design can be a snap! Snap-together assembly of the Radius battery charger meant 11 parts instead of 72, Six Sigma quality, and lower costs to customers.

Winner 1988 Malcolm Baldrige National Quality Award

instead of needing dozens of fasteners. Or powerful, like the Media Engine™ chip that delivers color graphics with stereo sound; or a new computer that integrates seamlessly with multiple products for new networking efficiencies. ■ At Motorola new ideas are constantly happening. Because creativity is constantly being encouraged.



The Motorola MultiPersonal™ Computer uses our 88000 RISC microprocessor to create a true network computing system that provides the power of a stand-alone workstation and the flexibility of a multiuser system.

Building On Beliefs

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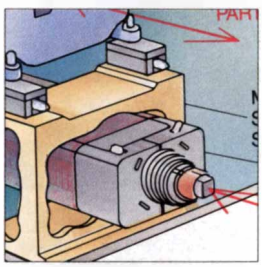
SCIENTIFIC AMERICAN

March 1991 Volume 264 Number 3

40 

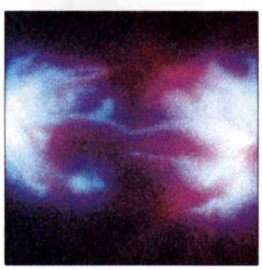
Patenting Life
John H. Barton

The last obstacle to patenting a nonhuman form of life fell in 1988, when the U.S. Patent and Trademark Office issued a patent for the "Harvard mouse." But the courts and lawmakers have not yet confronted many of the questions raised by granting patent protection to genetically altered animals, plants and microbes. The future of biotechnology depends on the wisdom of the answers.

48 

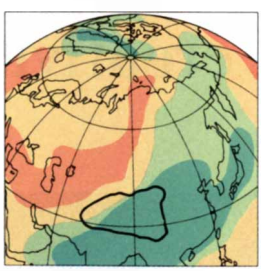
The Tevatron
Leon M. Lederman

Since the first protons swept around the powerful collider at Fermi National Accelerator Laboratory in 1983, the Tevatron has confirmed a host of predictions about fundamental particles. Here is the story of the technical challenges of designing and building this 6.3-kilometer ring of superconducting magnets, told by the scientist who headed the decade-long project.

56 

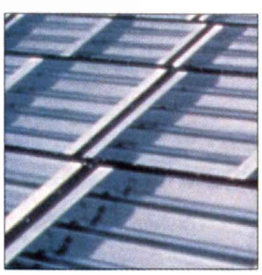
What Controls the Cell Cycle
Andrew W. Murray and Marc W. Kirschner

The way cells divide into two identical copies has been well known for nearly a century. But only now are scientists beginning to understand what orchestrates this marvelous process. The key seems to be a single protein called cdc2. Its discovery has profound implications for medicine, possibly leading to ways to heal damaged organs by inducing cell proliferation or to halt the growth of cancer.

66 

Plateau Uplift and Climatic Change
William F. Ruddiman and John E. Kutzbach

The earth of 40 million years ago was a warm, wet place. Forests abounded; grasslands and deserts were rare. Then the planet began to cool. Regional climate extremes developed. Many causes have been postulated, including continental drift and diminishing atmospheric carbon dioxide. The authors offer a new theory: continental uplift created huge plateaus that altered circulation of the atmosphere.

76 

Nonimaging Optics
Roland Winston

In childhood, most of us learned that one way to get heat out of the sun is to focus its light to a pinpoint with a magnifying glass. What few realize is that the ability of lenses designed to make images to concentrate solar energy falls far below the theoretical maximum. Nonimaging optics that are simply funnels for light can achieve intensities higher than those at the sun's surface.

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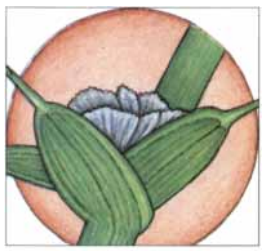
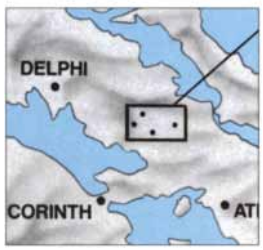
82 

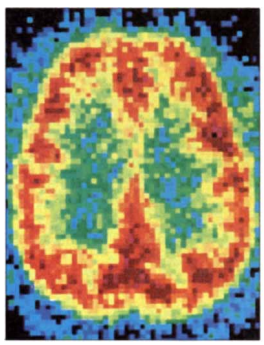
Tumbleweed
James A. Young

If there is a botanical metaphor for the rootless ways of the Old West, it is the tumbleweed. But when this immigrant Russian weed literally rolled through the Dakotas in the 1870s, the sod busters were not thrilled. In a matter of years this spiny thistle wreaked agricultural havoc across the plains states.

88 

Surveying Ancient Cities
Anthony M. Snodgrass and John L. Bintliff

Some important cities of ancient Greece lie buried beneath farmland. That is good news to these archaeologists. Rather than excavating, they build a surprisingly complete picture of long-term habitation simply by dating the debris, such as potsherds and roof tiles, that plowing churns to the surface.

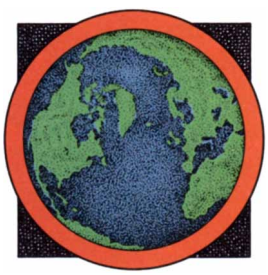
94 

TRENDS IN PHARMACOLOGY

R_x for Addiction
Marguerite Holloway, staff writer

Neuroscientists are making progress toward understanding the devastating and intractable problem of drug addiction. By deciphering the complex interplay of neurotransmitters and receptors, they are designing highly targeted drugs to treat addiction on a chemical and, eventually, genetic level. Their findings have implications for treating mental illnesses.

DEPARTMENTS

17 

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Science and Business

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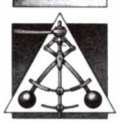
12 

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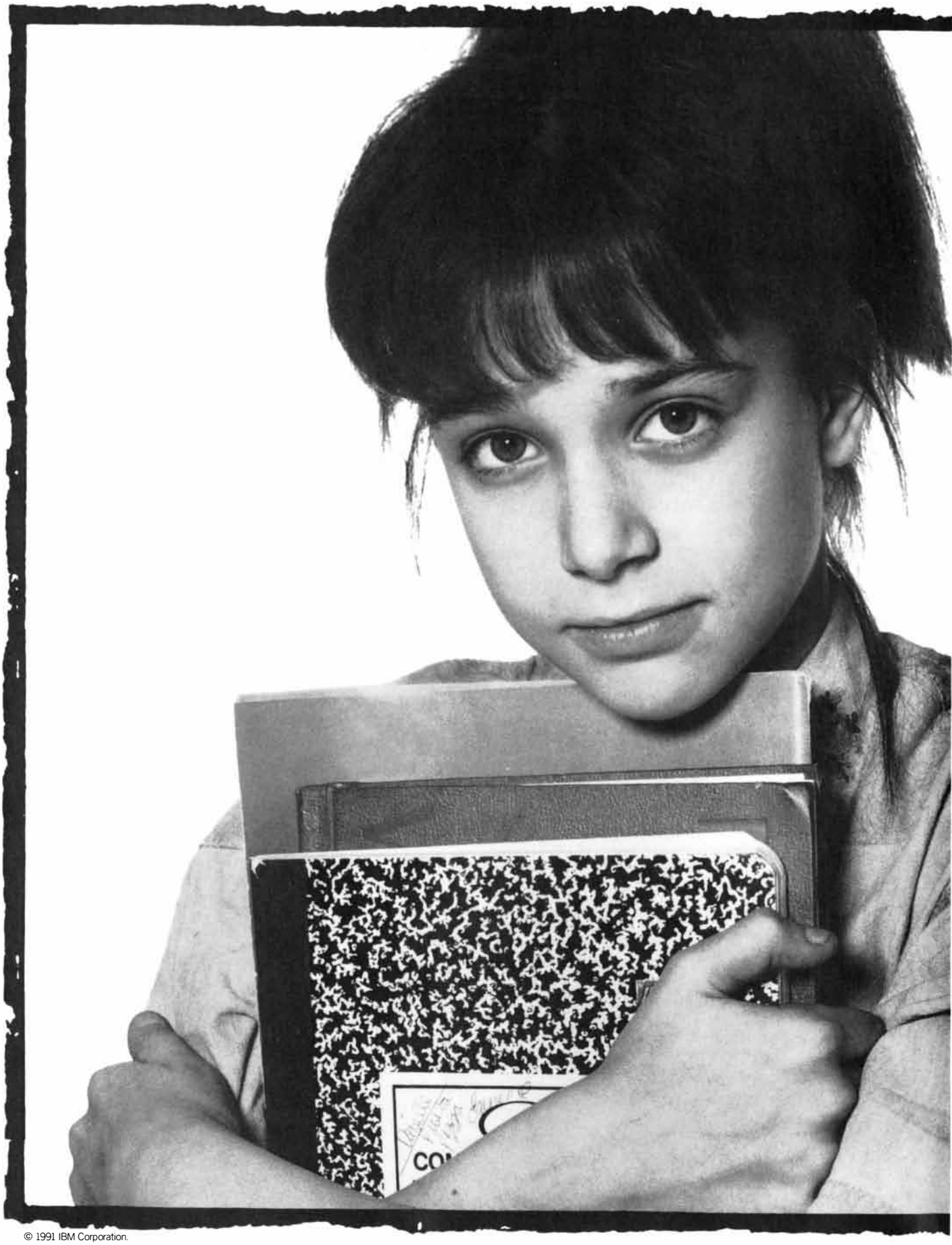

"Grown-ups tell us, 'Just say no.' That's easy for them to say."

"Maybe they forgot what it's like.

"At parties, at school, kids are saying to try this or do that, and they're my friends. I mean how many times can I hear I'm a loser.

"Sure I'm scared of drugs. It's just there's so much pressure. You want to say no. But you can take a lot of heat for it."

Simple yes-no decisions aren't so simple when they involve kids and drugs.

That's why IBM has helped develop a computer-based, interactive video program that's now in schools. It simulates realistic social situations, and allows kids to make choices—about drugs, about alcohol, about themselves—and to experience the consequences, but without getting hurt.

The program is sponsored by the National Federation of State High School Associations, and preliminary results have been extremely encouraging. To learn more about this program, write to us at IBM, P.O. Box 3974, Dept. 973, Peoria, IL 61614.

IBM®

THE COVER painting shows the first compound parabolic concentrator, developed in the 1960s to collect faint radiation in physics experiments. Carved into a block of lucite two feet in diameter, the funnels were colored to display them more effectively. Today concentrators built on the same principle can produce solar intensities greater than those at the sun's surface, leading to promising applications in solar energy (see "Nonimaging Optics," by Roland Winston, page 76). The concentrator was designed by the author, with Henry Hintenberger.

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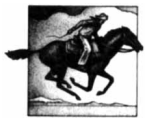
LETTERS



Our Energetic President

To the Editors:

I applaud your special issue on "Energy for Planet Earth" [SCIENTIFIC AMERICAN, September 1990]. One possible signal of our commitment to a sustainable and healthy future is in our recreational choices. Among water sports, for example, rowing, sailing and swimming are quiet and provide exercise without consuming fossil fuels. Conversely, driving power boats and water skiing are noisy and wasteful.

I wish that President George Bush would turn to sailing.

RICHARD REIS
Silver Spring, Md.

Nuclear Reactions

To the Editors:

In his article "Energy from Nuclear Power" [SCIENTIFIC AMERICAN, September 1990], Wolf Häfele naively dismisses the poor economics of nuclear power in his penultimate paragraph by blaming regulation rather than calling on the industry to learn from its mistakes. Yet the Japanese nuclear industry is both heavily regulated and highly productive.

His proposal to build 2,000 more reactors at a conservative cost estimate of $2 billion per reactor implies a $4-trillion investment—eight times the private, nonresidential investment in the U.S. during 1989. That estimate does not include front- and back-end fuel cycle investments or the costs of decommissioning facilities.

GEOFFREY ROTHWELL
Department of Economics
Stanford University

To the Editors:

Häfele's quixotic treatment of nuclear power ignores the reasons why the worldwide antinuclear movement is growing in size and strength. One reason is that people like Häfele limit their discussions of Chernobyl to only a few words along the lines of "massive contamination" rather than describing it as the unprecedented nightmare that it is. He also fails to do justice to the severe dangers of fuel reprocessing, nuclear waste and fast-breeder technology and to the serious loopholes in the nonproliferation regime of the International Atomic Energy Agency (IAEA).

As for the "advanced" reactors that Häfele lauds, a recent Union of Concerned Scientists study of several leading designs concluded that they are by no means "inherently safe" and that in some respects they are even more dangerous than existing nuclear plants. In any event, they are decades from implementation, which leaves us with time to supplant the very need for them with energy efficiency and with environmentally benign renewable sources. No need to squander more billions on nuclear power.

PETER GRINSPOON
Nuclear Campaigner
Greenpeace USA
Washington, D.C.

Häfele responds:

According to the IAEA, in 1988 and 1989 the average construction time for a nuclear power station in the U.S. was more than 100 months longer than it was in Japan. At an interest rate of 10 percent, such a delay doubles the capital costs. Given that cost uncertainty and the 40-year span until 2030—the target date discussed in my article—it does not make sense to apply 1990 U.S. economies to such a long-range global problem.

Moreover, for such a problem, a $4-trillion investment over 10 years is not disproportionate. It is not U.S. investment that should be the yardstick for the cost, but instead the global total of gross national product, which stands today at $17 trillion a year. Assuming a savings rate of 15 percent and a 30 percent share of energy investments, only $800 billion a year would be needed to meet the goal.

Misplaced Priorities?

To the Editors:

"Cannabis Comprehended," by Timothy Beardsley ["Science and the Citizen," SCIENTIFIC AMERICAN, October 1990], was more noteworthy for the medical biases that it revealed than for its news of recent brain physiology discoveries. Medical technologies that have unpleasant side effects, such as radiation therapies for cancer that cause headaches, nausea and hair loss, are considered acceptable. Yet a drug that makes patients "high" as its main (if not only) side effect will not even be developed!

Are we so afraid of pleasure that we would rather let people suffer than risk letting some of them have fun?

WILMA KEPPEL
Omaha, Neb.

Computer Chess

To the Editors:

For more than 2,000 years, humans have been making excuses for losing chess games. One of the favorites has been, "I had a cold," but others have included too much noise, poor lighting, hypnotism and negative psychic energy. In "A Grandmaster Chess Machine," by Feng-hsiung Hsu, Thomas Anantharaman, Murray Campbell and Andreas Nowatzyk [SCIENTIFIC AMERICAN, October 1990], the authors discuss Deep Thought's loss to Anatoly Karpov and conclude that "a stable six-processor version would have had enough speed to avoid the blunder." This is indeed something new in the history of chess: a computer's excuse.

I believe human players will learn to take advantage of the computer's many weaknesses, chief among them its inability to devise even simple plans. Not to detract from the programmers' worthy accomplishments, but the reasons for Deep Thought's wins lie more in the human grandmasters' lack of psychological preparation and less in the computer's calculations of billions of irrelevant variations.

JAMES L. WEINHEIMER
Princeton University

To the Editors:

Computer programs that tried to emulate human chess masters have not proved as successful as ones employing massive search approaches. Moreover, by searching very long sequences of chess moves, recent computer programs have shown that some endgame situations that were previously thought to be a draw (configurations involving a king and two knights versus a king and a pawn, for instance) can in fact end in a win. Some human chess players now memorize those sequences, and during tournament play they seek to achieve such previously overlooked winning situations.

In some ways, then, humans are now playing chess by emulating computers.

DAVID G. STORK
Ricoh California Research Center
Menlo Park, Calif.

MAN: This Eagle Talon TSi and Toyota Celica All-Trac both have all-wheel drive. But the Celica costs about 4,000 dollars more.

OFF-CAMERA VOICE: What do those guys at Toyota take us for?

MAN: About 4,000 dollars.

(MUSIC)

Advantage: Eagle

Chrysler's Newest Division

Eagle Talon TSi with all-wheel drive and 195 horsepower turbocharged, intercooled engine is backed by Chrysler's exclusive 7/70 Protection Plan. This plan protects the engine and powertrain for 7 years or 70,000 miles and against outerbody rust-through for 7 years or 100,000 miles. See limited warranty at dealer. Restrictions apply. Price claim based on comparison of sticker prices. For more information about Eagle Talon, or how to buy or lease one, call 1-800-JEEP-EAGLE. Buckle up for safety.

Jeep Eagle 7/70

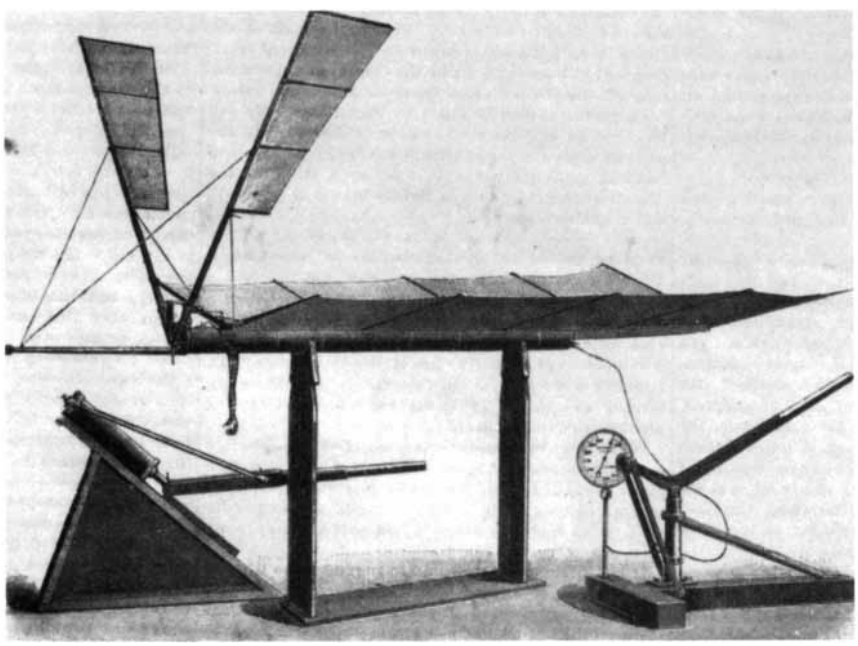
50 AND 100 YEARS AGO

MARCH 1941: "The two wolf-children of India were first seen living as wolves among wolves on October 9, 1920, by an Anglican missionary, Rev. J.A.L. Singh. Rev. Singh and his wife expected that a few years of association with the normal children in their orphanage would change the wolf-children from effective little animals back into human beings. They were to be disappointed. The children hated, feared, and shunned human beings, as would have a wolf-cub. Kamala, the elder surviving girl, gradually developed into a pathetic little, sub-normal, but clearly not idiotic, human being. She learned to speak about 50 words and occasionally to put them in short sentences. From the entire account it becomes clear that, while the normal baby is born with the potentialities to become a human being, man actually attains this only through association with his kind in the very earliest years."

"One of the strangest and at the same time one of the most versatile military vehicles yet tested is a tractor made by Minneapolis-Moline Power Implement Company. It pulled six-inch howitzers over almost impossible terrain, through mud and water 40 inches deep, and crashed through trees four and five inches in diameter, reports *Ethyl News.* The tractor was designated merely as a military high-speed prime mover, but the Army boys were quick to christen it the 'Jeep.' "

"The world has been kept well informed of the havoc wrought by insects, since winged or crawling pests are not likely to be overlooked, but the almost-as-deadly fungus works silently and out of sight. There is not a full-grown native chestnut tree left standing on the New England hills which, 40 years ago, were covered with these stately trees. Something introduced the chestnut blight and valuable timber stands were wiped out. The 'Dutch' elm disease is thus far classed as irremediable. The fungus of the disease is carried into the wood by a beetle, hiding so completely that treatment by fungicides is considered very difficult."

"Whenever electricity is in motion, it creates a magnetic field about itself. Therefore, *q.e.d.,* every electron in an atom creates its own magnetic fields—one for its orbital motion, one for its spin. We can leave the orbital effect out, because experiment shows that it has little or nothing to do with ferromagnetism. The spinning electron is thus the ultimate magnetic particle. Often the spins of the electrons in an atom add up to nothing at all. This is possible because the electron spinning clockwise cancels out the magnetic effect of a nearby electron whirling counterclockwise. But in ferromagnetic materials, instead of neatly counterbalanced plus and minus spins, we anticipate a marked excess of one kind over the other. And that is just the case."



A pneumatic flying machine

SCIENTIFIC AMERICAN

MARCH 1891: "Mr. Nikola Tesla has worked with dynamos giving as high as 25,000 alternations per second, and consequently has within his grasp a class of phenomena that are only hinted at so long as experiments are confined to the frequencies in ordinary use. An immense amount of energy is distributed through the medium surrounding the machine, and, in fact, the experimenter may almost be said to be working in the dielectric of a condenser. When incandescent lamps short-circuited by a bit of copper rod glow with intense brilliancy at some distance from the induction coil connected to the machine, and Geissler tubes, unprovided with any terminals whatever, spring into brilliant radiance, the experimenter suddenly awakes from his dream of electrical energy as a thing carried along a wire into the almost appalling consciousness that the energy in the dielectric is really the only thing with which he has to do."

"Mr. J. L. Balbi says: It is well known to the medical profession that every mental effort causes a rush of blood to the brain, and that the amount of blood depends on the 'intensity' of the thought; but rush of blood means a rise in temperature, and if we could measure this we would be able to determine, in a *rough* way, the 'power' necessary for the generation of any thought or mental effort. I make the measurement in the following manner: I have a head gear of some light, high-conducting (heat) substance. In its middle I fix a thermo-electric pile, and connect this to a sensitive galvanometer. By such a contrivance would we ascertain the 'brain power' of boys and girls, nay, even men, and thus be in a position to indicate in what direction their mental efforts ought to tend."

"This is a flying machine constructed by Mr. Lawrence Hargrave, of Sydney, N.S.W. It is propelled by an engine fed with compressed air, and, as will be seen from the engraving, which is from *Engineering,* the machine is a marvel of lightness and ingenuity. In a dead calm it flew 368 feet horizontally."

See how exciting perfection can be.

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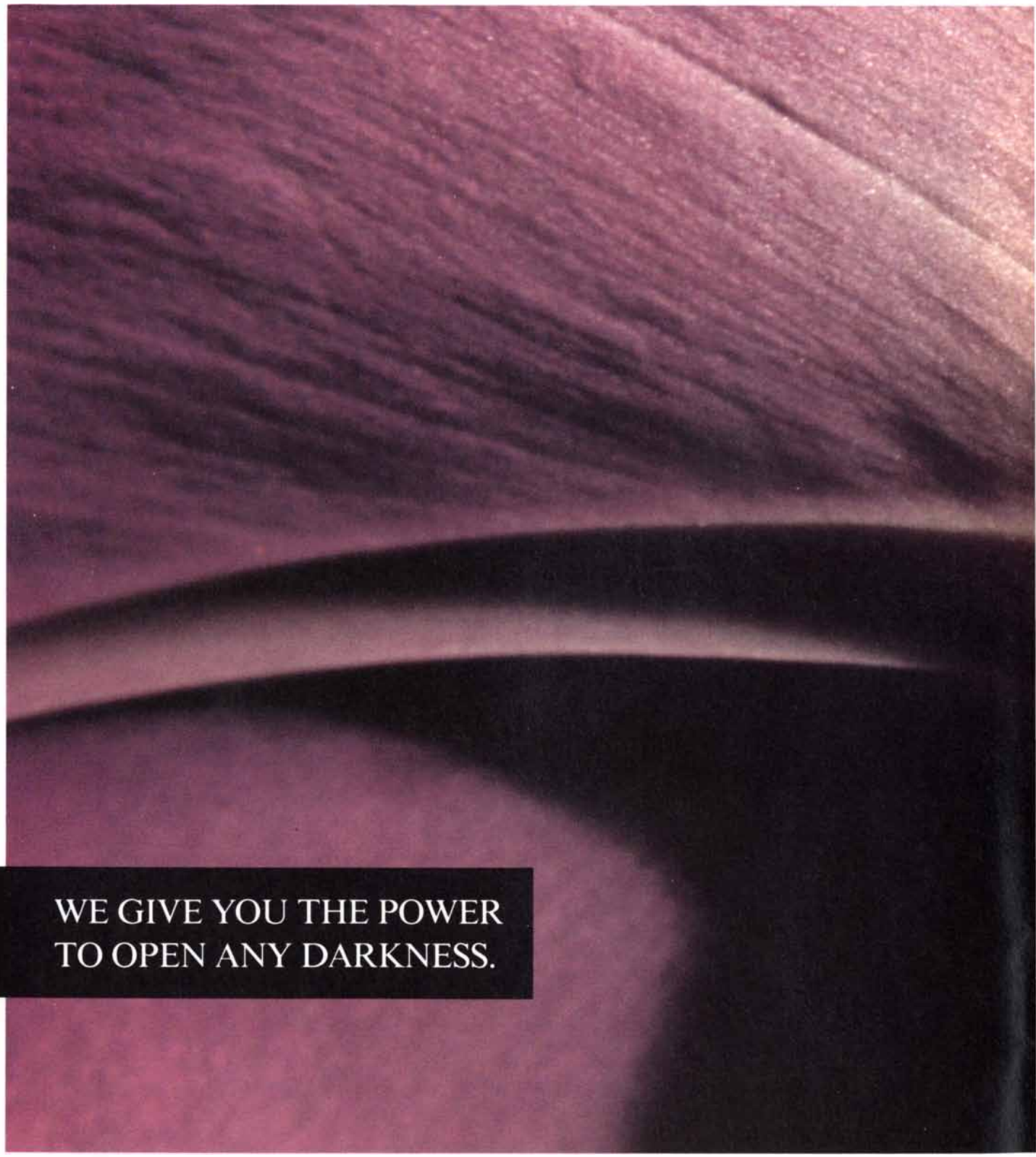

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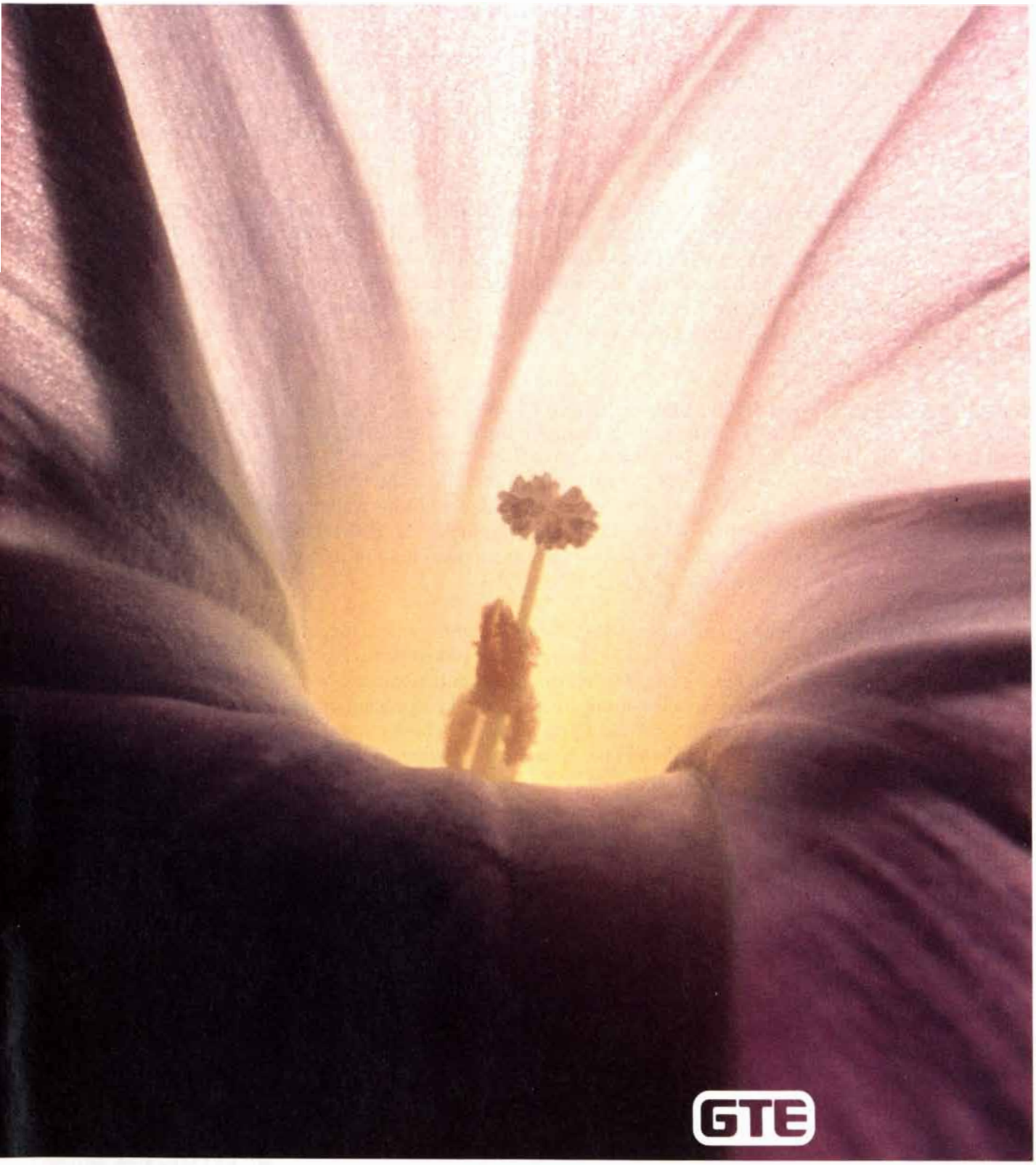

THE POWER IS ON

A new hydrogen maser "atomic clock" combines a compact size suitable for space applications with the highest long-term stability ever reported for this type of device. Developed and built by Hughes Aircraft Company for the U.S. Navy, the fully automated frequency standard is about 10 times more stable than currently-used cesium beam devices. Atomic clocks use the resonance frequency of an atom to provide a precise measurement of time, but use of hydrogen maser clocks in space has been limited due to their bulkiness. Other Hughes-built atomic clocks were developed for the Defense Department's NAVSTAR Global Positioning System.

An innovative computer program dramatically reduces the hours required to model the performance of new missile designs. Called Generic Missile Simulation (GEMS), the software, created by Hughes, cuts the evaluation time of new missile designs from six months to one to 20 days, depending on the complexity of the missile. The time saving is accomplished because GEMS contains a library of generic building blocks needed for missile system simulation. These building blocks are combined, or modified, as necessary to simulate a new missile design. In the past, each new design required its own, unique simulation software.

A thermal imaging system that turns night into day for crews of U.S. Navy SH-2F Light Airborne Multi-Purpose System (LAMPS) helicopters is aiding in the fight against drugs. LAMPS helicopters, equipped with the Hughes Aircraft Company's AN/AAQ-16 Hughes Night Vision System (HNVS), have been participating in law enforcement operations in support of the Coast Guard Carribean Squadron, flying hundreds of vital law enforcement surveillance sorties, sighting and reporting many suspect surface vessels which otherwise would have gone undetected. HNVS has been installed on a variety of U.S. Army, Air Force and Navy helicopters, and a derivative of the system has been selected for the U.S. Tri-Service V-22 Osprey.

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Death with Dignity

The Dutch explore the limits of a patient's right to die

Americans who are suffering from an intractable illness and want to end their lives can be driven to desperate measures. Last year a woman with Alzheimer's disease flew from Oregon to Michigan to meet a physician who had built a "suicide machine." She pulled the switch on the machine, giving herself a lethal dose of drugs, inside the doctor's Volkswagen bus in a motel parking lot.

Many others have no doubt followed the advice of the Hemlock Society, a leading advocacy group for humane euthanasia. It recommends taking an overdose of sleeping pills and then—just to be sure—placing a plastic bag over the head. "A clear plastic bag or an opaque one?" muses Derek Humphry, the Hemlock Society's founder, in a recent newsletter. "Loving the world as I do, I'll opt for a clear one if I have to."

Ideally, Humphry contends, physicians could help patients die painlessly and with dignity. But physicians in the U.S. are prohibited from administering or even (in most states) simply giving a lethal dose of drugs to a suicidal patient; withdrawal of treatment, which sometimes increases suffering, is the only legal option. In fact, although calls for "physician-assisted death" are increasing in the U.S. and Europe, only one country has begun allowing active euthanasia: the Netherlands. "It's a very pioneering effort," Humphry says. "People on both sides of the debate are closely watching it."

One leading advocate for—and admitted practitioner of—euthanasia is Pieter V. Admiraal, an oncologist and anesthesiologist at a Catholic hospital in Delft. He believes that, over time, the Dutch will demonstrate to the world that euthanasia can be "the last dignified act in the health care process." He points out, however, that the debate over who has a right to euthanasia and how it should be regulated is far from resolved in Holland. Terminating another person's life, even at the person's request, is still technically a crime, punishable by up to 12 years in prison.

Fish and sex ratios, cosmic X-ray puzzle, nitrogen-fixing wheat, black mortality

But beginning in the 1970s, a series of physicians, including Admiraal, openly violated the ban on euthanasia, spurring Dutch courts to set forth conditions that can serve as excuses for the act. The first and most important condition is that the patient be rational and request death repeatedly. The patient may receive euthanasia even if family members object. If the patient so desires, the doctor may not even inform the family of the patient's decision, Admiraal says.

A committee of the Royal Dutch Medical Association, which has issued guidelines supplementing or expanding on those of the courts, suggested four years ago that minors be allowed to obtain euthanasia over the objections of their parents. "Sometimes a 15-year-old child can have a mature judgment," a report by the committee stated, and "sometimes parents can have immature judgment." No such cases have come before the courts yet.

Another condition established by court rulings is that at least two physicians must agree that the patient's request is reasonable. A doctor may refuse to perform euthanasia or to approve of the act, but the Royal Dutch Medical Association has stipulated that he or she is then obliged—albeit ethically, not legally—to put the patient in contact with another physician.

In all cases, the patient must be suffering from "unbearable pain" with no hope of relief, according to the courts. But the patient's condition need not be terminal, and the pain can be mental as well as physical. In 1985 Admiraal gave a lethal injection to a woman who was in the advanced stages of multiple sclerosis but was not in imminent danger of dying. He was charged with murder but acquitted. More recently, prosecutors declined to press charges against a doctor who performed euthanasia on a woman paralyzed from the neck down.

Such cases—those in which patients are neither near death nor in great physical pain—are exceptional, Admiraal notes. Because Holland provides good care to the severely disabled, he says, they rarely seek an end to their lives. He estimates that 80 percent of the patients who request euthanasia suffer from terminal cancer.

A controversy has arisen recently over whether persons suffering primarily from mental rather than physical disorders have a right to euthanasia, according to Eugène P. R. Sutorius, an attorney who has defended Admiraal and other physicians prosecuted for euthanasia. Four years ago prosecutors decided not to try a psychiatrist who deliberately provided—but did not administer—an overdose of drugs to a man who had been institutionalized with severe depression and had repeatedly tried to kill himself. A similar case is now before the Supreme Court.

These cases have led to much agonizing over whether the mentally ill can be considered competent and in possession of free will, Sutorius says. "We don't want to discriminate against the mentally disturbed," he explains, "but everyone knows this can be very slippery." Admiraal doubts whether assisting the suicides of mental patients will, or should, become accepted. "I think we will hesitate forever," he says, "because there is always hope that we can cure these patients."

Only a physician may perform euthanasia. Admiraal recommends an injection of barbituates, which produces un-

Holland's Euthanasia Guidelines

- The patient must repeatedly and explicitly express the desire to die.
- The patient's decision must be well informed, free and enduring.
- The patient must be suffering from severe physical or mental pain with no prospect for relief.
- All other options for care must have been exhausted or refused by the patient.
- Euthanasia must be carried out by a qualified physician.
- The physician must consult at least one other physician.
- The physician must inform the local coroner that euthanasia has occurred.

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consciousness, followed by a shot of curare, which stops the heart and lungs. After death, the physician is required to inform the coroner, who in turn informs the local prosecutor. If the prosecutor suspects the death has occurred improperly, he may call for an autopsy and initiate a fuller investigation.

Approximately 150 cases of euthanasia are reported annually, but Admiraal says that many more cases probably go unreported. Estimates vary widely, but one commonly cited figure is 3,000 a year, or about 2 percent of the deaths occurring annually among Holland's 15 million people. If euthanasia occurred at that rate in the U.S., it would account for some 50,000 deaths a year.

Pro-euthanasia organizations in Holland contend that the ambiguous legal status of euthanasia, which gives prosecutors great discretion in initiating an investigation or pressing charges, discourages physicians from reporting. Klazien Sybrandy, founder of the Information Center for Voluntary Euthanasia, argues that the government should formally legalize euthanasia, replacing the vague guidelines of the courts with specific statutes. Such a move, she asserts, would encourage openness and so reduce the potential for abuse.

Others think such a step may be unnecessary and perhaps even inadvisable. "It wouldn't change much," Admiraal says. Sutorius worries that euthanasia might become "too mechanically done" if it is legalized. "You may take away some of the responsibility of individual doctors," he adds.

Has Holland set a good example for the rest of the world? Absolutely not, insists Richard Fenigsen, a cardiologist in 's-Hertogenbosch. Fenigsen argues that the acceptance of "voluntary" euthanasia (he invariably puts the term in quotes) will inevitably lead to the murder of those who are judged to be mentally or physically inferior and a burden to society. Such Nazi-like practices are already secretly occurring in Holland, Fenigsen claims, and have so terrorized the elderly and infirm that many are avoiding doctors.

Fenigsen has brought his message to the U.S. He has had articles published in the *Hastings Center Report*, an influential journal of bioethics, and the *Wall Street Journal*. He recently traveled to Washington State to attack an initiative to legalize voluntary euthanasia for the terminally ill that is expected to go before voters next November.

Yet Fenigsen's claims have been repudiated not only by Dutch authorities but even by some who share his distaste for euthanasia. "He's a wonderful Jewish Pole who went through hell" during World War II, says Teresa A. Takken, an ethicist at the Goleta Valley Hospital in Santa Barbara, Calif., and at the University of Utrecht, "but he exaggerates." Takken, a Catholic nun, thinks Holland's comprehensive health care and welfare system probably keeps requests for euthanasia to a minimum and makes the abuses envisioned by Fenigsen unlikely. But she contends that abuses could occur in countries that do not provide such care, notably the U.S. "We have no business even talking about euthanasia here until we have health care for all," she insists, "and even housing for all."

Corrine Bayley, an ethicist at St. Joseph Health System in Orange, Calif., agrees that economic considerations could corrupt decisions involving euthanasia in the U.S. She adds that American physicians generally have much shorter-term and less trusting relationships with their patients and so are less equipped to cope with requests for euthanasia. The litigiousness rampant in U.S. health care also poses a problem. Admiraal says he used to urge American physicians to test U.S. law by performing euthanasia according to the Dutch guidelines, "but they always tell me, 'No, no, no, we will be sued by some faraway relative or prosecutor.'"

All these factors would certainly complicate euthanasia in the U.S., acknowledges Margaret P. Battin, a philosopher at the University of Utah who like Takken and Bayley has studied euthanasia in Holland. "But I don't think the answer is to prohibit euthanasia," she remarks. "The answer is to change the U.S. health care system" so that abuses are less likely. Battin agrees with Humphry of the Hemlock Society that euthanasia should be a basic right. "The central issue is one of control," she says. "Doesn't a person have the right to determine the manner of his or her own death and to avoid suffering and pain?" —*John Horgan*

A Modest Proposal on Altruism

Why did Mother Teresa become a nun and dedicate her life to helping others? Why did a man in New York City's Central Park, on seeing a dog fall through the ice on a pond, jump into the water to save it? (Both man and dog died.) And why have hundreds of thousands of Allied soldiers risked their lives to liberate Kuwait, a strange and distant land?

Because they are docile and stupid. That, simplified and paraphrased a bit, is the message of an article in *Science* by Herbert A. Simon, a professor at Carnegie-Mellon University and an authority on psychology, computer science and economics (for which he won a Nobel Prize in 1978).

The acts above, Simon notes, are all examples of altruism, the sacrificing of one's own fitness, or reproductive potential, for that of others. For years, Simon has puzzled over how altruism could be made compatible with sociobiology. This school of neo-Darwinian thought, which traces the behavior of humans and other animals to the selfish urge to perpetuate genes, holds true altruism to be a maladaptive—and even illusory—trait. Individuals, sociobiologists argue, only help others who are closely related to them or who can bestow some benefit on them in return. But it seemed to Simon that many acts of altruism do not fit into these categories.

Simon finally concluded that altruism is a by-product of a more common human trait: docility. He notes that docility, which he defines as "receptivity to social influence," usually contributes greatly to the fitness of individuals. In other words, those who go along, get along.

Societies often exploit this trait by teaching people to do things that, while diminishing individual fitness, benefit the greater good—like paying taxes or enlisting in the army. According to a mathematical model devised by Simon, societies that foster altruism will thrive as long as the costs of altruism to individual fitness do not exceed the benefits from docility.

This scheme might be foiled if humans were truly shrewd creatures. Docile or not, we might calculate how various types of socially encouraged behavior affect our fitness and reject those that diminish it. There goes altruism. But humans are not very good at making such calculations, Simon argues, because we have "bounded rationality." That is a gracious way of saying that we are kind of stupid.

Simon acknowledges that his theory offers a somewhat cynical view of human nature. But that, he says, is an inevitable consequence of doing serious social science. —*John Horgan*

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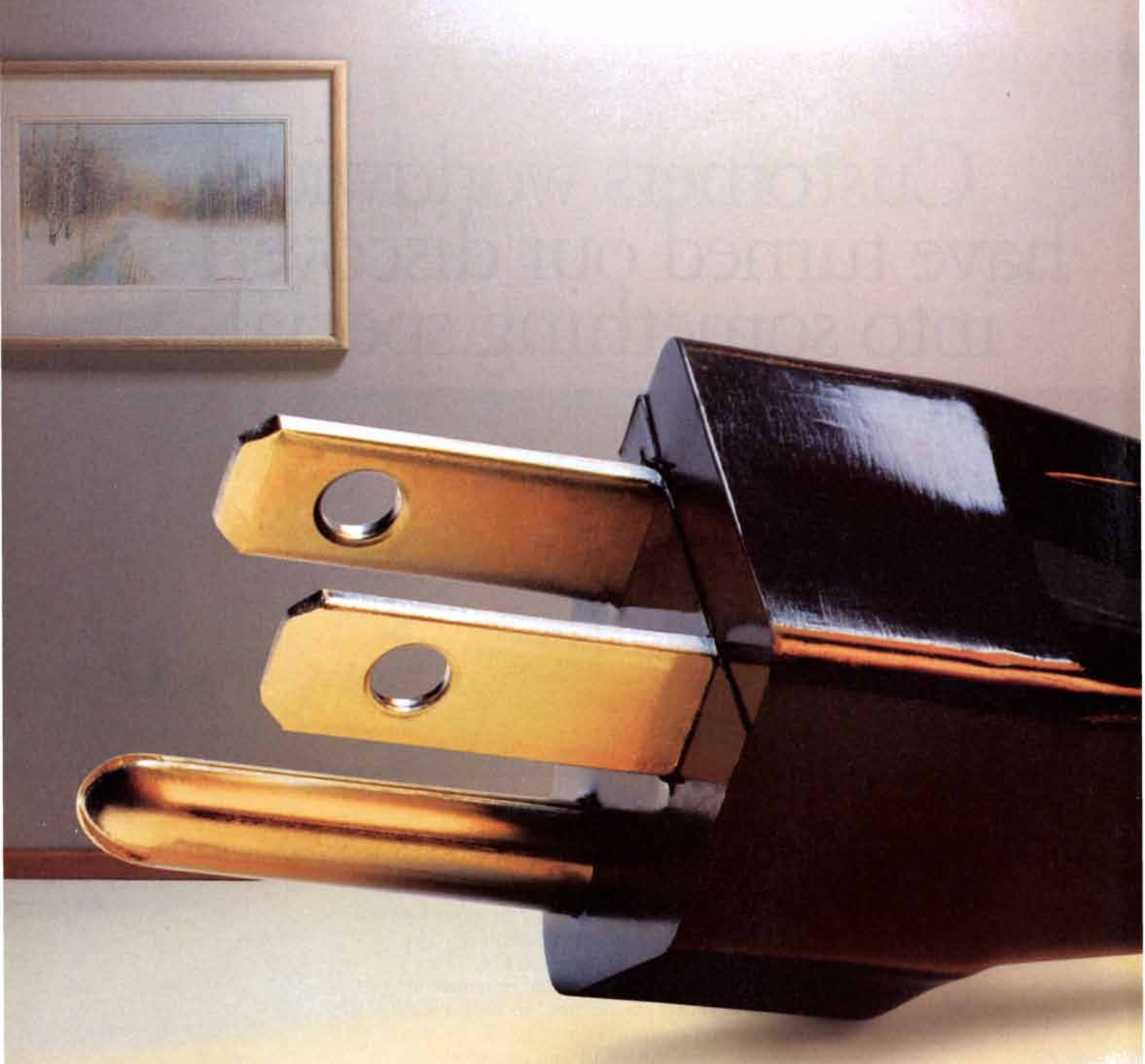

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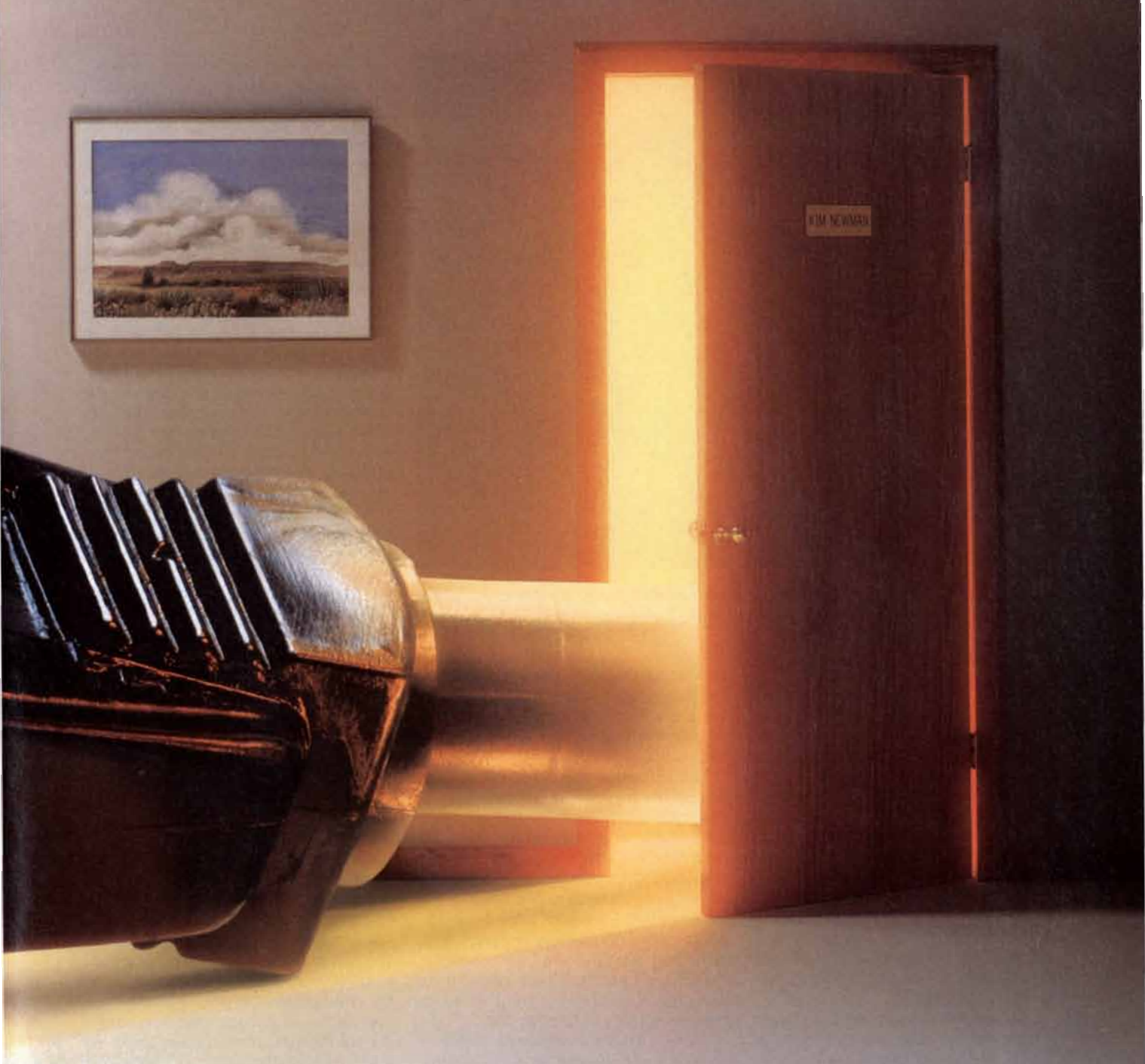

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ATLANTIC SILVERSIDE gender can be determined by water temperature, which varies by season and latitude. Photo: Al Grotell.

Sex and Silversides

An old theory gets fresh support

A small, slim, silver fish recently offered an old theory its first proof. The theory, proposed in 1930 by the famous geneticist Ronald A. Fisher, explains why most species produce equal numbers of male and female young (a sex ratio of 0.5). But while Fisher's theory has been well documented, no one had actually set about proving it—until the Atlantic silverside was recruited.

Using these common bait fish, David O. Conover, an associate professor of marine sciences at the State University of New York at Stony Brook, demonstrated the validity of Fisher's theory. "He empirically modeled the process of evolution toward that ratio," comments James J. Bull, an associate professor of zoology at the University of Texas at Austin.

Substantiating Fisher's theory after 60 years is no small accomplishment: the idea lies at the center of all sex-ratio theory. Fisher described what has come to be known as "frequency-dependent selection." Simply put—although Fisher himself did not put it simply, Bull says—whichever sex finds itself in the minority will also find itself in high demand as a sexual partner. This advantage favors the survival of genes producing that sex, ultimately redressing any gender imbalance in the population. "Now we don't have to be on uncertain ground anymore," Conover says.

The silverside was a perfect subject to test the theory. Sex in silversides is determined, in part, by the temperature of the water when the young are born. The low temperatures of the early season produce females; higher temperatures later on yield males. Atlantic silversides from different sites along the coast spawn at different temperatures, reflecting seasonal and geographical variations. Over the course of an entire breeding season, the ratio of males to females balances at one to one.

To test Fisher's principle, Conover and his colleague David A. Van Voorhees strong-armed the thermostat. "We can screw up the system by putting these fish in an artificial environment where the temperature is kept constant," Conover explains. The researchers monitored fish taken from several sites along the Atlantic coast and kept in laboratory tanks at constant temperatures for several generations.

If Fisher's theory did not hold, constant temperatures should lead to a batch of all males or all females. Instead Conover found a one-to-one sex ratio soon emerged. "It did so remarkably well," says Conover, who published his findings in *Science*. "It's almost embarrassing. I wanted to include a footnote saying this really did happen."

A population from South Carolina, for example, when held at a constant high temperature, reached the 0.5 ratio over the course of four generations. Fish from New York, also kept at a high temperature, reached this equilibrium after one generation. In each case, the 0.5 ratio was reached because the minority sex increased in the next generation—exactly what Fisher predicted.

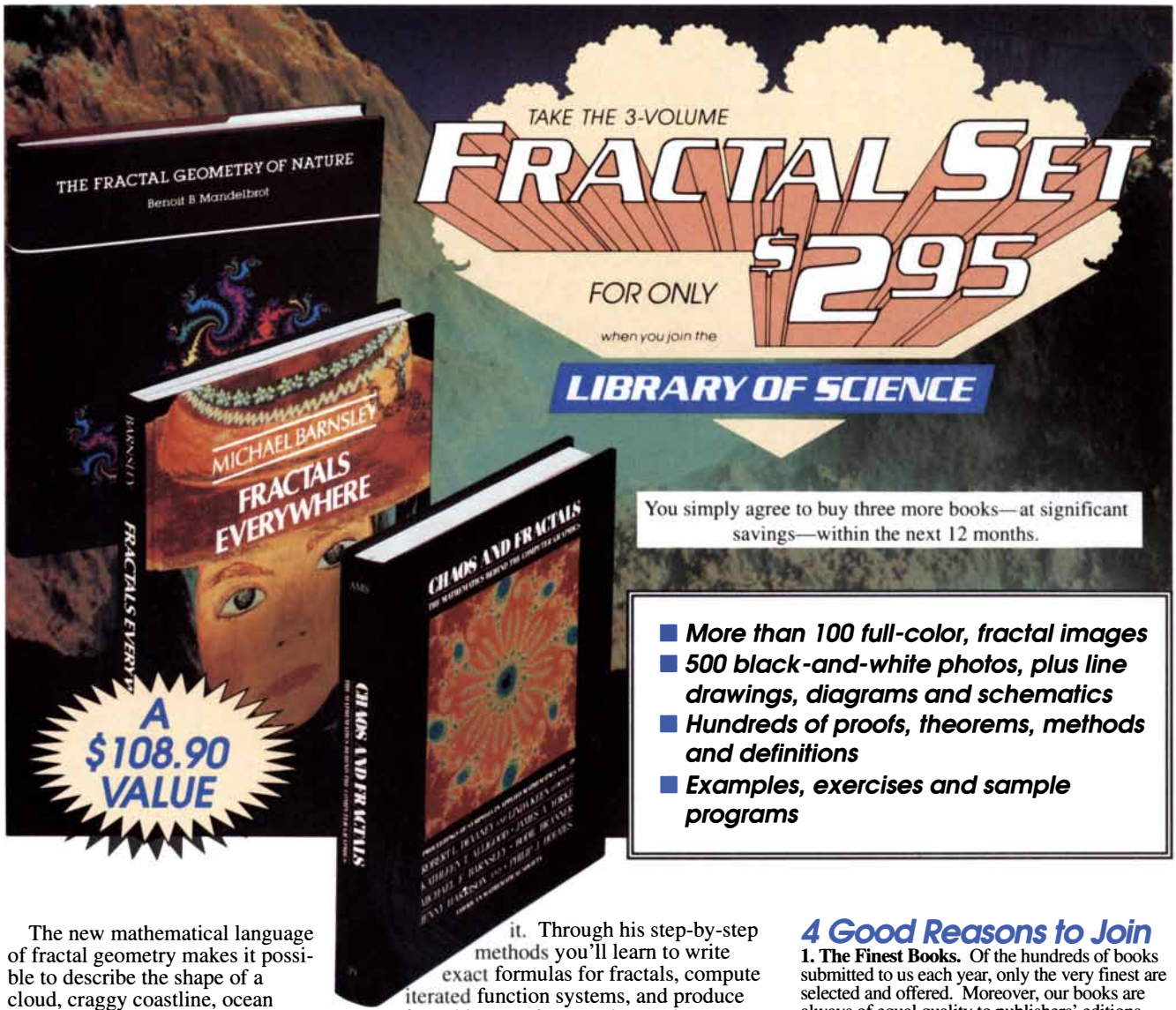
Bull and his colleague Eric L. Charnov, a professor of biology at the University of Utah, have offered an explanation of how the environment in which an offspring is produced can also affect sex-ratio evolution. Certain temperatures, for example, can improve the fitness of one sex over the other. Indeed, Conover has shown that Atlantic silverside females benefit more than males do from a longer growing period. Because bigger females are more fertile than bigger males, it stands to reason that females develop earlier in the season so they can feed for a longer time. (In contrast, even if the males ate more, their reproductive prowess would not be remarkably improved.)

In addition to giving Fisher's theory some legs to stand on, Conover's findings explore the genetic versus environmental control of sex in some species. For biologists, this issue has become one of pressing interest because of concerns about the greenhouse effect. Many have argued that species whose sex is determined by temperature could be wiped out if the climate changed dramatically.

Genetics, not the environment, appeared to be the controlling factor in determining the sex of silversides taken from Nova Scotia, where the natural temperature is consistently cold. The sex ratio of these fish held constant at one to one independently of the conditions in the laboratory. Conover and other scientists are now studying the precise genetic component of sex determination.

The silverside findings suggest that in cases in which genetic factors can adjust, or compensate, environmental changes could be weathered. But global warming may destroy species with a weak genetic component to sex, such as reptiles. Turtles, in particular, could be severely threatened.

Ironically, turtles themselves threaten Fisher's newly proved rule. These reptiles seem to violate Fisher's one-to-one sex ratio, and no one has quite explained why. After more than 10 years of working on turtles, Bull finally gave up. "You're talking to someone who is now working on bacteriophages because I couldn't answer that question," he says. *—Marguerite Holloway*



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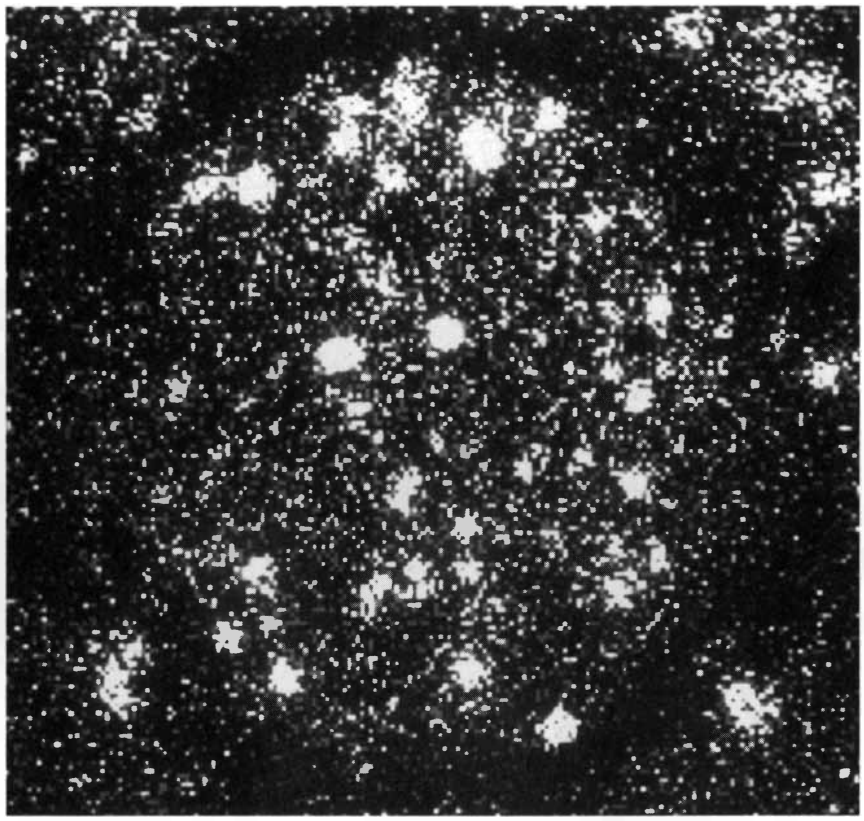


X-RAY BACKGROUND reveals its lumpy nature in this ROSAT *image. Most of the 40 distinct sources seen here have been identified as quasars.*

X-ray Riddle

Cosmic background is still unexplained

Even the most contentious people usually agree that the night sky is dark. Don't try arguing the point with an astronomer, however. In 1962 researchers discovered that when seen through instruments sensitive to X rays, the sky glows with a bright and oddly uniform intensity.

This pervasive radiation, rather unpoetically known as the diffuse X-ray background, has eluded easy explanation. Roughly 25 to 30 percent of the background has been attributed to quasars, tiny cosmic powerhouses that supposedly lie in the center of some galaxies. The origin of the rest has been a persistent mystery.

Two recent discoveries—one based on spanking new data, the other on a reevaluation of older findings—may put part of the mystery to rest. The results come from the *Roentgen Satellite,* or *ROSAT,* an X-ray astronomy instrument that is the fruit of a collaboration between the governments of Germany, Britain and the U.S. Since its launch some nine months ago, *ROSAT* has been mapping the sky with a sensitivity and resolution that far surpass previous X-ray instruments.

One of the goals of the mapping has been to resolve the X-ray background into discrete components and determine their nature. On January 15 at the annual meeting of the American Astronomical Society in Philadelphia, Joachim Truemper and Guenther Hasinger of the Max Planck Institute for Extraterrestrial Physics told scientists that *ROSAT* had revealed far more quasars than could be detected before—about 100 quasars per square degree. This implies the presence of about four million quasars over the whole sky, enough to account for 40 percent of the X-ray background, Hasinger estimates.

Even more intriguing, *ROSAT* has detected extended blobs of X-ray emission that lie between the discrete X-ray sources. Hasinger and Truemper propose that these blobs are actually clusters of quasars so distant that *ROSAT* cannot separate the emissions of individual ones. Assuming the universe is about 13 billion years old, these clusters appear to be some eight to 10 billion light-years distant and 15 to 30 million light-years across.

This is troubling news for cosmologists. They already have their hands full explaining how clumpy structures of galaxies could have evolved from a presumably smooth big bang. The existence of large, organized clusters of quasars "would pose an even bigger problem for big bang cosmology," Hasinger notes.

Yet quasars still can explain only about 50 percent of the X-ray background. At the Philadelphia meeting, Antonella Fruscione, Richard Griffiths and John MacKenty of the Space Telescope Science Insitute in Baltimore presented a possible source for some of the missing X rays. Combining old data from NASA's *Einstein X-ray Telescope* and the *Infrared Astronomical Satellite* with infrared measurements of their own, they suggest that 30 percent or more of the background comes from so-called starburst galaxies in which stars are forming at an extraordinary rate, triggered perhaps by a close encounter with a galactic neighbor.

Some massive newborn double stars in these galaxies rapidly evolve into X-ray binaries, systems in which one object—either a neutron star or a black hole—slowly consumes its companion, releasing torrents of X rays. As a result, starburst galaxies would be powerful X-ray emitters, and large numbers of these objects spread around the sky could produce much of the observed background.

There are still problems to overcome before the riddle of the X-ray background is solved, warned Stephen S. Holt of the Goddard Space Flight Center. Holt, the U.S. project scientist for *ROSAT,* points out that the spectrum of the background at very short wavelengths is fundamentally unlike that of quasars, and so quasars may have little to do with this component. Starburst galaxies "are a better way to fill in the X-ray background" at these wavelengths, he thinks. The *ROSAT* results are as yet inadequate to distinguish whether the observed blobs are clusters of quasars or clusters of starburst galaxies.

Or the blobs may be something else entirely. "Hasinger sees clumping, but the clumps are not necessarily composed of condensed objects," Holt says. In fact, the spectrum of the X-ray background closely resembles that of a thin, hot gas. Another satellite, *COBE* (the *Cosmic Background Explorer*), found no evidence of such a gas, but if the gas is concentrated into small clumps, *COBE* would not be able to detect it.

Could it be that the blobs observed by *ROSAT* are such hot gas clumps and not really quasar clusters after all? "It's totally ad hoc," Holt chuckles, "but it is possible." —*Corey S. Powell*

Down for the Count

The first estimate of protein components may not add up

Only 92 elements compose all earthly materials. It takes just four nucleotides to write the language of heredity in DNA. So how many different pieces are needed to assemble the tens of thousands of proteins made by living things? Seven thousand or so should do it, estimates Nobel laureate Walter Gilbert and his two Harvard University colleagues.

That is certainly an intriguing answer to a question that has occupied some scientists since the 1970s. At that time, biochemists began speculating that all proteins are crazy quilts of distinct modules—short amino acid sequences with specific functional and structural properties. Some biologists and chemists, however, are unimpressed by the Gilbert group's methods. Russell F. Doolittle, a protein researcher at the University of California at San Diego, has become the most vocal critic of the work, which he maintains is invalidated by many serious errors.

The idea that proteins were modular received a boost in 1977, when researchers discovered that the genes of all organisms more complex than bacteria are broken into separate coding

The Leading Theory of the Universe Survives Another Attack

Is the cold dark matter theory going under? Since the early 1980s the theory has been the leading explanation of how galaxies evolved after the big bang, but in recent years it has been encircled by a growing number of skeptics. Now a new galaxy survey has delivered another blow—fatal, some say—to the theory. The sharks are closing in.

But the theory is nothing if not resilient. Adherents acknowledge that it has been hurt by recent observations of clustered galaxies and that certain aspects of it will almost certainly need corrective surgery. But they contend that the theory has also been strengthened by other new findings regarding the mass of the universe. "We have no falsification of the basic tenets"—yet, declares Carlos S. Frenk of the University of Durham in England.

The theory holds that as much as 99 percent of the mass in the universe is made of some type of dark (invisible) and cold (slow-moving) matter. All the stars, galaxies and other hot, glowing objects that can be seen through telescopes are just whitecaps on an inky sea.

Doubts about this scenario have been building for several years. Astronomers could find only a fraction of the dark matter predicted by the theory. And while the theory suggested that matter should be scattered fairly smoothly through space, observations revealed galaxies clumping together in vast clusters surrounded by even vaster voids. Still, many cosmologists continued to view cold dark matter as the best explanation of the cosmos.

Then in January a group reported in *Nature* that a survey by the *Infrared Astronomical Satellite* (*IRAS*) revealed galaxy clumping on a scale too large to be accounted for by the standard version of the cold dark matter model. Frenk and other proponents of cold dark matter were in the group.

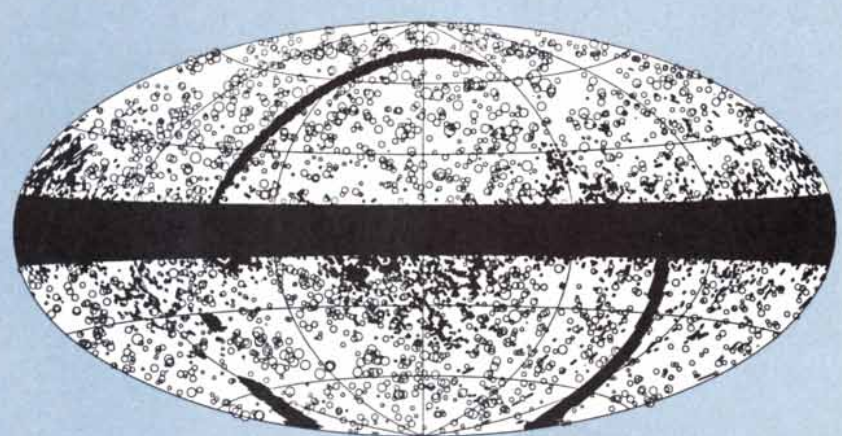
Noting this fact in an accompanying article, a *Nature* staff writer proclaimed: "Cold dark matter makes an exit." The *New York Times* spread that message further in a front-page story announcing that cold dark matter "is being discarded by some of its staunchest advocates." But Frenk says the press reports greatly exaggerated the paper's conclusions. He and his colleagues had stated that only one version—albeit the simplest, most popular one—of the cold dark matter theory needed to be discarded. Modified versions, Frenk asserts, which have different assumptions about the distribution of dark matter, may still work.

Moreover, the *IRAS* data support a key cold dark matter tenet, according to Nick Kaiser of the University of Toronto, another author of the *Nature* paper. By measuring the motions of the galaxies, Kaiser and Frenk were able to estimate the gravitational forces acting on the galaxies and thereby the density of mass in the universe.

Their calculations suggested that the universe contains much more matter than is visible—in fact, almost the same amount predicted by the cold dark matter model. "There is actually a consensus about this," Kaiser says, noting that Edmund Bertschinger of the Massachusetts Institute of Technology and others have arrived at similar conclusions.

Recent measurements of the masses of spiral galaxies provide still more evidence for dark matter. Dennis F. Zaritsky of the University of Arizona and others examined the motions of small "satellite" galaxies orbiting 40 or so spirals, including the Milky Way. The motions of the satellites indicated that the spiral galaxies are embedded in "halos" of dark matter at least 20 times broader and 100 times more massive than the visible core.

On the other hand, German astronomers recently announced that observations of quasars by an orbiting X-ray observatory were not compatible with some versions of the cold dark matter theory (see photograph on opposite page). The sharks are still circling. —*John Horgan*



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One rather opinionated participant firmly maintains that the best single malt Scotch whisky comes from the Highlands. Another is adamant in support of the Orkney Island whiskies from the far north. For another, nothing but a softer, sweeter Lowland malt will do, while a staunch advocate of the bold, peaty flavor of Islay insists on being heard. Being Scots, each remains convinced that his opinion is correct, in perpetuity. Of course, when all is said and done, many prefer a blended Scotch like Ballantine's Finest. Because Ballantine's blends 42 of the top single malts from all over Scotland, the taste of the Finest tends to resolve disputes in a most diplomatic manner.

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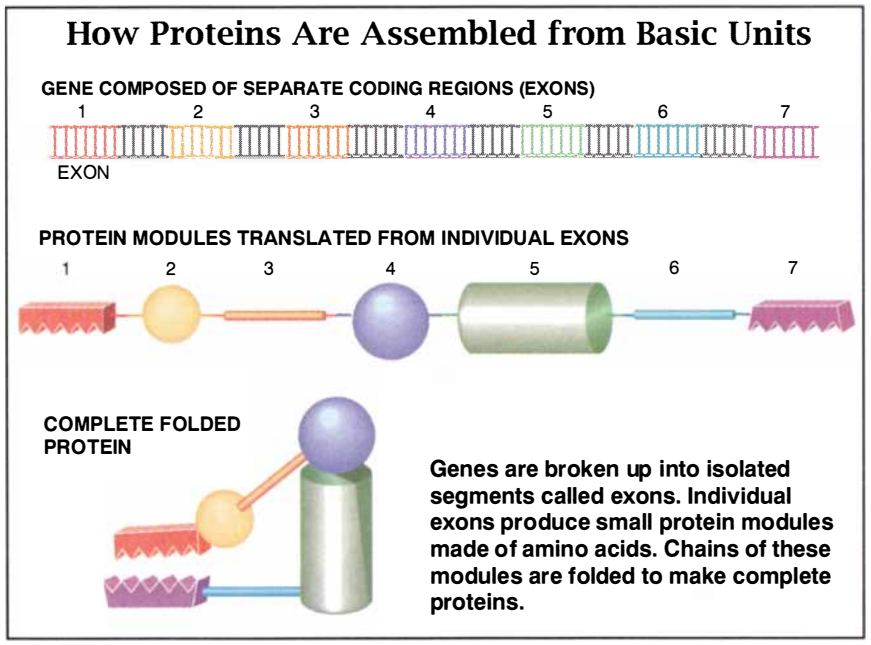

elements called exons. Almost immediately Gilbert proposed that exons were the genetic basis for the modules and that the evolution of complex proteins could proceed rapidly through the reshuffling of the fundamental exon set.

Two years ago Gilbert, molecular evolutionist Robert L. Dorit and computer scientist Lloyd Schoenbach set out to estimate roughly how many different exons might exist as a clue to how much protein diversity there is. Working from the assumption that today's exons descended from ones that arose billions of years ago, Gilbert's group decided to look for family resemblances. The researchers therefore checked for similarities in the amino acid sequences encoded by pairs of exons in dissimilar proteins. The number of matches they found would be statistically related, in theory, to the size of the exon universe.

After performing millions of exon comparisons, the researchers identified 14 pairs that they claim show significant similarities. They then calculated that the level of matching suggested a universe of 56,000 randomly mixing exons according to one statistical analysis or 950 by another. By taking a geometric mean of those numbers—a step that makes some other scientists uneasy—Gilbert's group arrived at their estimate of 7,000. "I'm happier thinking of [the estimate] as a bracket rather than a single number," Dorit says. "The compelling part of the story is that our upper and lower limits are both pretty darn small."

They are small compared with the number of possible exons. For a short 40-amino acid structure, there are 10^{52} variations. "But that's a straw man," Doolittle insists: evolutionists already assume proteins descended from relatively few components. Previous educated guesses about the exon universe by other researchers have often set it at 1,000 members or fewer.

Moreover, Doolittle argues that the Gilbert study has a major conceptual flaw: no matter how different two sequences may seem, it is impossible to be sure that they are not related. Completely dissimilar pairs of exons may only have diverged more widely from their common ancestor. Doolittle says that any statistical approach like Gilbert's is doomed because it cannot distinguish archetypal exons from ones whose relation to one another is lost in remote history.

Even on its own terms, Doolittle thinks the Gilbert study is defective. He charges that the researchers did not adequately purge their 1,255-exon data base of sequences that would skew the results. Several of the 14 exon matches found by the study involve related proteins that should have been excluded. In effect, those exons may match because they are the same exon, counted twice. Another matched pair—an exon from a keratin protein and one from an albumin—is misleading because the similarity is much more likely to derive from functional constraints on the proteins than from common exon ancestry.

If fewer than half of the 14 matched pairs are truly significant, as Doolittle suspects, then according to the Gilbert group's methods the upper boundary on the exon universe would rise to a half million or more. But Doolittle's point is even stronger. He contends that Gilbert's estimate is completely meaningless because unrecognized divergences or convergences could lower or raise the numbers unpredictably.

"We have some very able critics," Dorit admits. "Because this is the first formal attempt and because we are trying to plumb some deeply hidden aspects of evolution, there are lots of pitfalls." Nevertheless, he and his colleagues defend their general methods and conclusions. They are now extending their work by analyzing a larger—and perhaps better screened—data base. Dorit explains that almost three times as many protein sequences are available today as when they began their project. This time they also hope to include protein sequences from bacteria and other primitive organisms without cell nuclei, a group that was not included in the previous study.

"Our work is a prediction," Gilbert explains. "As more genes are added to the data base, we should find exons falling into the patterns we predict are there. Within five years, we should be able to identify all the primitive components and see how proteins are fitted together from them." By that time perhaps it will be clear whether they actually have identified the fundamental protein elements of the earliest organism or, as Doolittle suspects, a red herring. *—John Rennie*

Guessing Game

The EPA tries to decide if there's harm from ELF

Uncertainty, mystery, contradiction, fights over turf and accusations of bias. The argument over whether extremely low frequency (ELF) electromagnetic fields from power lines might cause health effects has them all. Until now, the majority of the studies have been funded by the Department of Energy and the Electric Power Research Institute, a research arm of the utilities. Although both have concluded that ELF can have biological effects, critics charge that their research reflects a pro-utility bias.

Now the Environmental Protection Agency has decided it ought to have an opinion on the specific question of whether such fields might cause cancer. The agency has produced a draft study that concludes there are insufficient data to decide. So nobody expects to find any hard answers anytime soon. But the EPA's entry into the long-running and acrimonious debate has moved the issue from the back

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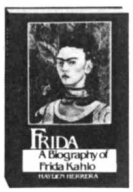

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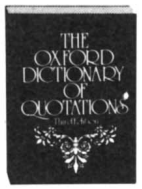

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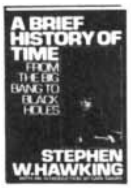

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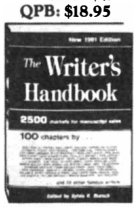

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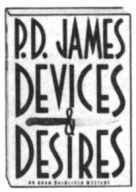

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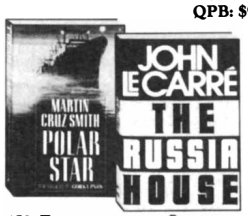

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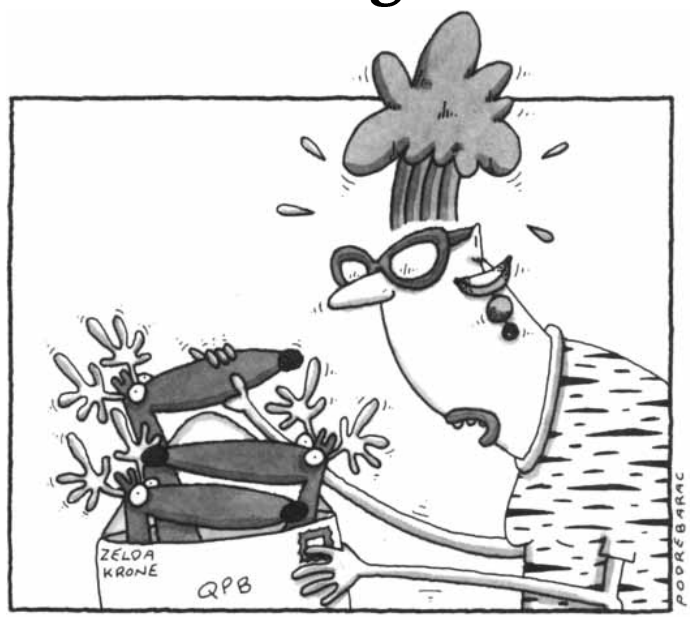

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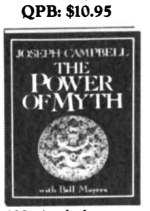

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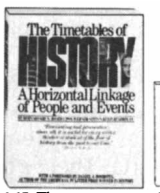

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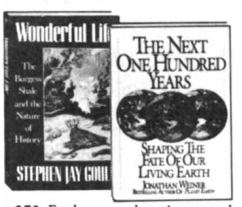

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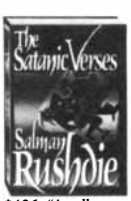

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to the front policy burner in Washington, D.C.

In January the agency attempted to refine its thinking by holding three days of hearings before a special committee of outside experts. Even before the politically charged hearings started there was trouble. President George Bush's science adviser, D. Allan Bromley, offered, uninvited, his own list of candidates for the committee, an offer the EPA declined.

When the hearings began on January 14, physicists, cancer biologists and epidemiologists took turns with a U.S. representative, distraught citizens and the mayor of Scranton, Pa., to make their arguments. Big-name scientists skeptical about the possibility of a link, retained by a consortium of utilities known as the Health Effects Group, were much to the fore.

Physicists on the witness stand explained that such weak fields could not affect cells, because the fields at cell surfaces would be far smaller than those present naturally. Citizens expressed their alarm over the now famous studies that seem to show an increased risk of leukemia in children who lived near high-current transmission lines. Epidemiologists rehearsed their warnings about how unconscious bias or unrecognized factors might explain the association. One proposed explanation: carcinogens emitted by traffic on highways that lie near high-power lines.

Tempers occasionally flared, and one or two people had their knuckles metaphorically rapped. David Korn, chairman of the National Cancer Advisory

A Nitrogen Fix for Wheat

Nitrogen makes up 80 percent of the atmosphere and is an indispensable nutrient for plants. But most species cannot tap the supply. Legumes such as beans and peas have a rare advantage. They, and a few other plants, play host to specialized root-dwelling bacteria that "fix" atmospheric nitrogen by converting it into ammonia, which the plants can then use. The dominant grains of human agriculture—rice, wheat and corn—lack that ability.

Now agricultural researchers at Australia's University of Sydney believe they have achieved the long-sought goal of infecting a nonleguminous food crop with nitrogen-fixing bacteria. Their work on wheat suggests it may be possible to produce high crop yields less dependent on chemical fertilizers.

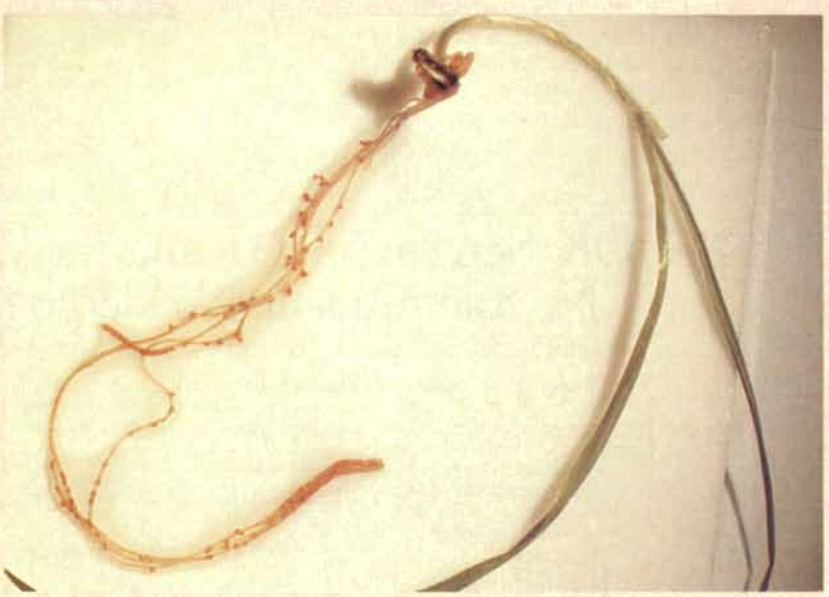
A. M. Zeman, Yao-Tseng Tchan and Ivan R. Kennedy were following up on earlier research by Yan-Fue Nie, then at Shandong University in China. The nitrogen-fixing bacteria of legumes, *Rhizobium,* live in nodules in the plants' roots, where they receive nutrients in return for the ammonia. Nie found that low concentrations of the herbicide 2,4-D, which softens cell walls, caused wheat seedlings to develop swellings on their roots that resembled the nodules of legumes. But neither he nor others could infect the artificial nodules with *Rhizobium.*

Zeman, Tchan and Kennedy decided to find out whether other nitrogen-fixing bacteria could do better. They first reproduced Nie's nodulelike structures, which they call *para*-nodules. Then they exposed the 2,4-D–treated wheat seedlings to *Azospirillum,* a nitrogen-fixing bacterium that lives freely in soil.

The bacteria infected the *para*-nodules. Using an indirect chemical test, the researchers then found "highly reproducible" and substantial nitrogen fixation in the treated seedlings—but not in untreated ones. "It is reasonable to say nitrogen is being fixed by *Azospirillum,*" Tchan concludes. Moreover, like *Rhizobium* in legumes, *Azospirillum* in *para*-nodules seems to be "closely linked to the normal metabolic processes of the plant," Kennedy notes. When photosynthesis in the seedlings was chemically inhibited, the evidence for nitrogen fixation also disappeared.

Kennedy and his collaborators have started to describe their research at meetings, but few biologists outside Australia are yet familiar with it. The findings, although surprising, are "not inherently implausible" and "need to be looked into," comments Charles Hagedorn, a professor of agronomy and an expert on nitrogen fixation at Virginia Polytechnic Institute and State University in Blacksburg, Va. The Australian researchers are now using radioactive nitrogen as a tracer to find out whether seedlings can incorporate nitrogen fixed by *Azospirillum.*

Kennedy cautions that there are many differences between *Azospirillum* and *Rhizobium.* For example, *Azospirillum* seems to infiltrate between cells, but *Rhizobium* enters them. And Kennedy does not yet know whether *Azospirillum* infection can persist for a long time in *para*-nodules, which would be necessary to benefit a crop. He suggests that selective breeding and genetic engineering might eventually lead to field applications but emphasizes that they are "10 years away." —*Tim Beardsley*



NITROGEN-FIXING nodules are visible on the roots of a treated wheat seedling.

Panel and a member of the "no mechanism has been identified, so I don't believe it" school, was told tartly by one committee member to read the relevant literature before venturing any further opinions on whether weak fields have biological effects. Committee members reminded more than one witness that sharks and other animals navigate by low-intensity fields.

Others managed to inject a bit of levity. Robert K. Adair, a Yale University physicist and founding member of the "I don't see how it could happen, so it can't happen" school, disagreed with committee chairperson Genevieve Matanoski about a study by Samuel Milham, Jr., of Washington State's Department of Health that found high cancer mortality in amateur radio operators. "He's a very good epidemiologist," Matanoski muttered. "I'm sorry to hear that," Adair retorted. Solomon M. Michaelson, a physicist at the University of Rochester, suggested the anxiety generated by "overinterpretation of data" could be "a greater biological hazard than the fields we're talking about."

Disagreements abounded over what to make of inconsistent and puzzling findings. The EPA's approach was to consider the "weight of evidence" from laboratory studies employing tissue cultures and animals, as well as epidemiological surveys. The agency declined to throw out studies with clear weaknesses—for example, those that used proximity to a substation as a rough measure of ELF exposure. And the EPA tolerated the notion that responses to fields might occur only in particular bands of intensity and frequency.

The weight-of-evidence approach was crisply dismissed as producing "shoddy data and bad science" by Eleanor Adair, wife of Robert and a researcher at the John B. Pierce Laboratory of Health and the Environment in New Haven. She was not alone. But M. Granger Morgan, head of the department of engineering at Carnegie-Mellon University, asked, "In public policy, should standards be the same as in basic research?"

Usually in such policy debates the one point everyone can agree on is the need for more research. The ELF-cancer debate is unusual. Eleanor Adair, for one, is so underwhelmed by the "very poor" science in the field that she would rather see the big money go somewhere else. But serious federal funding is not likely to be forthcoming unless the EPA and other agencies decide there is a clear case to settle. When will that be? A final version of the EPA document is, according to the latest estimate, at least a year away. *—Tim Beardsley*

Grim Expectations

Life expectancy of blacks is sliding

Since early in this century, the life expectancies of whites and blacks had been converging steadily. But the 1988 numbers, the latest from the National Center for Health Statistics, indicate an ominous reversal of that trend: the gap widened because the life expectancy for black Americans declined throughout the mid-1980s. "We're seeing a pattern that we've never seen before," says Harry Rosenberg, chief of mortality statistics at the center. "The life expectancies of the two major race groups are diverging."

In 1910 the difference between black and white life expectancy was 15 years. By 1984 it had closed to 5.6 years. Since then the difference has increased 14 percent, to 6.4 years. According to the new data, the life expectancy of a black person born in 1988 has dropped to 69.2 years—its lowest point in seven years. Whites, meanwhile, can expect to live to 75.6 years.

Age-adjusted death rates, calculated to eliminate the effects of aging in the overall population, currently stand 50 percent higher for blacks than for whites. "Heart disease, cancer, stroke—the big-ticket items—account for the major portion of the difference," Rosenberg says. These conditions, which cause more than 60 percent of all deaths for both races, affect the black population 30 to 90 percent more severely than the white population.

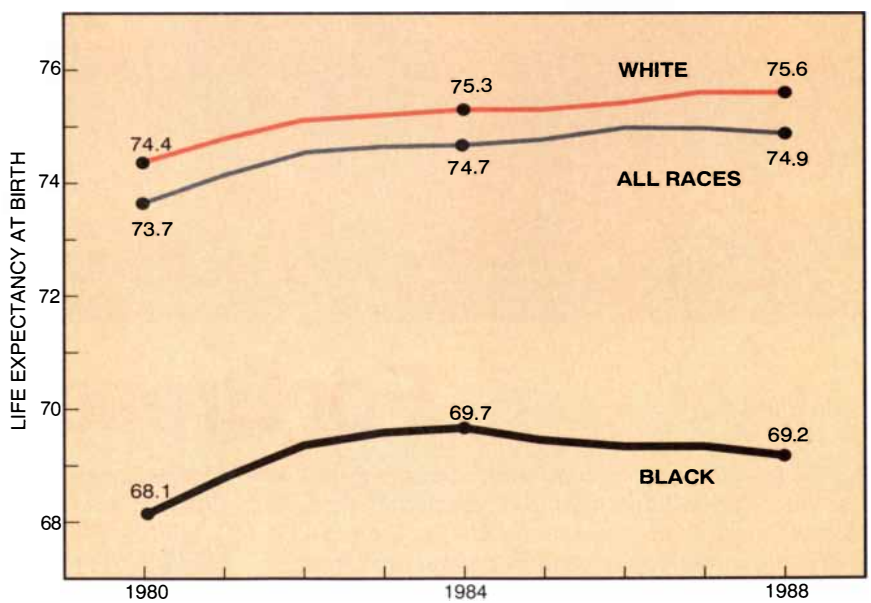
Yet it is not these diseases that are primarily causing the divergence in life expectancy seen since 1984. Deaths from these three causes have been steadily declining, and for the black population such gains "are still moving in a direction that parallels those of the white population," Rosenberg observes.

Then why the divergence? Homicide, Rosenberg says. Death rates for homicide and legal intervention (which represents the handful of deaths caused by police activity, about 1 to 2 percent in the category) among blacks exceeded that for whites by 6.4 times. Hardest hit are black males 15 to 24 years of age. Indeed, "the major thrust [for the widening gap] comes from the young black male population," Rosenberg points out.

Because the homicides are concentrated in poor urban areas, researchers have tried to determine the extent of the role that socioeconomics plays in the different rates. Poverty runs about three times higher in the black population than in the white, and the median wealth of white households exceeds that of black households by more than a factor of 10, according to Census Bureau statistics. "When you control for socioeconomic status," says W. Reynolds Farley, a sociologist from the University of Michigan at Ann Arbor, "you ought to find that blacks and whites have the same homicide rates."

But researchers who have tried to correct for economic levels found that "there seems to be an important, independent effect" based on race, asserts Farley, who studies black-white differences in U.S. society. Some possi-

The Decline in Black Life Expectancy



SOURCE: National Center for Health Statistics

ble causes are cited in a recent report on black homicides from the Centers for Disease Control.

The CDC study points to such factors as ready access to firearms, drug trafficking, racial discrimination and possibly even an acceptance of violent behavior in those communities with high homicide rates. Contrary to the common perception that most homicides result from random violence, more than half of all homicides are committed by persons known to the victim, according to the report. "It's a touchy area," Farley adds.

No one has yet been able to examine race and economics separately in mortality studies. Death certificates currently do not contain sufficient information, such as the wealth of the deceased. But that will change in the next few years. The National Heart, Lung and Blood Institute is compiling a national data base that will contain more detailed population characteristics, including income and education level. Most states have already added educational attainment to death certificates since 1989, and because income strongly correlates with education level, Rosenberg thinks that "certainly in two years we ought to be able to begin looking at some of these problems by socioeconomic status." —*Philip Yam*

PROFILE: SUPERCOMPUTER SOLO

Toshio Shimada seeks a different path to parallelism

In Japan, where rigid hierarchies are a way of life and bucking the trend is discouraged, Toshio Shimada is not a member of the crowd. For more than a decade, Shimada has bet his career on a radical hardware and software design for a very high performance computer. "Everybody is thinking about [conventional] von Neumann computers," declares the 45-year-old computer designer, "but I want to do different research."

As chief of the computer architecture section at the Electrotechnical Laboratory in Tsukuba, Japan's government-backed and -planned Science City, Shimada has had both the opportunity and the funding to carry on this crusade. But even if his technological gamble pays off, he will still face an enormous obstacle: convincing one of Japan's supercomputer manufacturers to put the idea of "dataflow" parallel computing into practice.

Shimada was not always so driven to be different. Like many young Japanese, he cultivated a taste for mathematics in elementary school and eventually won a spot as a graduate student in Japan's most respected university, the University of Tokyo. Yet as he pursued his studies in industrial control engineering, Shimada became troubled by the gulf he saw between theory and practice in factories. "I wanted to study a more abstract field," Shimada recalls. He chose computer science.

After earning a master's degree in applied mathematics and measurement, Shimada joined the Electrotechnical Laboratory, the country's oldest and most prestigious research facility. There researchers were thinking about the long-term future—and potential bottlenecks—of high-performance computers. Shimada immediately set to work studying the possibilities for parallel computers, which rely on a large number of simple processors working in harmony to solve a problem. These promise to perform complex computations more rapidly than conventional computers, in which a single processor performs every operation in series.

The pivotal experiences that would shape Shimada's attitudes toward research and focus his career came about two years later. Beginning in the sum-

mer of 1980, he spent a year's sabbatical at the Massachusetts Institute of Technology, working with computer scientists, including Jack B. Dennis and his colleague Arvind.

In Cambridge, Shimada was struck by the open atmosphere, which contrasted sharply with the aloof system of seniority found in Japanese academia and companies. Shimada remembers going to a laboratory late one evening when most offices were closed and finding Dennis hard at work at a computer terminal in a darkened room. "In Japan, it is rare that a great scholar would still be doing research work," he says. "I was much impressed."

More important, Shimada became entranced with a computational approach, called dataflow, which had been proposed several years earlier by Dennis and Arvind. They "were doing very creative work," Shimada recalls with enthusiasm. To Shimada, the dataflow technique was "very clean, clear."

When Shimada returned to Japan, he began his energetic campaign to translate dataflow into a working computer. "I guessed that we could make some nice hardware to execute the model," he says. Although a few research groups in the U.S. and in Europe had attempted to build dataflow prototypes, Shimada's project became the most ambitious and lengthy.

On a whiteboard in his spacious office, Shimada sketches a diagram of dataflow that looks much like a backward chain reaction, which starts with many atoms and condenses down to one. In his model, however, every atom is a node, or processing element tied to a memory unit. Two pieces of data converge on each node, which then "fires," carrying out a specific calculation and generating a result. This number in turn becomes an input to the next level of nodes.

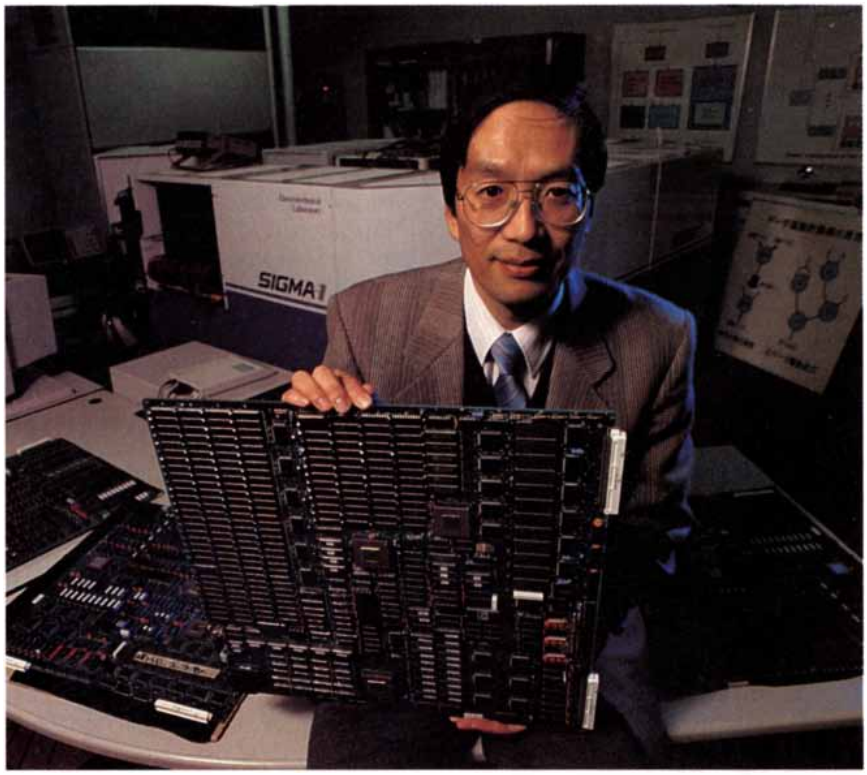
Shimada is far from alone in his quest to build a parallel computer. Other computer designers, particularly in the U.S., are also turning to massively parallel architectures. The key difference lies in the computational models at the heart of the various systems. The computational model is critical because it dictates how a programmer must write software to use the machine efficiently.

The most widely recognized computational model at this point may be the data parallel scheme that is being used by companies such as the Thinking Machines Corporation in Cambridge, Mass. In these computers, every real or "virtual" processor (which exists logically but not physically) is associated with a datum. A single instruction is broadcast to all processors, which then carry out operations on their local data.

Shimada argues that the dataflow model neatly skirts problems encountered by such massively parallel approaches. For example, coordinating the operations of many processors can be tricky. Dataflow avoids explicit synchronization, he says, because nodes simply fire whenever they have received two inputs. Yet even Shimada concedes that turning dataflow into a real system is no simple matter.

As a result, building hardware has consumed most of Shimada's time during the past decade. Now two prototype dataflow computers sit just across the hall from Shimada's office. Eight shoulder-high, white metal cabinets arranged in a square and connected by ribbon wires running out of a central hub cabinet house the SIGMA-1. Less than 10 feet away stands a smaller air-conditioned cabinet with "EM-4 prototype" stenciled on its side. Physically smaller but computationally more powerful, the EM-4 is the second generation of the SIGMA-1.

Shimada and his colleagues began building the SIGMA-1 in 1982 with funding from the National Supercomputer Project sponsored by the Ministry for International Trade and Industry (MITI). The machine was unveiled at



TOSHIO SHIMADA, a computer designer at Japan's Electrotechnical Laboratory, holds a board from his SIGMA-1 parallel processing computer. The machine relies on a computational model called dataflow. Photo: Dennis Gray.

the end of the project in January 1990. SIGMA-1 has 128 processors, each with a theoretical peak speed of 3.3 million floating-point operations per second (megaflops). The newer EM-4 is currently equipped with 80 custom-designed processors, each with a theoretical peak speed of 12.5 million instructions per second. The machine is expected to be expanded to its design limit of 1,024 processors by 1993.

But the machines are far from ready to leave the lab. EM-4 has yet to run software. SIGMA-1 has averaged only 100 megaflops—less than a quarter of its full theoretical peak speed—when running benchmark programs. And benchmarks have been the only code it has run. Software development has consequently become one of his most pressing challenges. Shimada's current goal is to write a "large-scale, practical program" for SIGMA-1 by the fall of 1991. He adds: "I hope."

Shimada concedes that working for a decade on a computer system that has yet to run a practical program can be frustrating. His team has devoted five years to developing a dataflow compiler, software that translates programs into binary code. Even after writing 100,000 lines of code in the computer language called C, the compiler is not yet complete. "Our group is small, 10 people, so it's very hard to work both in hardware and software," Shimada says. Even though most of the group's efforts have focused on hardware, "now I'm looking for people who can work on software," he adds.

Through it all, though, Shimada thinks he has one advantage over many scientists elsewhere in the world: long-term funding from MITI. "When a project starts, we have much to worry about," he says. "But once a project is started, it's almost guaranteed to run for five or six years. That's great." In the U.S., researchers must keep showing results every few years to win funding, he notes.

When Shimada is asked about differences between Japanese and U.S. research efforts in parallel computing, his excellent English becomes precise and cautious, even diplomatic. "American researchers can explain their work very logically, very clearly," he muses, not referring to language problems. "Usually a Japanese researcher, even if he is doing very nice work, cannot explain his work nicely," he adds. Shimada keeps up with U.S. efforts similar to his via electronic-mail communications with researchers, including his mentors at M.I.T.

In spite of support from MITI, Shimada has met with caution from Japanese commercial computer manufacturers who could shepherd his dataflow architecture to market. For instance, Keiichiro Uchida, manager of the supercomputer development department at Fujitsu, is a proponent of parallelism but remains wary of dataflow. He acknowledges that its effectiveness is based on how data are distributed between processors. But, he says, the algorithms for "such a precise division [of data] are difficult to develop commercially."

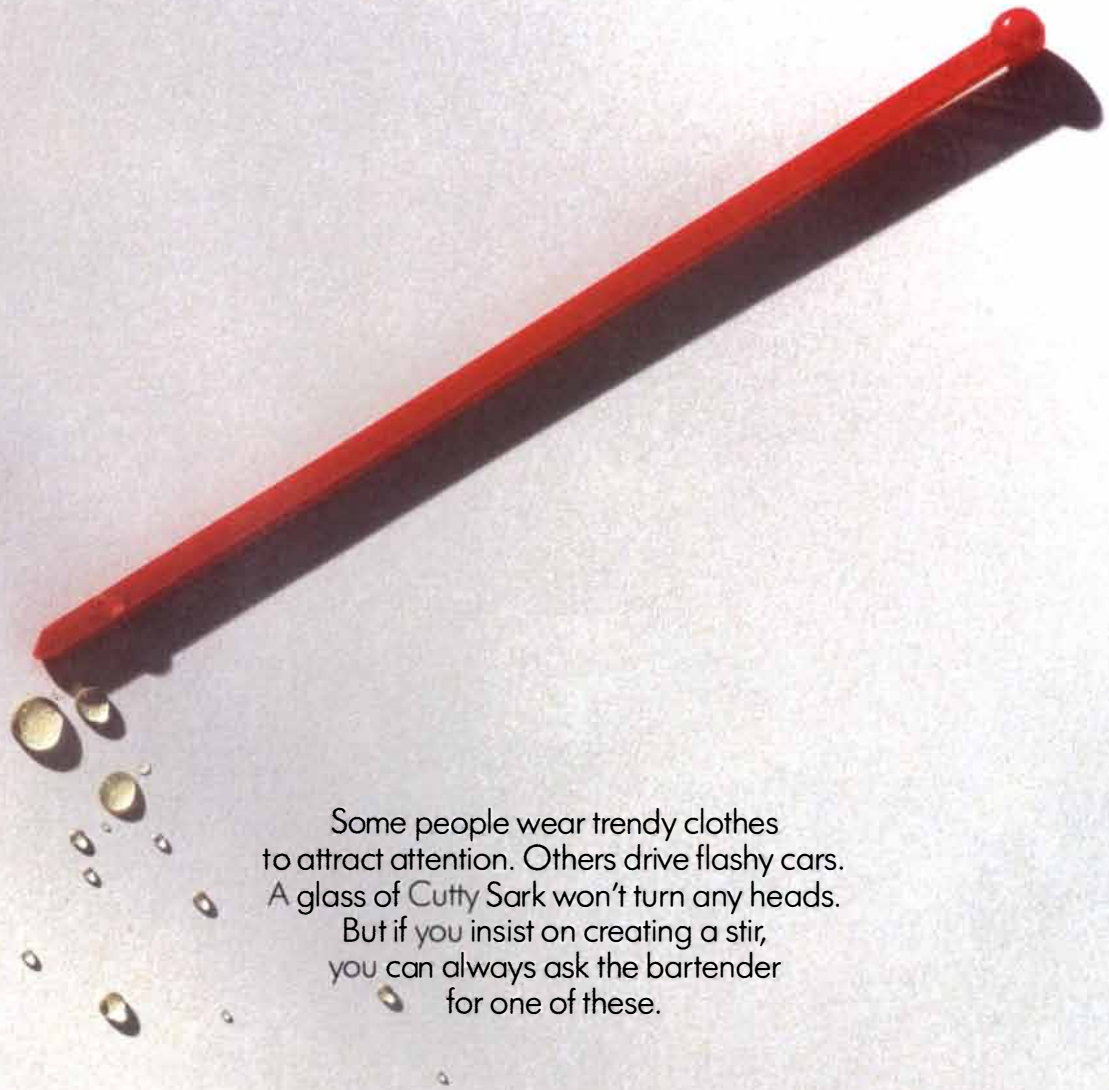
"Dataflow is a natural parallel processor system," adds Tadashi Watanabe, an assistant general manager at NEC and the principal architect of the company's supercomputer series. But he doubts dataflow will find its way into mainstream computing because many scientific calculations work on arrays of data that are more easily handled by conventional parallel processing schemes. Even so, "our target is to get the highest performance from single processors," Watanabe emphasizes. And by combining a limited number of such processors, "we can get very high [overall system] performance," he adds.

Nevertheless, Japan's supercomputer makers are taking their own tentative steps toward parallel designs. For instance, at NEC's central research laboratory just west of Tokyo, one highly specialized parallel machine is already hard at work verifying integrated-circuit designs. Such efforts are likely to become more widespread in Japan with prodding from a MITI game plan released last March called the New Information Processing Technology Project.

Shimada believes that eventually the time will come for dataflow computers. Pacing before his whiteboard, felt pen in hand, he sketches out plans for his next dataflow computer, the successor to the EM-4. It will be a monster of a machine, harnessing 10,000 to 20,000 processors. He predicts that by 1996 or so such a dataflow machine will achieve speeds of about a trillion operations per second.

It's that kind of mind-boggling computing speed that Shimada asserts will finally push dataflow parallel computing into the commercial arena. "The only way [dataflow will get attention] is if we are 10 times faster than the best machines," Shimada declares.

Like a member of the driven technical teams that work around the clock to produce some U.S. computers, Shimada and his associates put in long hours. "Every two weeks, one Saturday is a holiday, but usually I come and work," Shimada says. "Many colleagues also work even on Sunday." And after 11 years, he is not about to give up the race. —*Tom Koppel, Tokyo*



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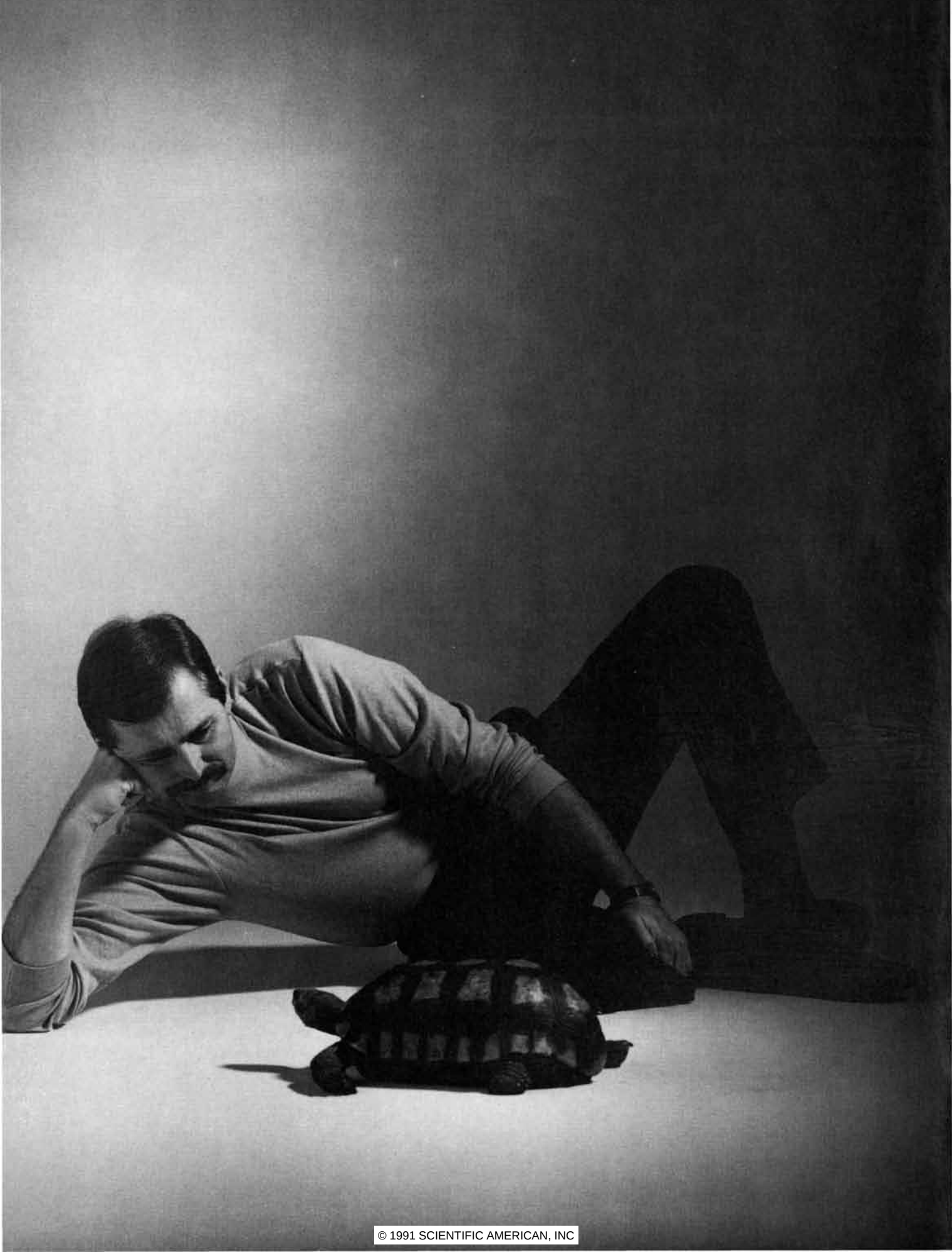

Tom Ditty found a way to make your Turtleneck last longer: subtract the seam.

A turtleneck is an ungainly garment. You sort of have to wriggle into it. And all that wriggling takes its toll.

Especially on the neck. It oftens rips at the seam. Or comes away from the rest of the shirt.

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Tom ticks off its advantages: "There's no seam to tear out, first of all. No bulk or lump against your neck. More resiliency from the circular knit–no drooping or falling down. Even looks neater, without all that stitching."

Only a few other companies offer a seamless neck turtle, despite its obvious superiority. Tom explains why: "It's an expensive process. You've got to do it on circular knitting machines, which most manufacturers don't have, and aren't willing to invest in. And, there are a lot more problems in the dying, getting the color of the neck to match the rest of the turtleneck."

No wonder then that those other seamless neck turtles are $20 and up. The Lands' End Turtle, on the other hand, is only $15. (Okay, okay: $18 for Talls, $19 for Tall XXL's.) How does Tom explain this seemingly miraculous price?

In a word: "Volume. I don't know of anybody who sells more turtlenecks than Lands' End. We also produce a lot of our turtles in the off-season, when it's slower for the knitters, and more cost-efficient for us."

Tom points out another advantage of the Lands' End Turtle: it's a good 10% heftier than its competitors.

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SCIENTIFIC AMERICAN March 1991 Volume 264 Number 3

Patenting Life

Although entrepreneurs can now legally protect any novel plants, animals or microorganisms they invent, the courts have not yet settled many questions about the reach of biotechnology patents

by John H. Barton

A white mouse from Harvard made legal history in April 1988: it became the first animal ever to be patented in the U.S. Philip Leder of Harvard University and his colleague Timothy Stewart, now at Genentech, Inc., had developed the extraordinary mouse through genetic engineering by inserting a human cancer gene into mouse egg cells. Because such a creature was novel and useful for future cancer research, the U.S. Patent and Trademark Office determined that the "Harvard mouse," as it is now often called, satisfied the requirements for protection as an invention under standard patent law. In making that decision, the patent office removed the last obstacle to patenting any form of nonhuman life.

The patenting of life-forms is rapidly expanding in the U.S., which now provides intellectual property protection to microbes, plants and animals. The Commission of the European Communities has issued a controversial proposal for comparable protection within Europe. In trade negotiations the industrialized nations have been pressuring the developing ones to strengthen their intellectual property systems—and rights for biotechnology are high on the agenda.

Yet certain peculiarities of living things raise problems for which there are few precedents in patent law. In this article, my goal is to identify and explore the major issues surrounding biotechnology patents. Because the courts and lawmakers have not yet confronted many of these questions, it is impossible to predict with certainty how they will be settled. In some cases, however, I can offer an opinion about what the most reasonable and probable outcome of future deliberations may be.

Before moving on to the specific problems of patents on life-forms, it will be valuable to review the general rationale for patents. A patent system attempts to encourage innovation by providing a limited monopoly to protect an inventor from imitation. The inventor should therefore be more willing to invest in research and development. Although the monopoly increases the price of the invention to the consumer, the profits are expected to favor and encourage the inventor in a way that reflects the market's evaluation of the worth of the invention.

This economic analysis does not take the dynamics of invention into account. New ideas are most likely to arise in a world where scientific information and research materials are exchanged freely. Patent systems may slow such exchanges because inventors may delay publication of their work in a peer-reviewed journal until after they have applied to patent it. Otherwise the invention would cease to be legally novel and become unpatentable.

Nevertheless, in the absence of a patent system, businesses will be tempted to protect their technology through secrecy. A company that has developed a microorganism for an industrial fermentation process, for example, could create an effective monopoly by conducting the fermentation and selling the products while keeping its organism secret. A desire for protection has traditionally inspired plant breeders to focus their efforts on developing hybrid varieties. Because hybrids do not breed true to type, no one can raise a crop of them without permission by planting their seeds. Thus, the breeders achieve a physical equivalent of intellectual property protection. Finally, if neither trade secrecy nor a patent system is available, an idea may not be developed into a product at all.

The empirical evidence that patents actually favor innovation is limited but moderately supportive. Studies have shown, for example, that private plant breeding increased following the introduction in 1970 of plant variety rights, a specialized form of intellectual property protection for plant breeders. The importance of the patent system is particularly great in the pharmaceutical industry, in which product research is relatively expensive but imitation is relatively easy. Patents will probably be similarly important in biotechnology for much the same reasons.

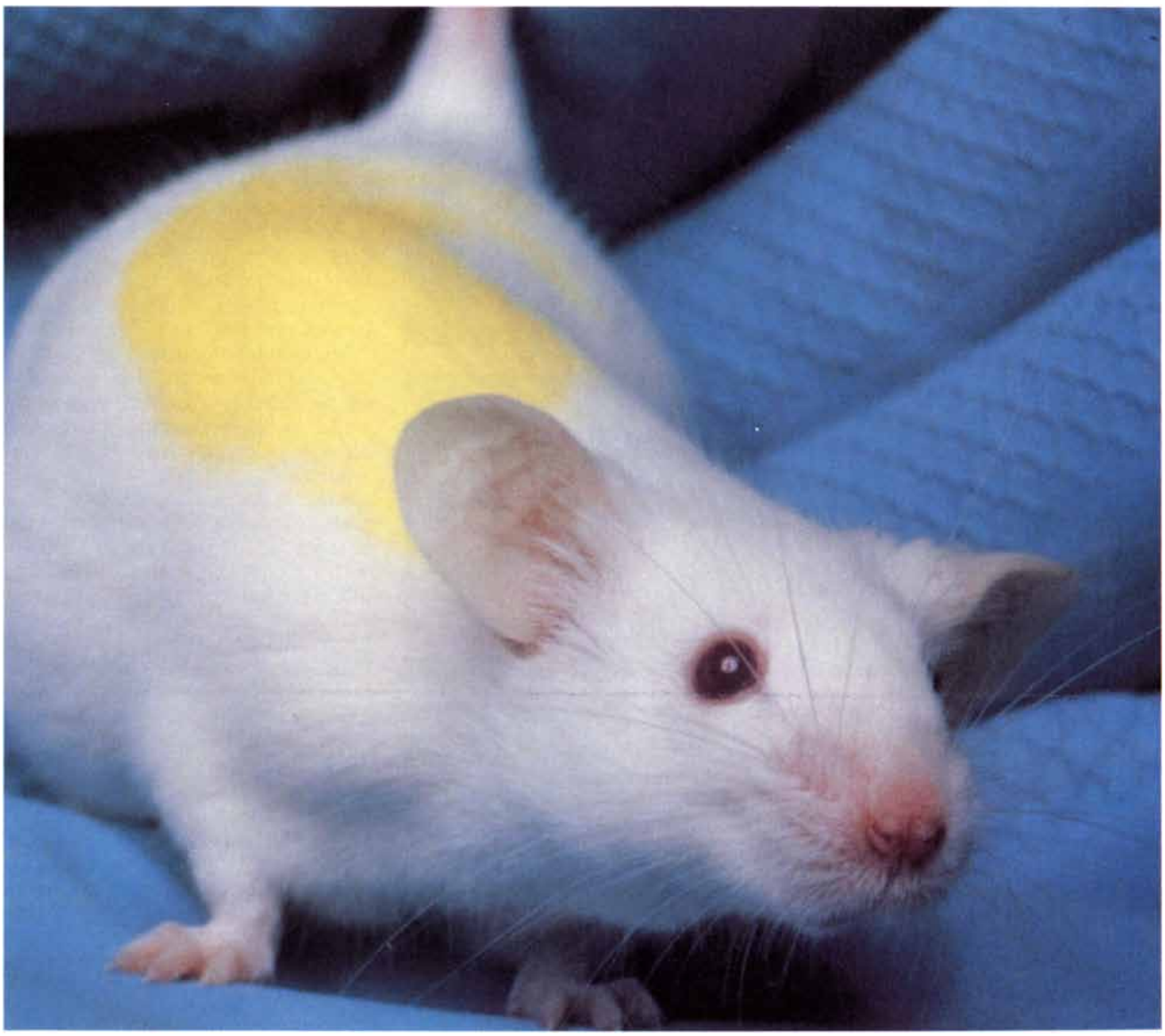
JOHN H. BARTON has for many years been concerned with the special legal challenges posed by agricultural biotechnology patents. At Stanford Law School, he is professor of law and director of the Law and High Technology Program. Barton graduated from Marquette University in 1958 and received his law degree from Stanford University in 1968.
He wishes to thank Donald Chisum, Jeffrey Ihnen, Naoki Koizumi, Richard Nelson, Bertram Rowland and the Crop Science Society of America for their contributions to the ideas expressed in this article. Work in preparing this article was supported in part by Stanford Law School and by the Rockefeller Foundation's Rice Biotechnology Program.

Although consumers may be hurt in the short run by the higher prices associated with the patent monopoly, economists generally believe the expected improvement through innovation offsets the cost. Moreover, when the patent expires, competition is likely to lower the price.

Experience also suggests that the price of patented products is set to give the purchaser much of the benefit. In the seed industry, for instance, the farmer normally receives two thirds to three quarters of the benefits of an improved hybrid seed, whereas the breeder receives the smaller share. If the seed is expected to yield an extra $100 worth of crops on every hectare, then a hectare's worth of seed may cost the farmer only about $30 more than the same amount for competing varieties. The farmer then profits by about $70. More broadly, economists have argued that competition between different patented products will often pass the benefit of the inventions on to the consumer; that result is less likely to occur with patents on process innovations.

Most developed nations accept that the benefits of a patent system outweigh its costs. The benefits are less obvious, however, for the developing nations. If there is little competition, the patent monopoly may impose serious social costs, especially when fundamental needs of the poor are at stake. Consequently, many developing nations have excluded pharmaceutical and food-related inventions from full patent coverage. In many such countries, public sector research is also more important than the private sector research that benefits from patents. Even without a patent system, developing nations can usually still import products of technologies patented in other countries.

The attitudes of developing nations are changing, however. In part the changes are a response to political pressure from the U.S. in international negotiations such as the Uruguay Round of the General Agreement on Tariffs and Trade. (Those talks collapsed last December but are expected to resume.) More nations are also hoping to encourage their own industries, among them biotechnology, in which a



GENETICALLY ENGINEERED MOUSE carries a human cancer gene that makes it valuable for medical research. In 1988 such mice became the first—and so far the only—animals protected by a U.S. patent. More patents on animals can be expected as transgenic experiments continue. The yellow spot of dye on the mouse's back is an identification mark.

patent system is likely to encourage innovation and foreign investment.

In short, the developed nations and many developing ones are now considering what forms of intellectual property protection are desirable for biotechnology. The design of such protection involves decisions about what biotechnology products and processes should be patentable and about how far those patent claims should extend.

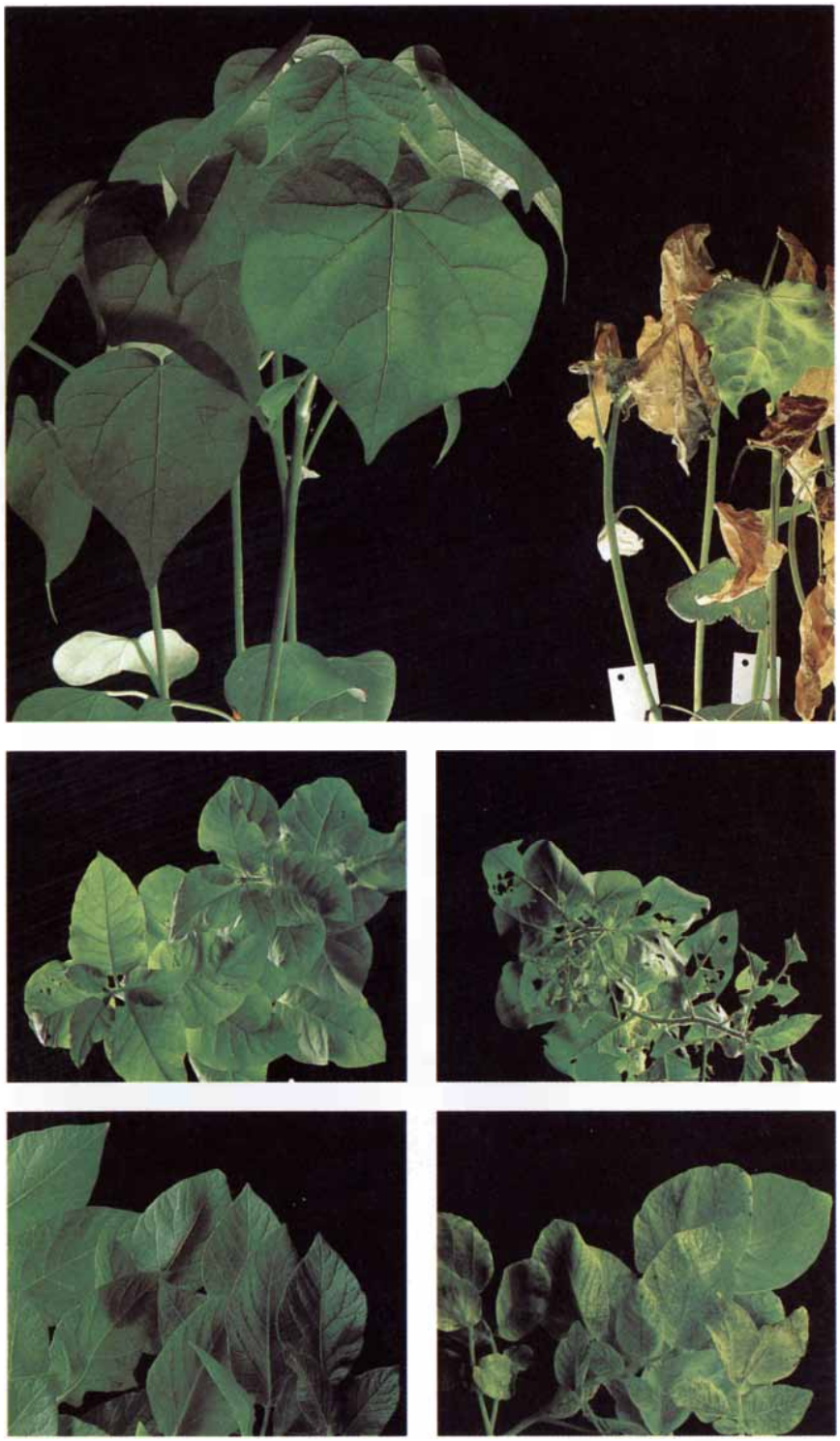
Patents can apply to life-forms and their constituent genes if they meet the essential requirements of being new, useful and not obvious. By those criteria, a completely artificial gene may be patentable. If the protein that the new gene makes and the organism into which the gene is inserted are also novel and seem to have desirable qualities, the inventor may sometimes extend the patent claim to include them as well. Patents involving artificial genes and novel life-forms are therefore relatively straightforward.

Yet one of the most political issues in biotechnology concerns the patenting of useful genes found in nature. A wild plant may have a gene for disease resistance, for example, that can be transferred into commercial crops. Because such genes are arguably discovered rather than invented, they may not satisfy the novelty requirement of patent law. It would be ridiculous to accuse people of infringing a patent because they naturally carried a protected gene in their cells.

Patents on genes derived from organisms that are native to developing nations would also probably exacerbate the political tensions that already surround the international use of genetic materials found in nature. Imagine the political outcry if a company discovered a useful disease resistance gene in a natural Mexican weed and then sought to patent its use in commercial varieties of maize that would be sold back to Mexico.

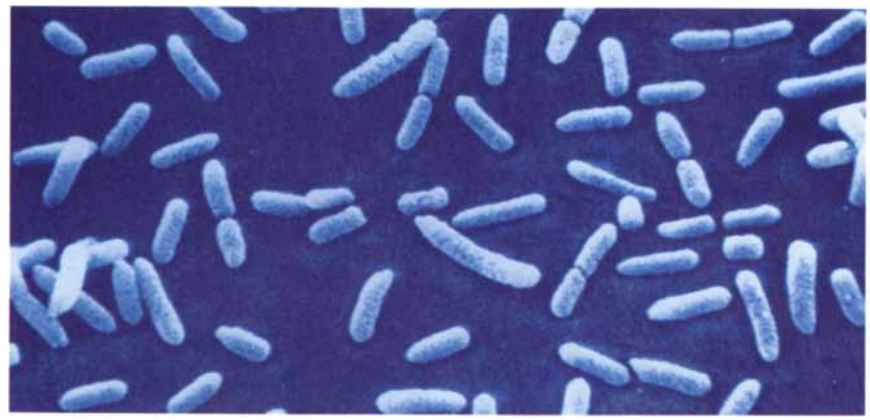
The counterargument is that companies should be rewarded for undertaking the difficult task of making natural genes useful. A company faces enormous costs in identifying, cloning and sequencing a natural gene and in inserting it into an organism for commercial purposes. Furthermore, competitors may find it easier to imitate such a gene after the first company has pioneered the technology. This situation, in which the innovation costs are heavy and the imitation costs are slight, is precisely one in which patent protection can be most beneficial as an incentive.

Although the law in such cases is both confusing and changing, it is likely to evolve in a generally reasonable direction. The starting point in the U.S. is a long-standing doctrine that the purified form of a chemical can be patented if the chemical is found in nature only in an unpurified form. This rule permits the first person to isolate a pure protein, or the gene that encodes the protein, to patent it. In contrast, Great Britain defines its standards for innovation more severely. Its courts recently held that a naturally occurring gene sequence could not be patented.



SOME PATENTED PLANTS have genetically engineered traits that help them to withstand environmental assaults. Such crops include herbicide-resistant cotton (*top, left*), insect-resistant tobacco (*middle, left*) and virus-resistant potatoes (*bottom, left*). Normal, susceptible plants of each species are shown in the right-hand column.

Neither the U.S. nor Great Britain, however, is likely to grant a patent for the use of a gene in a species in which it evolved naturally or in a species to which it can be transferred by normal breeding: in those contexts the gene would not be novel. Both governments seem to permit the patenting of novel organisms in which a gene has been transferred from another species. As gene transfers become more common, however, a specific transfer may need to be more difficult or unusual to satisfy the patent law requirements that it not be obvious. These emerging guidelines seem reasonable.



OIL-EATING BACTERIA were the first organisms to be protected under a standard U.S. patent. They were developed as a possible means of cleaning up oil spills.

Fair principles still need to be worked out for many of the questions about the scope of a biotechnology patent. The most controversial of these issues—and one being argued before Congress now in the context of patents on animals—is whether a patent's claims should ever encompass progeny. The sale of a patented product used to take it out of the monopoly: the purchaser could use the product in any way without further restriction. Yet organisms are self-reproducing. Breeding or otherwise reproducing a patented organism amounts to copying the invention, which is normally prohibited without the consent of the patent holder.

Suppose, for example, that an inventor develops a way to insert an artificial gene into lambs, with the result that those lambs produce more, leaner meat from less feed. Under current U.S. law, the inventor can obtain a patent that extends the inventor's monopoly to all the lambs bearing the artificial gene. Any farmer who bought such a lamb would be entitled to fatten it (if that would still be the right term) and sell it for meat. It is nonetheless still uncertain whether the farmer could legally breed the animal and raise its offspring without the permission of the patent holder—after all, some of those offspring will have the artificial gene.

That problem has already been settled for plants covered by the plant variety protection act: a farmer does have the right to replant seeds harvested from a protected variety. Some firms, however, are now protecting seeds under the regular patent act, which is also the only one that applies to animals. Under that act, the issue is not clearly resolved and is likely to be contested fiercely by farmer organizations before the courts and Congress.

A realistic policy analysis is essential to ending the standoff between the logical arguments for both sides. Policymakers should also remember that the expectations of the involved parties may plausibly differ in various cases. The sale of a patented brewer's yeast is meaningless, for example, unless the yeast can be allowed to reproduce during the brewing process. Sales of livestock for the purpose of fattening them, on the other hand, are less likely to include an assumption that the animals will be bred.

In general, however, a reasonable analysis will probably conclude that progeny should be covered under patent law. If the law does not allow patent holders to restrict the replication of their protected plants or animals, some of them will conclude that their most profitable option is to keep the organisms and to market only the ultimate products. Consequently, the production of related agricultural goods would probably become more consolidated under the control of single businesses. Such integration already occurs in the poultry industry, which carefully controls all its breeding materials.

The replication of some organisms cannot be limited practically. There is no realistic way to bar farmers from planting several generations of a protected nonhybrid seed. In those cases, however, it is unimaginable that the sellers of the organisms will not simply expect and permit such use and set their price or licensing fee accordingly.

A closely related issue to that of the patent control of progeny, and one that is similarly controversial, is whether a patent holder should have the right to limit the use of patented organisms for experimental breeding and research. On this issue, industry is pushing strongly for wide patent-holder control—and it should probably be resisted.

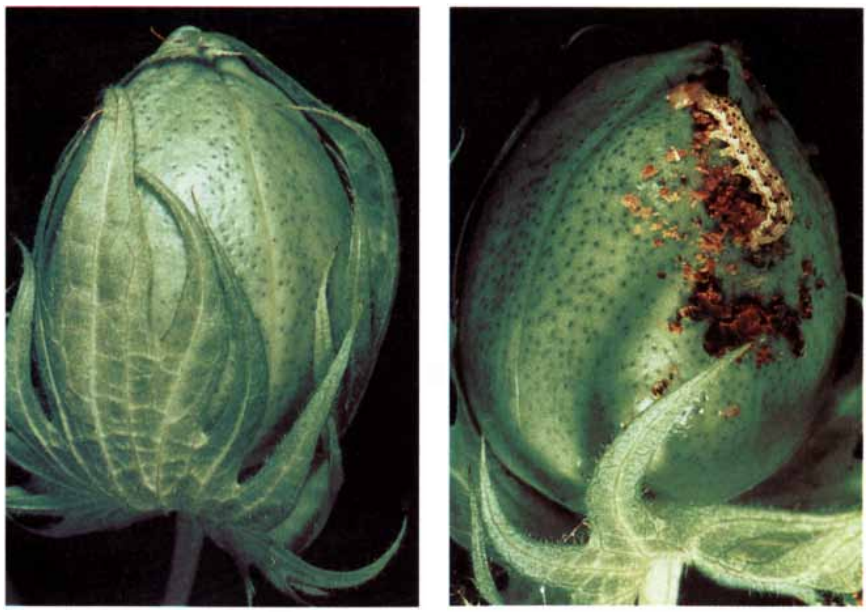
The idea that patented inventions should be baselines for further innovation is fundamental to patent law. For this reason, the plant variety protection laws clearly specify that protected varieties can generally be used as parents in breeding experiments. The regular patent laws of most nations also provide for research exemptions under which the use of a patented innovation for experimental purposes does not infringe the patent.

The U.S., however, does not have such a general exemption. It has only a narrow statutory exemption that applies to the manufacturers of generic pharmaceuticals and a history of weak statements taken from case law. The basic theme of the case law precedents is that experimentation is permissible only to satisfy academic curiosity and not for commercial purposes.

Such a principle is unfortunate. The progress of breeding and of science in general would be best served if all laboratories, commercial and academic, had the right to experiment more or less freely with patented organisms. That freedom would increase the incentives for follow-up research—and in biotechnology, follow-up research would very likely contribute at least as much economic benefit as the initial breakthroughs.

Again my hypothetical example of a patented lamb can prove useful. The DNA sequence of the artificial gene that affected the lamb's fat-storing properties would normally be disclosed in the patent and would also probably be protected by a patent claim. Under a broad research exemption, competing companies would have the right to experiment freely with that gene and the patented lambs in an effort to understand better the metabolic process at work.

From that research, a second group might be able to develop a complete-



WORM-RESISTANT COTTON (*left*) is less easily destroyed by bollworms than are untreated varieties (*right*). This genetically altered plant awaits patent approval.

ly different gene that accomplished the same result in a better way. Depending on the details of the claims, the new gene would probably not infringe the original patent, and the further improved lamb could be patented and sold by the second researchers without restrictions.

Another possibility is that researchers might develop a modified version of the patented gene, consisting of the original and a new supplementary sequence, that would permit the lamb to use more kinds of feed. The combined form of the gene probably would infringe the original patent, but the supplementary sequence might be patentable itself. If the combined gene were more valuable than the original, the two companies could negotiate arrangements allowing one or both of them to sell lambs carrying the combined gene, and each company would share in the monopoly profits according to the relative importance of its unique invention.

Under a narrow exemption, none of this research would have been possible without the prior permission of the original patent holder. The would-be follow-up inventor would have been in a very weak bargaining position because nothing new or valuable would have been developed yet.

The subject of variations on a patented property, as in the preceding example, is central to another hotly contested topic: the legitimate breadth of biotechnology patent claims. In some cases, a patent can cover the application of an idea to many different species. The key to permitting such coverage is whether the idea could reasonably be expected to work more broadly than has been demonstrated in the examples of the patent disclosure.

An illustration of this point is provided by the basic Cohen-Boyer patent on the plasmid method of genetic engineering. The inventors, Stanley N. Cohen of the Stanford University School of Medicine and Herbert W. Boyer of the University of California at San Francisco, discovered a method of inserting genes into cells using microscopic rings of DNA called plasmids. Their patent disclosure detailed only how several different genes could be inserted into *Escherichia coli*, a common species of intestinal bacteria. Cohen and Boyer nonetheless obtained a patent that conveyed a monopoly over the use of the plasmid technique with a diverse number of host cells, including other bacteria and unicellular organisms. Thus, their rights went far beyond the use of *E. coli*.

Harder and less settled questions are posed by the problem of similar gene sequences. Suppose that after an inventor patents a novel sequence for a useful protein, a competitor changes one codon, or amino acid–specifying element, in the gene. Would the almost identical protein that the competitor's gene produced infringe the inventor's patent? Conversely, could the inventor have circumvented such a problem by claiming a wide variety of related gene sequences and proteins under the original patent?

Probably the reasonable answer is that the initial innovator should be entitled to claim and prevail against very similar gene sequences that perform essentially the same as the patented sequence. On the other hand, the competitor should be entitled to nearly full rights if the new sequence has any surprising or unexpected properties. At most, the competitor should have a duty to pay for a license from the inventor if the modified sequence includes the same properties as the original one.

Nevertheless, as reasonable as those principles may seem, they offer no guarantees that patent law will always afford innovators broad protection against similar biological products. Indeed, the first case to consider the issue seriously struck down the effort by an inventor for broad protection.

That case was part of a series of suits between Amgen, Inc., and other companies over patents relating to erythropoietin, a hormone secreted by the kidneys that stimulates the production of blood cells. Both Amgen and Genetics Institute, Inc., had filed applications for the patents at roughly the same time. In several decisions the courts eventually ruled that Amgen's patent covers the gene sequence for erythropoietin and a host cell that has been transformed by the addition of that gene but that Genetics Institute's patent covers purified erythropoietin itself. The decision on an appeal of these rulings is pending as this article goes to press.

Amgen had maintained that, according to its patent, its rights extended to any "amino acid sequence sufficiently duplicative of that of erythropoietin to allow possession of the biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells and to increase hemoglobin synthesis or iron uptake." In ruling against Amgen, the court reasoned that the company had not disclosed enough about the "sufficiently duplicative" sequences to make such comprehensive claims.

That decision kept patent claims narrow. Nevertheless, claims for patented gene sequences may still be effectively extended in other infringement cases. There is an infringement doctrine pertaining to a device that is not technically covered by the patent claim but performs substantially the same function in substantially the same way for substantially the same result. This doctrine might support the argument that a new sequence designed from the disclosed sequence and having only a few unimportant changes should be held to infringe the patent.

The most controversial question of scope is exemplified by the claims of a patent held by Kenneth A. Hibberd of Molecular Genetics, Inc. (now MGI Pharma in Minnetonka, Minn.). Through tissue culture experiments, Hibberd and his colleagues developed a variety of maize whose seeds are especially rich in the amino acid tryptophan. In its patent the company claimed a monopoly over any kind of maize that produced seeds with "an endogenous free tryptophan content of at least about one-tenth milligram per gram dry seed weight."

The Hibberd claim does not specify why or how its maize overproduces tryptophan. It may do so, for example, because a mutation disabled some genetic control mechanism that normally regulates tryptophan production. Yet a competitor might be able to achieve overproduction in a different way—for instance, by inserting more tryptophan genes into maize. That possibility raises the question of whether such a competing maize would infringe the Hibberd patent.

The U.S. Patent and Trademark Office has generally been granting broad claims to patent holders in such cases. Its decisions may be based on the tradition that the first producer of a new chemical can patent the chemical itself and obtain protection against other inventors who find different ways to produce it. When such extended claims are before the courts, however, the courts tend to be willing to find evidence of infringement only when the product in question has been made by the process described in a patent.

For biotechnology products, such court decisions are correct. Two organisms that overproduce a substance for different reasons are genuinely different life-forms—they are not like two identical compounds produced by different processes. Moreover, the social risk of permitting a monopolistic claim on all organisms with a valuable property seems more strict than is necessary for encouraging innovation. Unfortunately, the current status of patent law is unnecessarily confusing in this respect: it misleads those not trained in law who may not realize that the claims of an original patent may not be enforced as comprehensively as they read.

Domestic patent laws can be confusing in themselves, but the complications multiply when international competition and differences in nations' patent laws become important. One set of international patent issues involves access to patented life-forms. A patent must describe an invention well enough for others to reproduce or use it. For a patented yeast produced by genetic engineering, a description of the procedures involved in making it might be adequate.

Yet for some patented life-forms, would-be innovators must have access to the actual organisms. It would normally be impossible, for example, to describe how to re-create a yeast with a rare mutation that gave it industrial value. Instead the mutant yeast must be deposited in a facility where access to it could be guaranteed. Several privately operated depositories have sprung up around the world for this purpose. (One of the largest is the American Type Culture Collection in Rockville, Md.)

The existence of the depositories raises the tricky issue of whether a competitor can take an organism from a depository and use it for profit in nations where the depositor has no patent protection. An argument permitting such uses is that the living material has, in essence, entered the international scientific literature and should be available to all. The opposing argument is that it would be unfair for the deposited material to be available for commercial use over the objection of the inventor.

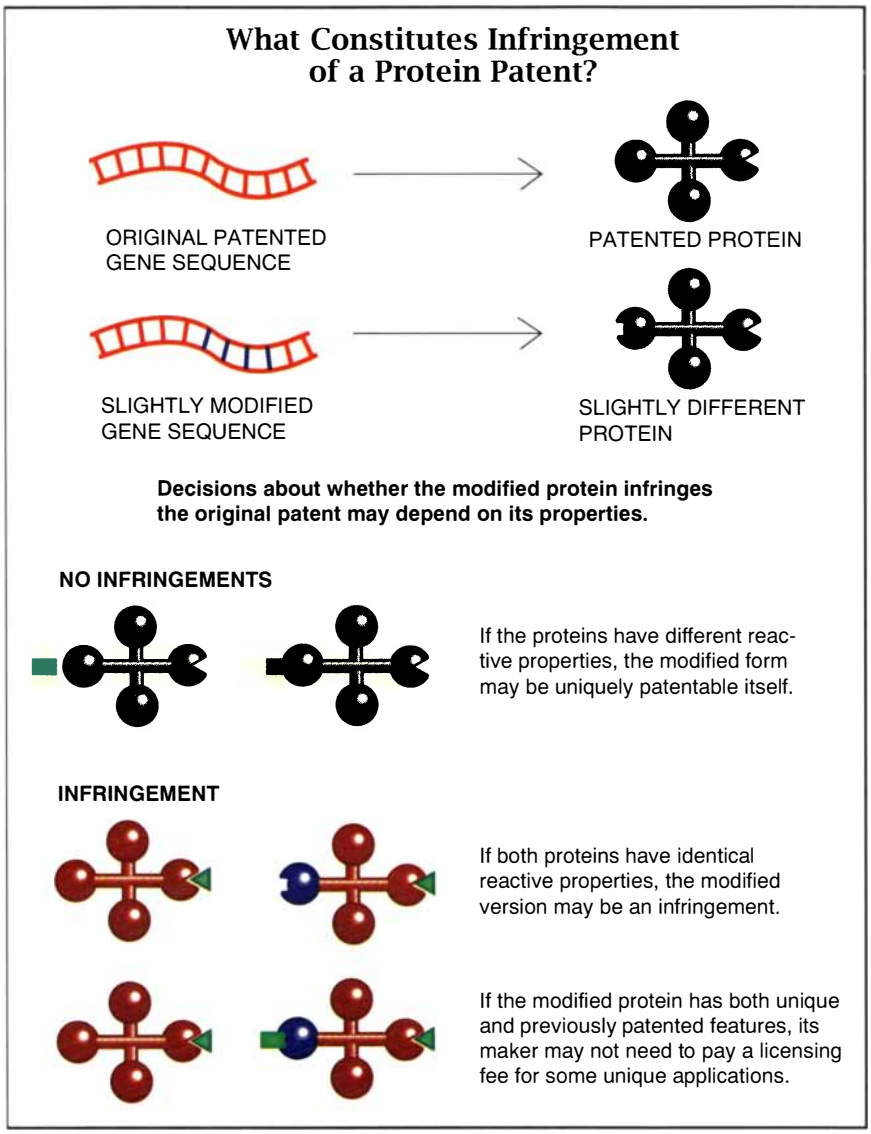
Several schemes for preventing such problems by limiting some users' access to the depositories have been proposed. The U.S. government eventually decided, however, that it had no legal basis for restricting depository access, just as it had no basis for restricting access to the other information in the patents.

The other international patent issue relates to trade. A patent brings no direct protection outside the nation in which it is issued. Except in certain special cases, the only way to obtain protection in a number of countries is to patent in all of them. Nevertheless, there is an indirect form of protection against foreign production: almost every nation will permit barring the importation of a product if producing it domestically would have infringed a domestic patent.

For standard industrial processes, that rule offers reasonable protection, but it is difficult to decide how far to apply its logic in many biotechnology contexts. Suppose that grain patented in the U.S. has been purchased and shipped to a country that does not allow patents on plants. The grain is then used as seed, and a fresh generation of grain is harvested. Can the new grain be barred from the U.S.? What about bread made from it?

The answers are not yet clear. Prohibiting the direct products of patented processes seems reasonable. A more extended right to ban indirect products, however, would probably intro-

SPECIMEN REPOSITORIES freeze and preserve organisms in tanks of liquid nitrogen. Such storehouses ensure public access to specimens of patented life-forms.



duce economic inefficiency and development costs that would far outweigh any benefits to innovation.

The U.S. nonetheless has two statutes relevant to these questions, both of which lean toward broad rights for barring imports. The more extensive statute, generally called Section 337 of the U.S. Tariff Act, which was strengthened in the 1988 Trade Act, sets no limitations on the "directness" of patent infringement whatsoever. Yet an international panel set up under the General Agreement on Tariffs and Trade recently declared that the statute violated trading law principles in other respects, and its future is now uncertain. The other statute seems to suggest that the use of an imported protein in the U.S. should be banned only if it was made by a genetically engineered organism prepared by a U.S. patented process.

Both statutes affect only the products of patented processes, but there is pressure on Congress to extend them further to include materials that are made by patented organisms, genes and other biotechnological products. This movement was inspired by the recent litigation between Amgen and the Chugai Pharmaceutical Company, which had licensed Genetics Institute's patent for erythropoietin. The court determined that Amgen's patent covers the host cell transformed by the addition of the erythropoietin gene as a product but not as a process for making erythropoietin. Consequently, Amgen can prevent Chugai from manufacturing erythropoietin with transformed host cells in the U.S., but it cannot stop Chugai from making erythropoietin abroad in this way and then importing the product into the U.S.

If the U.S. statutes were extended to block the importation of materials made by patented organisms, Chugai would not be able to market erythropoietin in this country any longer. It is not at all clear that broadening the patent holder's ability to block the importation of such products would be to the advantage of consumers or society.

The real impact of the spread of intellectual property rights systems to include biotechnology and life-forms will ultimately depend on the structure of the affected industries. In the pharmaceutical sector the effects are likely to depend first on whether conflicts of the Amgen-Chugai type prove common—and with so many biotechnology firms going after essentially the same protein-based products, they probably will be. If so, then the question is whether the firms will be able to settle the disputes and compete with new products and product improvements without the courts.

There is greater cause for optimism for the future of the agricultural sector: companies should be able to invent unique genes for disease resistance, better protein quality and other traits. Still, varieties that combine several novel genes will almost certainly be economically preferable to those with only one. Businesses will therefore probably license their new genes to breeders, who can repackage and combine selected genes in plants and animals that will appeal to particular markets. A farmer will buy a variety that has one company's disease resistance gene, another's drought resistance gene and a third's package of nutritional enhancement genes.

Such a positive outcome from the regulation of biotechnology patents is within our reach—but its likelihood depends on whether the legal system reaches wise answers to the questions explored here.

FURTHER READING

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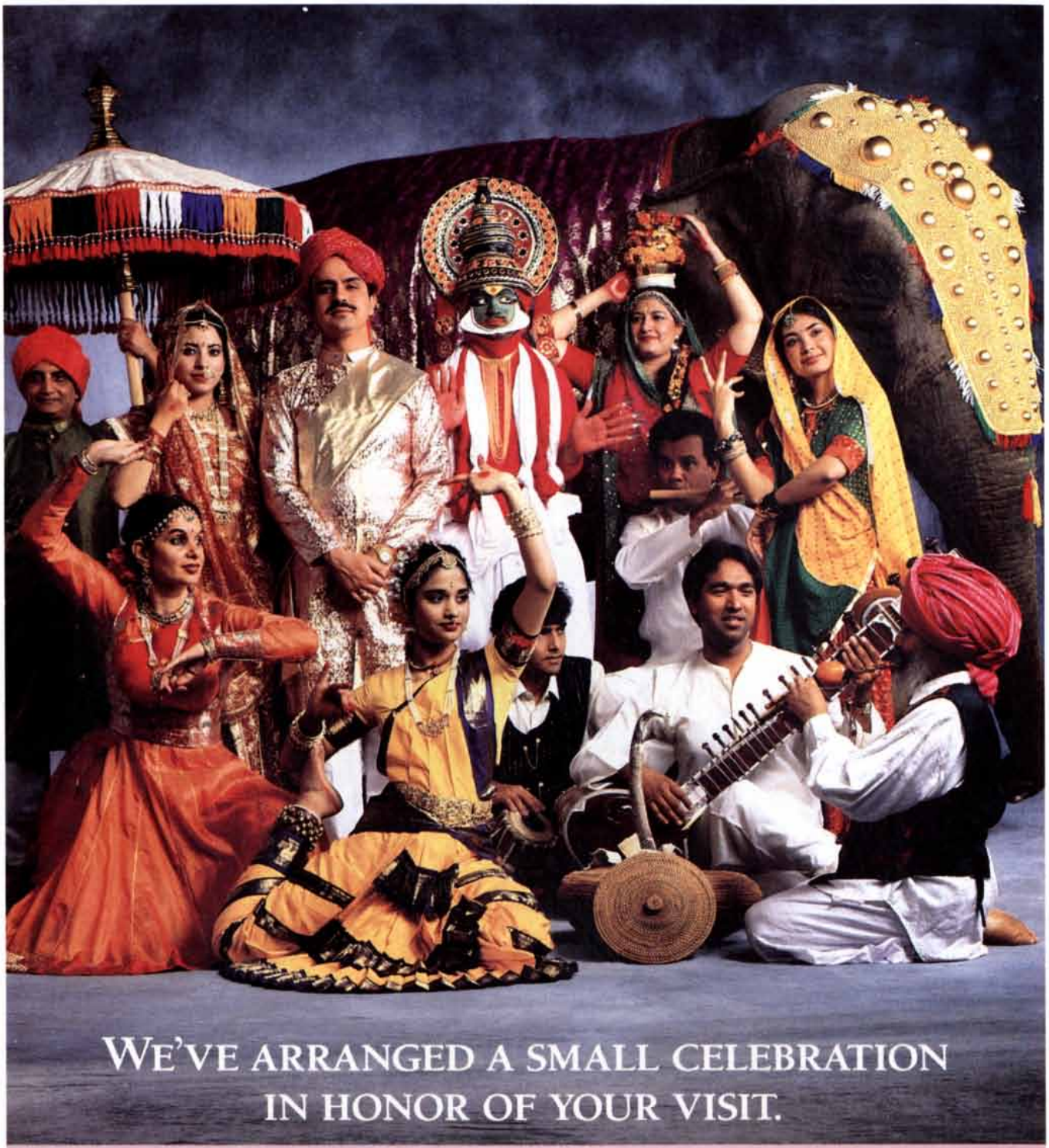

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The Tevatron

Because it produces antiprotons, accelerates them in a ring using superconducting magnets and smashes them into protons, it is now the world's most powerful source of data on elementary particles

by Leon M. Lederman

On July 3, 1983, my colleagues and I at Fermi National Accelerator Laboratory (Fermilab) near Chicago started the countdown for the inaugural run of the world's first superconducting synchrotron, the Tevatron. It would send a trillion protons on a speed-of-light journey, ending in a collision unlike any that has occurred since very shortly after the birth of the universe. The Tevatron would also launch physicists on an unrivaled adventure in understanding the nature of matter and the discipline of building and operating colossal accelerators.

To begin the test, we activated the Main Ring, Fermilab's older synchrotron, to energize the positively charged protons to a mere 120 billion electron volts (GeV). In a nerve-racking instant the protons were injected into the Tevatron, where more than 1,000 superconducting magnets literally took charge. The magnets efficiently produced a powerful field to guide the protons around a 6.3-kilometer circular path no more than a few millimeters wide. In the control room, technicians supervised the computer program that ramped the magnets up in precise synchrony with the increasing energy of the protons: 200, 300, 400 GeV... When the magnetic field reached test-level strength, the protons were smashed into a target at a world record 512 GeV.

The feat capped a 10-year effort to master the technology of superconducting magnets in accelerators, and it marked the beginning of an era in the physics of matter, energy, space and time. The new "atom smasher" was heralded in newspapers across the U.S. and was praised in messages that poured in from many institutions, including, in particular, the U.S. Department of Energy (DOE), which had allocated the funding.

During the past eight years, Fermilab has taken many steps to ensure that the Tevatron will remain a preeminent fa-

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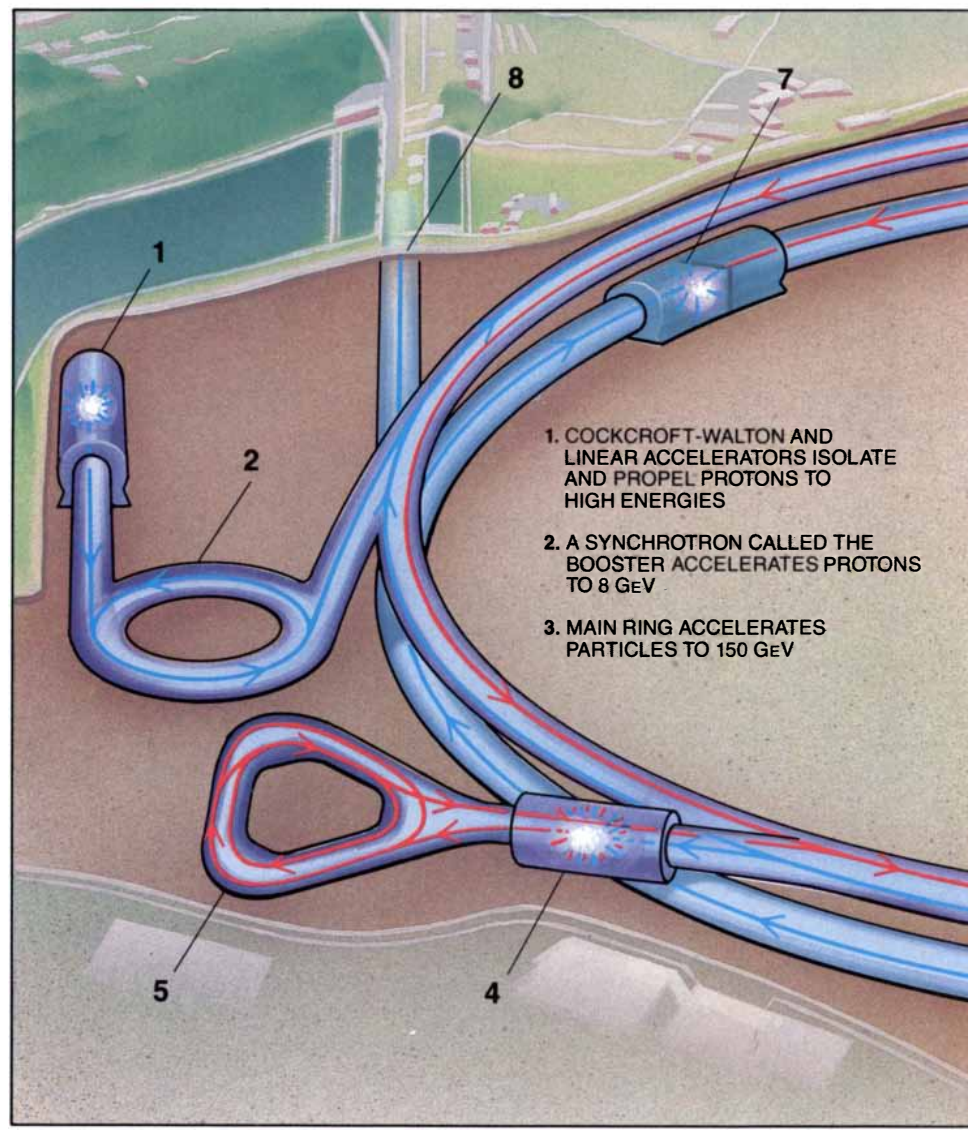
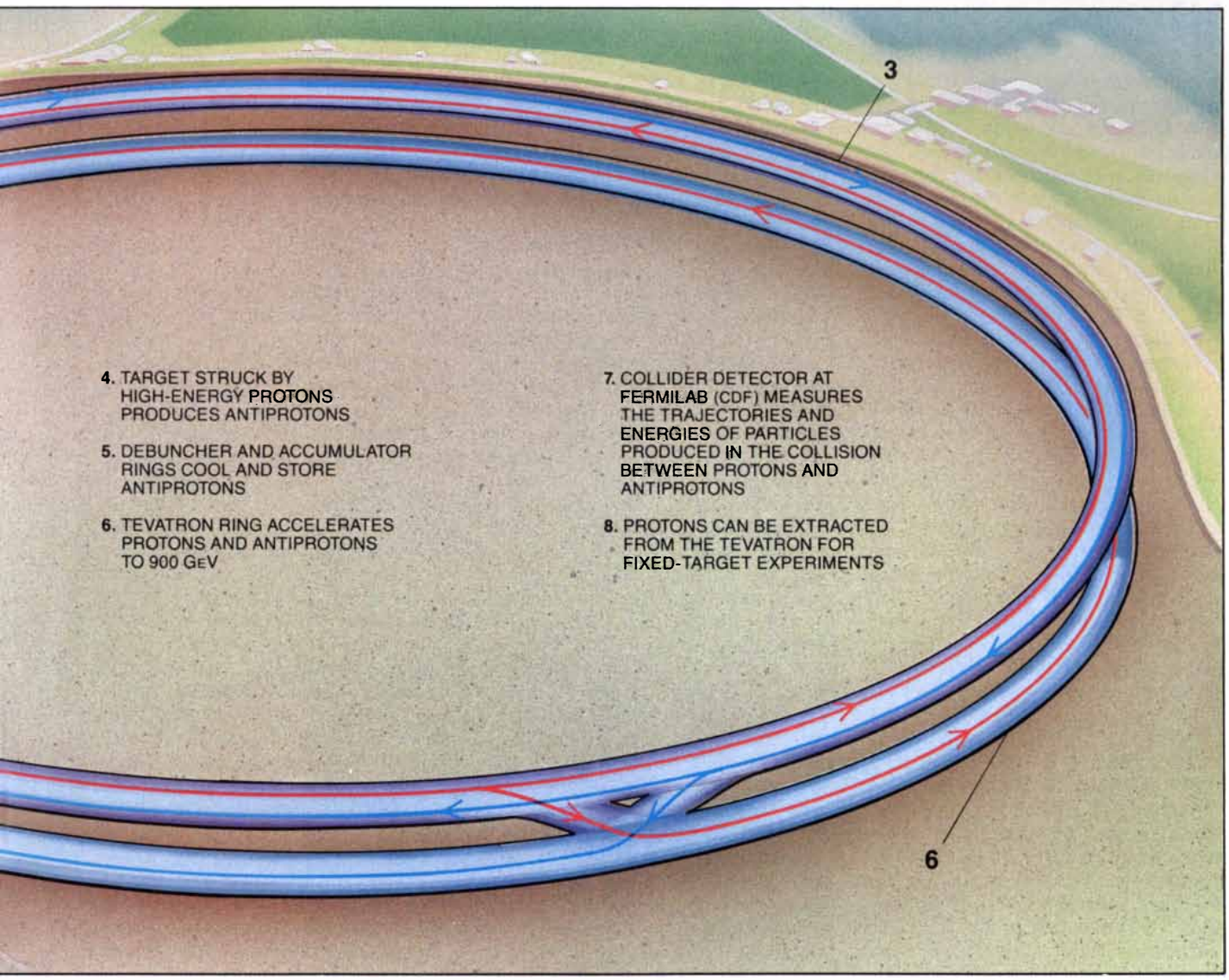


TEVATRON, the world's most powerful particle accelerator, propels protons (*blue arrows*) and antiprotons (*red arrows*) to 900 billion electron volts (GeV) and col-

cility for particle physics. Fermilab has improved the superconducting magnet system, developed an antiproton source and constructed a particle detector. The Tevatron can now collide 900-GeV protons with 900-GeV antiprotons to generate an unmatched 1.8 trillion electron volts (TeV).

With each burst of energy, the Tevatron creates a host of exotic particles, producing data of unprecedented quality. The Tevatron has confirmed many predictions of the Standard Model, the central theory of elementary particles. It has also allowed investigators to explore a domain where "no human eyeball has ever set foot," according to a student with a penchant for mixing metaphors.

The Standard Model proposes that matter is composed of six kinds of quarks and six leptons, and so far all these particles have appeared in ex-



lides them at an energy of 1,800 GeV. The resulting debris has been analyzed to help secure the foundations of physics. Lessons learned from building the machine will help guide the development of the Superconducting Supercollider.

periments except for the sixth quark, known as top. As the Tevatron evolves during the next five years, it will generate, by most physicists' reckoning, enough collisions to produce the top quark. If it does not emerge, the Standard Model will face a major crisis.

The elusiveness of the top quark is connected to the most seminal issues confronting particle physics. Why do all quarks and leptons have different masses? Does an undiscovered force of nature bestow mass on a particle? Are quarks and leptons composed of even smaller particles? What do the interactions between quarks and leptons suggest about the high-energy environment of the early universe? Theorists have devised many explanations, which have exotic names such as supersymmetry, technicolor, constituent models and superstrings. The Tevatron seeks to illuminate the speculative jungle.

The Tevatron program began more than 15 years ago in anticipation of the needs of the particle physicist today. During the 1970s, elementary particle physics progressed as two kinds of accelerators propelled particles to ever higher energies. Synchrotrons at Fermilab and the European laboratory for particle physics (CERN) near Geneva smashed protons into fixed targets, and accelerators at Stanford University, Cornell University and the Deutsches Elektronen-Synchrotron (DESY) in Hamburg collided electrons with their antimatter twins, positrons.

Although the proton synchrotrons could accelerate particles to much higher energies than the electron-positron colliders, they were in the final analysis no more powerful than the colliders. When a proton boosted to, say, 1,000 GeV is smashed into a target, most of its energy is expended to accelerate the particles produced in the collisions. Only 42 GeV is available to produce new particles. Here the colliders have an advantage. When particles collide head-on, their combined energy is available for creating particles or exploring a new energy regime. Hence, a 1,000-GeV proton that smashes head-on with a 1,000-GeV antiproton releases 2,000 GeV.

The power of an accelerator is not measured by its energy alone, however. An accelerator must generate enough high-energy collisions to produce statistically significant results. Collision rates are generally lower for colliders than for fixed-target machines because particles in a diffuse beam are much more likely to collide with a dense, fixed target than with particles from another diffuse beam. Overall, the colliders sacrifice a high collision rate for greater energies.

During the 1970s, the two proton synchrotrons—the Super Proton Synchrotron at CERN and the Main Ring at Fermilab—were competing fiercely. Both laboratories were pushed to improve their machines to study the Standard Model and the fundamental interactions of nature—the weak, electromagnetic and strong forces.

In 1977 CERN went all out to convert its machine from a proton synchrotron to a proton-antiproton collider because it sought to confirm or refute the existence of the so-called intermediate vector bosons (the W^+, W^- and Z^0). These massive particles are responsible for the weak force. From 1977 to 1981 CERN developed a device that collected and stored antiprotons. The device then squeezed the antiprotons into small bunches using a technique called stochastic cooling. The antiprotons were then injected into the CERN Super Proton Synchrotron, where they eventually smashed head-on into protons.

In 1983 and 1984 CERN discovered the W and Z particles. For this accomplishment, Carlo Rubbia, the leader of one of the experimental groups, and Simon van der Meer, the inventor of stochastic cooling, won the 1984 Nobel Prize [see "The Search for Intermediate Vector Bosons," by David B. Cline, Carlo Rubbia and Simon van der Meer; SCIENTIFIC AMERICAN, March 1982].

Fermilab chose a different route to advance the field of high-energy physics. The increasing power of the Super Proton Synchrotron was a major concern to Robert R. Wilson, Fermilab's visionary first director. He realized that if Fermilab could develop a superconducting magnet system, it could ultimately build an accelerator more powerful than CERN's. The proposed Fermilab machine could boost charged particles to higher energies because superconducting magnets can produce a much stronger field than can conventional systems. In 1973, therefore, Wilson started a program to develop superconducting magnets for a new accelerator. Later Alvin V. Tollestrup, who came to Fermilab in 1975 from the California Institute of Technology, became the intellectual leader in developing these magnets.

As director-designate of Fermilab in the fall of 1978, I reviewed various proposals to build an accelerator that would use superconducting magnets. We concluded that such magnets not only could sustain a more powerful accelerator but could also reduce consumption of electricity. (From 1972 to 1978 Fermilab had nearly doubled its power consumption, while its electricity costs increased sixfold.) Because superconducting components do not resist the flow of electricity at all, a superconducting magnet system would consume considerably less power than a conventional one would. How best to use the new technology was not at all clear. I therefore consulted with an outside group of accelerator geniuses dubbed the three wise men: Boyce D. McDaniel of Cornell University, Burton Richter of Stanford University and Matthew Sands of the University of California at Santa Cruz.

On November 11, 1978, I held a staff meeting to discuss the long-range plans of the laboratory. It was Armistice Day, an appropriate time to call a truce among several groups who had opposing ideas about how to use the superconductor technology. After 18 continuous hours of passionate debate, a clear consensus emerged—at least it seemed clear to me and my advisers. We came up with two major initiatives. First, we would build an accelerator based on a superconducting magnet system and install it in the 6.3-kilometer tunnel occupied by the Main Ring. This machine would smash protons into fixed targets as before but at an energy level more than two times higher. Second, like CERN, we would construct an intense source of antiprotons, inject them into the accelerator and collide them with protons. The goal was to accelerate protons and antiprotons to 1 TeV and produce about 50,000 collisions per second at a total energy of 2 TeV.

From 1979 to 1987 the program was implemented as envisioned in the 1978 plan, at a cost of about $250 million. The DOE supervised and funded the program, but not without Sturm und Drang. The saving grace was Andrew E. Mravca, a DOE official who believed in the program and knew how to negotiate skillfully with a bureaucracy.

The story of the Tevatron is a very human one, dominated by a collection of heroic figures. Physicists, professional engineers and a corps of gifted amateurs devoted themselves to making the Tevatron the world's most powerful accelerator. If a single factor accounts for the success of this enterprise, it was the happy juxtaposition of physicists and engineers.

When Fermilab set out to design the Tevatron in 1979, we knew it would be significantly more complex than any previous accelerator. The Tevatron would require a huge cryogenic system to cool the magnets below the temperature at which they become supercon-

ductors. It would need an intricate vacuum system to provide both thermal insulation and a clear space in which to accelerate particles. It would demand an elaborate safety network to protect the apparatus and workers from the energy stored in the particle beams and the magnet system. It would involve high-speed computers to monitor and control such parameters as the temperature, pressure, field strength, radiation level and beam position. Finally, the Tevatron would entail sophisticated particle detectors to measure the energies and trajectories of particles formed in collisions between protons and antiprotons. Each of these systems took years to design and build.

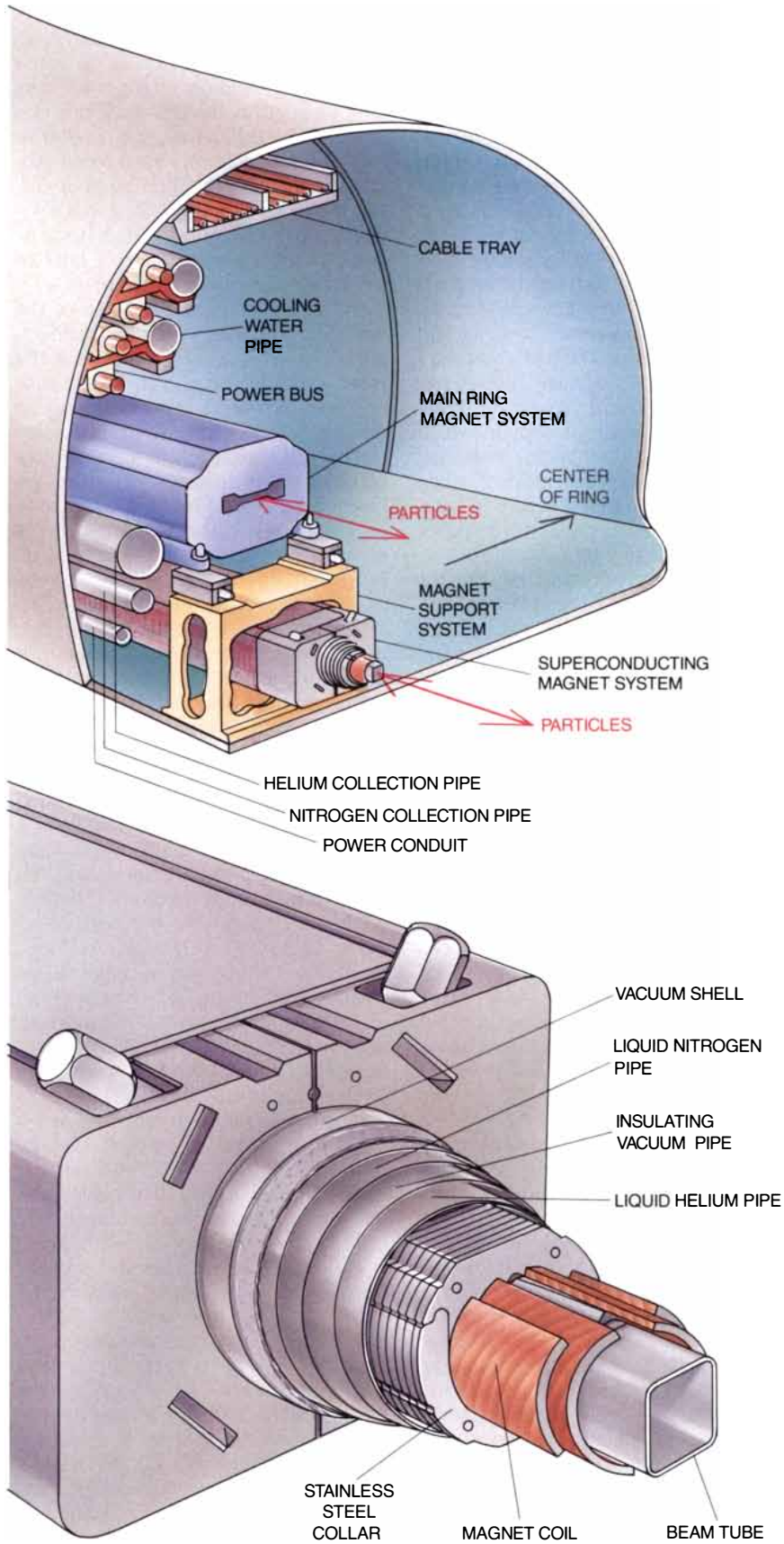
J. Richie Orr was in charge of the Tevatron project. Helen T. Edwards became Orr's deputy and technical manager. Machine guru Thomas L. Collins was principal designer of the accelerator system. Tollestrup and Wilson, with help from Richard A. Lundy, were responsible for the assembly line to produce, test and modify magnets.

The superconducting accelerator magnets posed major technical challenges. The magnets must confine particles within a one-centimeter region in the center of the vacuum tube as they steer the particles around a 6.3-kilometer orbit, 50,000 times a second. The accelerator magnets generate a field as electric currents flow through superconducting wires. The quality of the field depends on the precision with which the superconducting wires are placed around the vacuum tube.

To guide particles, the magnets have to generate a nearly perfect dipole field—one described by a north pole above the orbit and a south pole below. Because it is practically impossible to do so, such magnets as quadrupoles and octopoles were needed to correct for errors in the dipole field.

Accomplishing this task presents several formidable engineering problems. Huge forces push on the wires when they carry the electric currents that create the required magnetic field. The stainless steel clamps that hold the wires must withstand tons of force without yielding more than a thousandth of a centimeter over the 6.4-meter length of each dipole magnet.

Perhaps the most obstinate problem occurs during the acceleration of particles, when the currents change rapidly and increase to 4,000 amperes in about 30 seconds. Changing fields tend to shake and twist wires, creating friction and heat, which are anathema to the superconducting state. The solution to these problems evolved over a decade of research in laboratories around the



FERMILAB TUNNEL (*top*) houses the Main Ring and the superconducting magnet system that makes up the Tevatron. The tunnel is 3.0 meters wide and 2.4 meters high. In 1982 the Tevatron was installed underneath the Main Ring. One of the Tevatron's dipole magnets appears in the cross section at the bottom. Liquid helium and nitrogen cool the magnet system. They are then collected as gases and recycled.

world, but Fermilab's physicists and engineers were the first to achieve success in the period from 1973 to 1979.

Fabrication of the superconducting wire was still an exotic technology in 1979. The alloy of niobium and titanium, after elaborate metallurgical treatment, was packed into hollow copper tubes. A set of 2,000 rods was then bundled together in a copper shell 250 millimeters wide. The assembly was heated in an oven, extruded through a press and drawn through dies to make strands 0.6 millimeter in diameter and 50 kilometers long. The niobium-titanium rods became fine filaments 10 microns in diameter separated from one another by a sheath of copper, which acts as an insulator at superconducting temperatures (below five kelvins). When 23 strands are woven together to form a cable, they can carry 5,000 amperes at superconducting temperatures.

A mass-production assembly line for the superconducting magnets was supervised by Lundy. His group built about 100 small models and several hundred prototypes before they could get the magnets to perform satisfactorily. They then fabricated about 900 dipoles, 250 quadrupoles and hundreds of other types of magnets used to correct imperfections in the fields of the dipoles and quadrupoles. The total included a reasonable number of spares to replace magnets that might fail in operation.

In 1980 Fermilab built a large facility to test each magnet for mechanical, cryogenic and magnetic properties. The vital statistics of each magnet were logged into a computer program that later served to advise where in the ring the magnet should be placed to cancel residual field errors.

To provide enough coolant for all the superconducting magnets, physicist William B. Fowler and engineer Claus H. Rode directed the construction of the cryogenic system. A major component was a liquid-helium plant that for a time was the world's largest. The facility can now produce simultaneously 4,500 liters of liquid helium per hour and a comparable amount of liquid nitrogen. Liquid nitrogen had previously been delivered by commercial trailers, one arriving every four hours.

In addition to meeting the specifications of the Tevatron, designers of the magnet and cryogenic systems devised safety measures to manage three awesome sources of stored energy that could destroy the machine. First, the Tevatron's magnets store as much as 400 million joules of energy, equivalent to about 1,000 sticks of dynamite. Second, the beam accelerated by the Tevatron to 1 TeV is equivalent to more than 10 million joules, enough to drill a hole through the surrounding magnet. Third, the magnets require 25,000 liters of liquid helium, which could rapidly expand to 50 million liters of gas, enough to fill a blimp as long as a football field and five stories high. Each of these energy sources raises a host of terrifying engineering problems.

For instance, if a tiny fraction of the particle beam hit several superconducting wires, the particles could heat the wires enough to cause them to cease superconducting, a process known as quenching. The wires would then resist the flow of electricity, dissipate power and consequently heat themselves and adjacent wires to even higher temperatures. Hence, the enormous energy stored in the magnetic field could be released, heating the helium and expanding it in pipes at explosive rates. To protect against such a disaster, Fermilab designed an automatic shutdown procedure, which would in rapid sequence extract the beam from the machine, drain the currents from the magnets and vent the evaporating helium into a large pipe.

In June of 1982 Fermilab suspended operation of the Main Ring, and Peter J. Limon, C. Thornton Murphy and Laurence D. Sauer began supervising the orchestrated chaos involved in assembling the Tevatron. At the peak of activity, some 200 technicians, welders, electricians, engineers and physicists occupied the tunnel. All the resources of Fermilab were focused on fabricating the 1,200 superconducting devices as well as the associated power supplies, utility components, refrigerators and cryogenic connections.

After workers assembled all the parts, made all the connections and sealed all the leaks, they cooled the magnets to an operating temperature of 4.7 kelvins. In June of 1983 Fermilab injected the first bunch of protons from the Main Ring into the Tevatron.

As the Tevatron began demonstrating its power, Fermilab focused its attention on the antiproton source and the detector for the proton-antiproton collider. John Peoples, Jr., managed the antiproton source project along with his systems chiefs, John D. McCarthy, Gerald Dugan, Stephen Holmes and Ernest Malamud. Their ambitious goal was to build a facility that would produce, collect and store at least 10 billion antiprotons per hour so that the antiprotons could be injected into the accelerator in a series of bunches.

Tollestrup and Roy F. Schwitters of Harvard University supervised the development of the Collider Detector at Fermilab (CDF) until 1988, when Schwitters left to direct the Superconducting Supercollider Laboratory in Dallas and was replaced by Melvyn J. Shochet of the University of Chicago. More than 200 scientists—including workers from 10 universities, national laboratories and institutions in Japan and Italy—helped to build the detector.

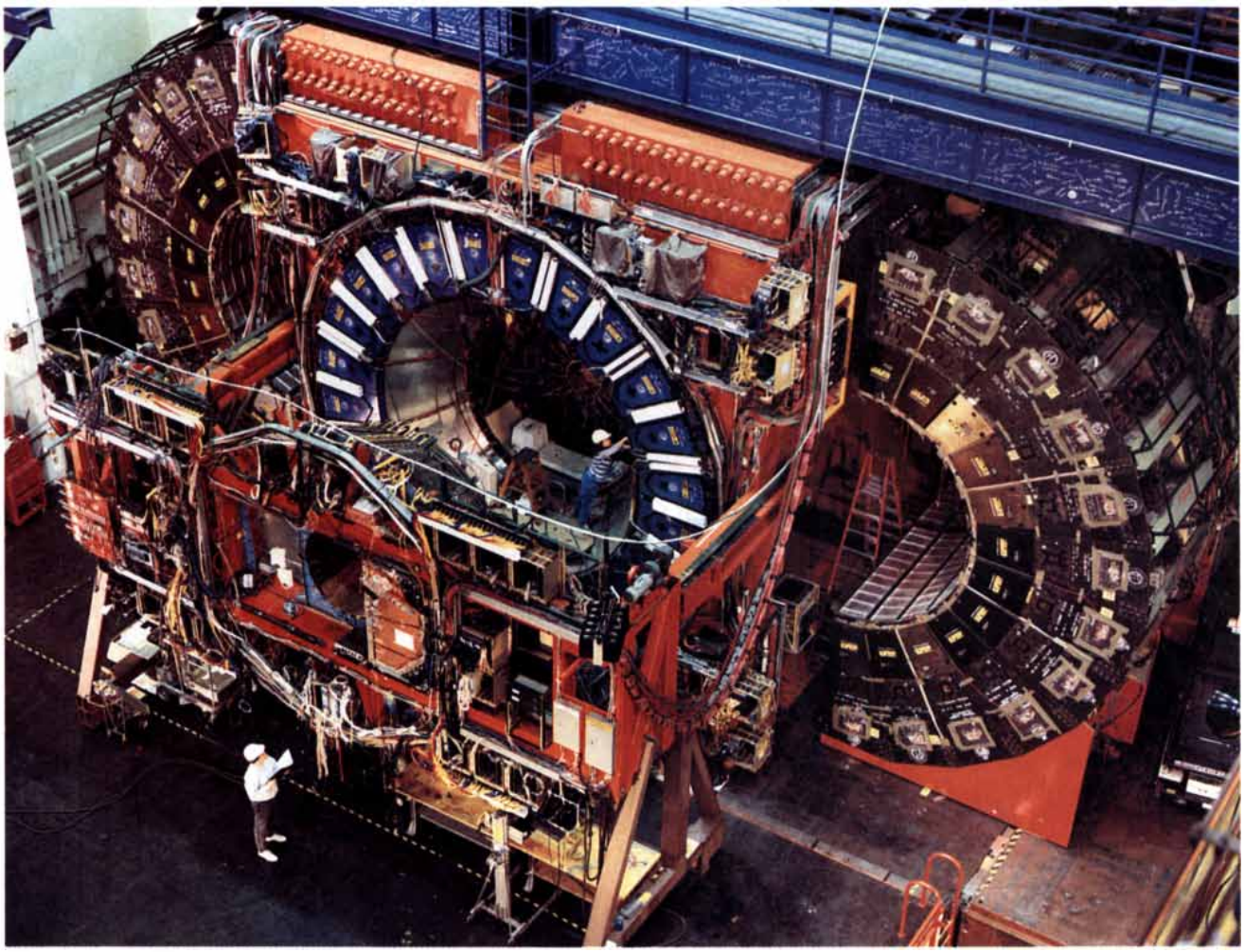
CDF could be characterized as a 5,000-ton Swiss watch. It represents a state-of-the-art device for examining more than 100,000 collisions per second. The energies of the resulting particles are measured by numerous heat sensors; the particles' trajectories are recorded by a wire mesh that carries the electric pulses produced when charged particles pass nearby. For each of the 30 or more particles produced in a typical collision, CDF produces more than 10,000 bits of information about its trajectory and energy. In more than 100 billion collisions it examined, CDF selected for detailed analysis about five million events that were of "more than routine interest."

The Tevatron, the antiproton source and CDF were baptized in a series of experiments that began in January of 1987. These systems required the most sophisticated choreography of accelerator rings ever attempted. The procedure for accelerating particles in the Tevatron is reminiscent of a NASA launch. Control room technicians review an elaborate checklist before they initiate the process that ends in proton-antiproton collisions.

In the first step, negative hydrogen ions composed of two electrons and one proton are released in a device called a Cockcroft-Walton accelerator, which produces an electromagnetic field to propel the ions to an energy of 750,000 electron volts. The ions then enter a 150-meter-long linear accelerator. By inducing an oscillating electric field between a series of electrodes, the linear accelerator boosts ions to an energy of 200 million electron volts. The ions then pass through a carbon foil, extracting the protons from the ions.

In the second step, the protons are guided into the Booster, a synchrotron 500 meters in circumference, where the energy is raised to 8 GeV. The protons are then injected into the Main Ring. Here more than 1,000 conventional, copper-coiled magnets continuously guide and accelerate protons.

In the third step, protons are focused into short bunches at 120 GeV. They are then extracted from the Main Ring and strike a copper target, producing



COLLIDER DETECTOR AT FERMILAB records more than 100,000 proton-antiproton collisions per second. The 5,000-ton apparatus slides into alignment with the Tevatron's particle beams so that collisions take place in the detector's center. The arches pushed to the side for maintenance are part of the calorimeter, which measures the energies of particles.

antiprotons. About 20 million antiprotons can be collected from each pulse. The antiprotons are then focused by a lithium lens—a cylinder of liquid lithium that transforms a current pulse of 600,000 amperes into a focusing magnetic field.

In the fourth step, the lithium lens directs the antiprotons to the first antiproton storage ring, known as the Debuncher, which is about 520 meters in circumference. The Debuncher is designed to squeeze the antiprotons into as compact a "space" as possible. One can begin to understand how the Debuncher works if one can imagine sitting on an antiproton in the middle of a bunch. From this interesting but precarious vantage point, one can see other antiprotons—some racing faster, some moving slower and some oscillating from side to side. All in all, the antiprotons take up a great deal of space, making it difficult to manipulate the assembly and add more antiprotons.

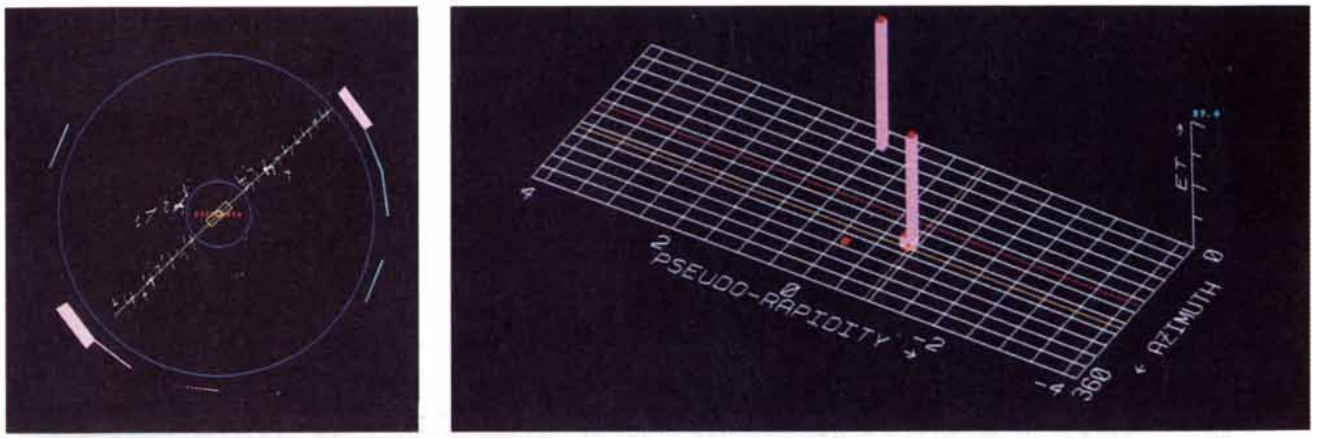
To increase the density of antiprotons, the Debuncher uses two cooling processes. The first, called debunching, is a Fermilab innovation. As a bunch of antiprotons circulates around the ring, a complex, computer-coded radiofrequency voltage speeds up slower particles and slows down faster ones, thereby decreasing the energy distribution of the stored beam. The other process, stochastic cooling, decreases the sideways motion of antiprotons. In this method, particles whose orbits are far from ideal are identified by sensors, which then send correction signals to kicker electrodes that adjust the paths of the errant particles.

After the Debuncher squeezes the beam in energy and size, the fifth step begins: it sends about 20 billion antiprotons per hour to a concentric ring called the Accumulator. Several independent systems in the Accumulator cool the beam of antiprotons further, ultimately increasing the density of antiprotons by a factor of one million. After four hours, the accumulator ring contains some 200 billion antiprotons, enough for a "shot" to the Main Ring.

Meanwhile, during the fourth and fifth steps, the Main Ring accelerates 500 billion protons to 150 GeV. The protons are then transferred to the Tevatron ring where they await the antiprotons.

In the sixth step, a portion of the stored antiproton beam is transferred to the Main Ring. The antiprotons are boosted to 150 GeV in the Main Ring and then injected into the Tevatron ring where protons have patiently been circulating. Because the protons are positively charged and the antiprotons are negatively charged, the protons circulate in a direction counter to that of the antiprotons. The antiproton bunches pass through the proton bunches many times, but at this stage the bunches are much too diffuse for significant collisions to take place.

During the first 60 seconds of the final step, both bunches of particles are



COMPUTER DISPLAYS represent particles forged by the collisions between protons and antiprotons in the Tevatron. The diagrams at the left indicate the trajectories of the particles. The "Lego plots" at the right show where the particles hit the Collider Detector and indicate how much energy the particles released. The pair of displays (*above*) show a Z^0 particle de-

accelerated to full energy. Strong quadrupole magnets in the Tevatron's ring then squeeze the particles together. During this stage the delicate stability of the circulating bunches can easily be disrupted, scattering particles everywhere. If all goes well, the beams are focused down to a diameter of about 0.1 millimeter, comparable to the diameter of a human hair. The focusing greatly increases the density of each bunch. Each time the bunches cross, there is now a 50 percent chance that a single proton will collide with a single antiproton. According to the original design, more than 50,000 collisions per second should take place in the center of the particle detector.

The first series of collider experiments ended in May 1987, and a second series was started in July 1988 and ran for 11 months. During that period the Tevatron achieved a collision energy of 1.8 TeV. The collision rate improved from a few hundred per second to 120,000 per second, more than twice the design rate. The Tevatron produced a total of about 100 billion collisions between protons and antiprotons. Furthermore, it could sustain a beam of circulating particles for as long as 20 hours, but over time the beams would slowly decrease in size and density as they were scattered by residual gases in the vacuum tube and by other effects that are not yet understood. The Tevatron accomplished these feats using only 20 megawatts of power (as compared with Fermilab's consumption of 60 megawatts in 1979).

One of the most satisfying aspects of these first experiments was to confirm the hypothesis that proton-antiproton collisions can be analyzed in a straightforward manner. This hypothesis is not obvious when one considers that the proton is a mess: it is composed of three quarks and many force-carrying particles called gluons. The antiproton is, similarly, an antimess. It seemed plausible that a collision between a proton and an antiproton could have produced an indecipherable hodgepodge in which most particles would mask the interesting behavior of others. It turned out, however, that most particles produced in the collision were so low in energy as to be mere spectators of the main events. Only a few high-energy particles emerged, indicating a clean collision between one quark in a proton and another quark in an antiproton.

A variety of high-energy particles can be resolved by CDF. Electrons, muons and photons are easily identified by their trajectories and energies. The quarks appear as jets, that is, bundles of pions, protons, neutrons and kaons. Short-lived particles such as W and Z also decay into a recognizable spray. In many cases, neutrinos, which are not recorded by CDF, can be located by noting "missing" momentum.

By the end of 1990, Fermilab investigators had published some 25 papers. These detailed such new insights as the size of quarks, the nature of the weak and electromagnetic forces, the properties of "bottom" quarks and the lower limit of the mass of the top quark.

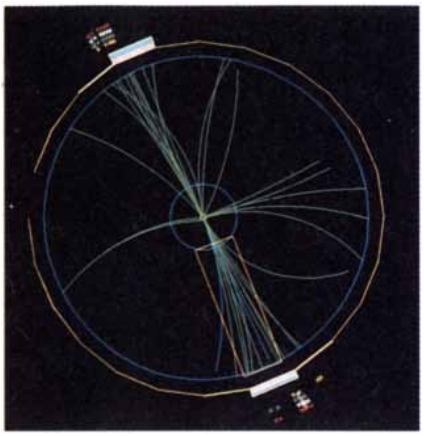
The Standard Model assumes that quarks are truly fundamental: they have neither structure nor spatial dimension; they are point particles with no radius. If so, quarks should scatter off one another in different ways than they would if they have a finite radius or any type of structure. Investigators may be able to determine whether quarks have structure, therefore, by studying the distribution of jets produced in collisions between quarks. So far the results from CDF agree with the Standard Model. If quarks do have a finite radius, it is less than 2×10^{-19} meters (that is, at least 4,000 times smaller than the radius of a proton).

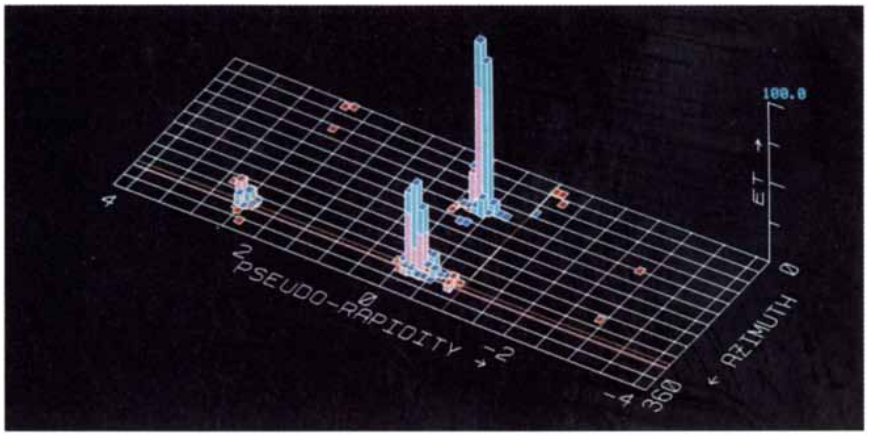
To determine crucial parameters of electromagnetic and weak forces, Fermilab has studied the masses and decay properties of the W^+, W^- and Z^0 particles. Although the 1987 results from CDF gave the most precise value for the Z^0 mass, this was very soon superseded by the "Z" factories, Stanford's and CERN's electron-positron colliders. On the other hand, CDF supplemented by results from the CERN proton-antiproton collider provides the primary data on W properties.

In the past two decades, physicists have come to recognize that the weak and electromagnetic forces are expressions of a more profound interaction now designated the electroweak force. Fermilab has precisely measured a crucial parameter of the electroweak force, the so-called weak mixing angle. This parameter essentially describes the relative strengths of the electromagnetic and the weak forces in their electroweak alliance.

Fermilab has recently reported exciting evidence for the production of B mesons (particles made of a bottom quark and an antidown or antistrange quark). The run in 1989 recorded about as many B meson events as those observed in all the electron-positron colliders combined. The 1991 run should increase the yield by 100 times in the CDF detector.

Physicists generally believe that a detailed study of the decay of B mesons will lead to a better understanding of the origin of matter. In recent years we have learned that the origin of matter in the early universe was derived from a tiny violation of a deep symmetry of





caying into an electron and a positron. In the other pair, a quark degenerates into two jets containing protons, neutrons, mesons and other baryons. The grid in the Lego plots represents the interior of the detector as though the cylindrical device were cut across the top and flattened. The energy scale (labeled "ET") is given in billions of electron volts.

matter and antimatter, known as the charge-parity symmetry. Hence, the study of this symmetry violation in *B* mesons will be a major focus of Tevatron during the next decade.

One of Fermilab's highest priorities has been to search for events that would suggest the production and decay of a top quark. So far CDF has observed only one dubious event. Applying theoretical predictions for the number of events that should have been observed in the CDF data for any assumed mass of the top quark, CDF concluded that the mass of the top quark is greater than 90 GeV.

Why is the top quark so much heavier than its closest relative, the 5-GeV bottom quark? The answer is connected to the most interesting issue in particle physics—the nature of mass and the mechanisms by which the particles of matter acquire mass. The most elegant theories predict that the quarks should have small or vanishing mass. Is the top quark just an anomalously heavy spectator, or is it the key to the internal structure of the Standard Model? The Tevatron is now the only accelerator in the world that can address this issue. In the next decade CDF is planning to increase its sensitivity gradually to find the top quark.

During the past six years, while Fermilab developed and used the Tevatron collider, it continued to produce important results with the fixed-target program. Here the power of the Tevatron was used to create beams of muons, neutrinos, pions and other particles. The Tevatron's high energy and superior time structure have yielded data of unequaled precision for more than 20 experiments.

One of the most interesting examples is the research on the properties of particles carrying the "charm" quark. In a 1987 run, this experiment amassed more fully analyzed charm events than had previously been collected by all the world's facilities since the charm quark was discovered in 1975. The result was a bonanza of data on lifetimes, new states and modes of decay.

The Tevatron entered final phase of its program in July 1989, when I retired as director of Fermilab and was succeeded by John Peoples, Jr. The program, called Fermi III, includes, notably, a more powerful linear accelerator and a new Main Ring to inject particles into the Tevatron. Fermi III should improve the collision rate of the Tevatron from 120,000 per second to more than six million per second. Because of these improvements, by 1996 the Tevatron should be sensitive to a top quark with a mass as high as 250 GeV.

Fermi III also plans to complete a second detector called DZERO for experiments to begin in 1992. DZERO incorporates a great deal of the experience acquired by CERN in its pioneering proton-antiproton research. Paul D. Grannis of the State University of New York at Stony Brook and H. Eugene Fisk of Fermilab led the DZERO project and enjoyed assistance from some 17 U.S. and foreign institutions. As the detectors are gradually improved to match the machine's performance, the Tevatron will seek again to peer inside the quark and the electron, and it will subject the Standard Model to tests of great precision.

Fermilab's pioneering efforts in superconducting magnet technology will strongly influence the future of accelerators. Several machines will soon use superconducting magnet technologies, including, this year, the 800-GeV proton ring at the DESY laboratory and, in 1995, a 3-TeV proton accelerator at the Soviet accelerator laboratory at Serpukhov. The most dramatic occurrence, however—certainly from the perspective of the U.S.—is the decision to build the Superconducting Supercollider. It will use 10,000 superconducting magnets in a pair of 20-TeV proton rings.

As the Tevatron program enters its second decade, it maintains an approach consistent with Fermilab's founding philosophy: the laboratory exists to serve the university science community. It is important to point out that the typical university group that collaborates at Fermilab is about the same size as those that do experimental science anywhere in the university. Fermilab and other "big science" projects should be judged on the scientific value of their work and the opportunities they provide to both experienced professors and young investigators. Oceanographers, astronomers, genome biologists and particle physicists have been wrestling with the problem of managing large, shared facilities for some time. We must learn to cope with the human problems, particularly the preservation of creativity and initiative, if we are to continue to probe nature's deepest secrets.

FURTHER READING

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What Controls the Cell Cycle

Although the recursive events leading to the birth of new cells are well known, biologists are only now learning how those events are regulated. One protein is the major regulator in virtually all organisms

by Andrew W. Murray and Marc W. Kirschner

By 1900 scientists had already identified the basic events of the cell cycle—the growth and division of a single cell into daughter cells. Yet until recently, little was known about what regulated that cycle, which in humans is vital not only to reproduction but also to growth, tissue repair, immunity and countless other processes.

In the past five years, two separate experimental approaches to the problem have converged on an astonishing finding. The regulation of the cycle in eukaryotes (all living organisms except bacteria and viruses) seems to depend to a great extent on changes in the activity of a single molecule, called the cdc2 protein.

The discovery is exciting not only because it illuminates a problem that has puzzled cell biologists for decades but also because a deepened understanding of cell-cycle regulation could have profound implications for medicine. On one hand, the work could lead to new ways to induce proliferation of cells needed to reconstruct damaged organs or tissues—perhaps including mature neurons, which do not divide. On the other hand, improved understanding of the cycle may help yield ways to halt the promiscuous reproduction of cancer cells.

In a way, the recent history of cell-cycle research is reminiscent of the building of the first transcontinental railroad in the U.S., during which two separate groups labored in splendid isolation before uniting their tracks with a golden spike at Promontory Point, Utah, in 1869. In the case of the cell, biochemists and physiologists (studying eggs) and geneticists (studying unicellular yeast) have finally achieved a satisfying intellectual union some 20 years after they began separate lines of investigation.

ANDREW W. MURRAY and MARC W. KIRSCHNER are colleagues at the University of California, San Francisco. Murray, who is assistant professor of physiology, obtained his Ph.D. from Harvard University in 1984. He worked in Kirschner's laboratory before taking his current post. Kirschner, who holds a 1971 doctorate from the University of California, Berkeley, has been professor of biochemistry and biophysics at the San Francisco campus since 1978. He moved to San Francisco from Princeton University.

When the two scientific groups began their work on the cell cycle, they had a common foundation of knowledge. For instance, 19th-century microscopists and other researchers had established that the cycle has two main phases: interphase and mitosis [*see illustration on opposite page*].

In interphase the cell nucleus remains intact. A cell grows continuously, stockpiling material enough for two cells. It also replicates its chromosomes, shortly before mitosis. The chromosomes, which are made of DNA and are stored in the nucleus, contain the genes.

In mitosis, two nuclei are formed from one. First the envelope encasing the nucleus breaks down, and the now duplicated chromosomes become attached to a structure called the mitotic spindle. Then the spindle segregates the chromosomes, ensuring that each daughter nucleus will have one copy of every chromosome. Next a nuclear envelope re-forms around each set of chromosomes, after which the rest of the cell, including the cytoplasm, divides to form two complete daughter cells that are genetically identical to the parent [see "The Mitotic Spindle," by J. Richard McIntosh and Kent L. McDonald; SCIENTIFIC AMERICAN, October 1989].

Sometimes a process called meiosis substitutes for mitosis. During sexual reproduction, new individuals are formed by the fusion of an egg with a sperm. Hence, if the cells of successive generations of an organism are to contain the same number of chromosomes as the cells of the parents, the egg and sperm must each carry only half that number. This halving of chromosome number is accomplished by meiosis, in which precursors of eggs and sperm undergo two rounds of chromosomal segregation in rapid succession without an intervening period of replication. In males the precursors divide symmetrically, producing four sperm. In females the precursors divide asymmetrically, producing one large egg and, usually, three very small cells that are discarded.

By 20 years ago it was also clear that the cell cycle is exquisitely regulated. One type of regulation concerns the control of cell size. At the end of mitosis, newly formed somatic (nonreproductive) cells are the same size the parent cell was at its birth, which means the parent somehow paces its division to occur precisely when its mass has been doubled.

Cells also have to coordinate various events in the cycle. For instance, they must avoid entering mitosis or meiosis until their chromosomes have been replicated; failure to wait can yield cells that lack a particular chromosome—an aberration that can kill a cell or, at times, promote cancer. What remained unclear was just how cells managed to coordinate the segregation of chromosomes with their replication and also to coordinate those processes with cell growth.

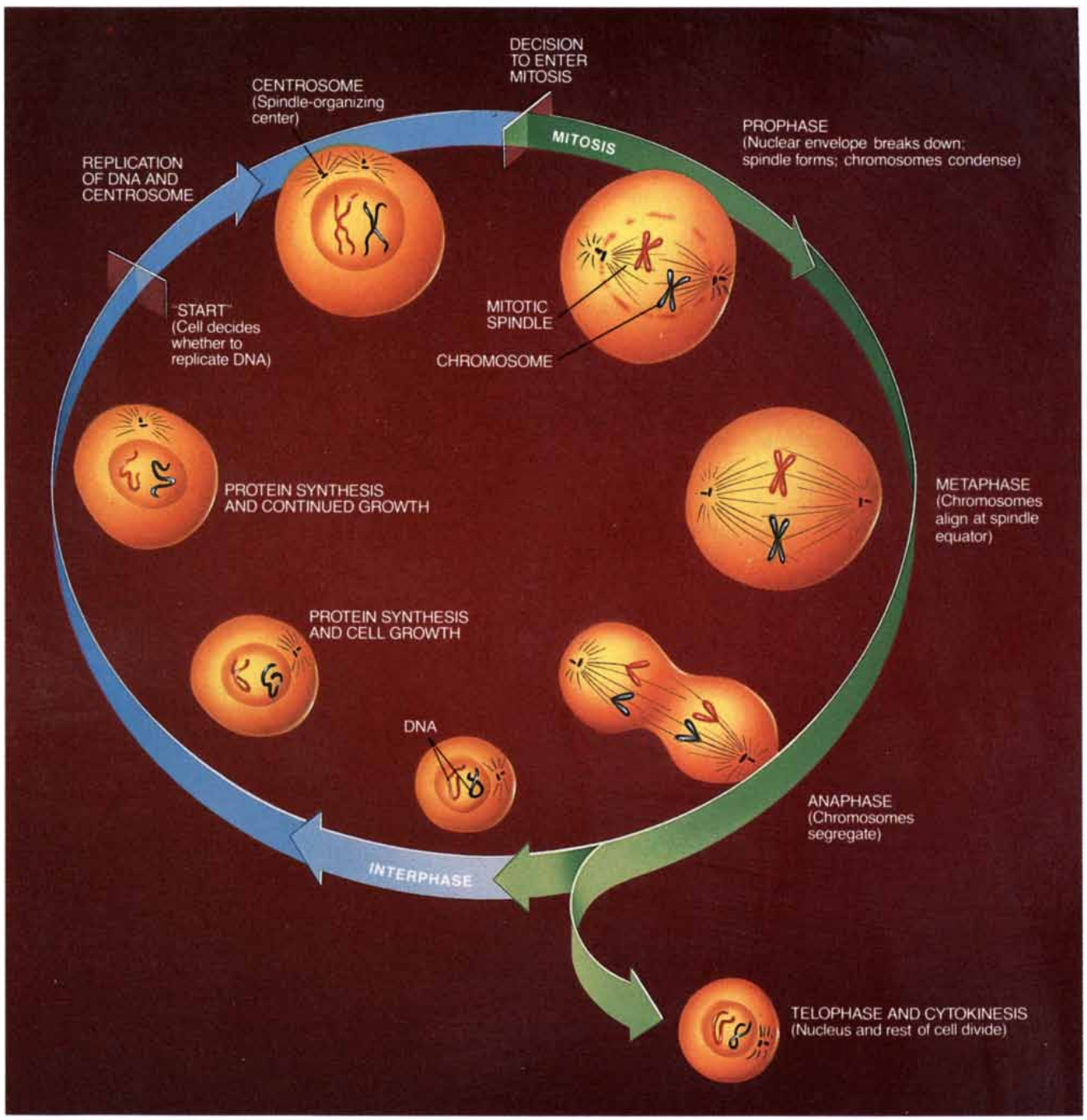
Yoshio Masui, then at Yale University, and L. Dennis Smith, then at Argonne National Laboratory, took a giant step toward answering that question in 1971. They independently identified a substance in frog eggs that seemed to control when mitosis and meiosis began.

The basic development of those eggs must be sketched briefly if Masui and Smith's findings are to be understood [*see illustration on page 58*]. The pre-

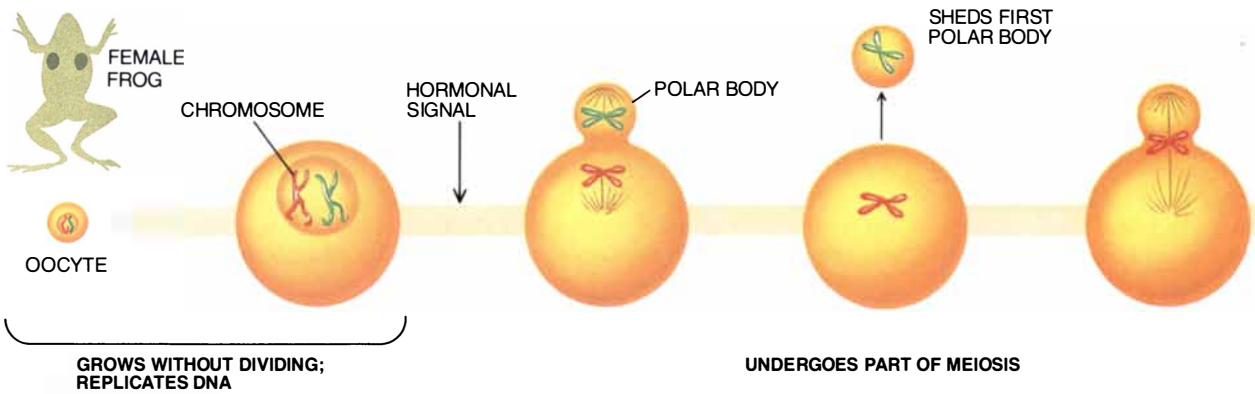
cursors of eggs, called oocytes, are born as small cells in the ovary. There they replicate their chromosomes and grow to many times their original size without dividing. Then they become "frozen" in that state indefinitely—until a hormonal signal stirs them. Under the influence of the hormone, they pass through the initial stages of meiosis and are released from the ovary as eggs. If they are fertilized by sperm, they complete meiosis and soon begin repeated mitotic cell cycles.

Masui and Smith found that frog oocytes undergoing meiosis contain a substance capable of inducing that same process in "immature" oocytes, those that are fully grown but have not yet received the hormonal signal to begin meiosis. Because meiosis is often referred to as maturation, Masui named the material maturation promoting factor (MPF).

Other workers then found that the same factor was active in all mitotic cells studied, including those of yeast, marine invertebrates and mammals. Hence, it appeared the MPF, which was not isolated until 1988, was a major regulator of both mitosis and meiosis.



CELL CYCLE, which culminates in the reproduction of cells, typically includes two phases—interphase, during which the cell grows, and mitosis, during which the nucleus and then the rest of the cell divide. (Temporally, mitosis takes up about 40 percent of the cycle in the cells of early embryos and less than 10 percent in most other cells.) Often the cycle includes two highly regulated transition points. In one, called START, the cell decides whether to replicate its DNA. In the other, the cell decides when to initiate mitosis. The protein cdc2 is the main regulator of passage through both points.



TWO KINDS OF CELL CYCLES occur as frogs are formed. Cells that will become eggs, called oocytes, are born in the ovary and then replicate their DNA and grow. Later a hormonal signal triggers meiosis: a specialized form of cell division that yields cells having half the normal complement of chromosomes. The oocytes divide asymmetrically. First, half of the

Considering that mitosis and meiosis involve many changes in the nucleus, such as construction of the spindle, it seemed reasonable to suspect that events in the nucleus might influence the machinery that ran the cell cycle, including the activity of MPF. Yet Koki Hara and Peter Tydeman of the Hubrecht Laboratory in Utrecht and one of us (Kirschner) found evidence that argued against this notion.

Doubt was first raised when the collaborators explored the cause of a dramatic contraction that occurs in frog eggs just as the eggs enter mitosis. The contraction was thought to participate in cell division, but surprisingly it continued at regular intervals even when mitosis was blocked. Neither prevention of spindle formation nor complete removal of the nucleus stopped the periodic recurrence of the contraction.

The group concluded from these data that the cell cycle in frog eggs was not controlled by events in the nucleus. Instead the process was driven by an autonomous oscillator: a set of chemical reactions in the cytoplasm that, with the regularity of a clock, produced the periodic contractions of the egg and presumably controlled other aspects of mitosis as well.

Did the oscillator, or "clock," in fact control the activity of MPF? John C. Gerhart and Michael Wu of the University of California at Berkeley and one of us (Kirschner) demonstrated that it did. They found that the activity of MPF fluctuated: the factor was always detectable during mitosis but never during interphase. Moreover, the activity oscillated even when events in the nucleus were disrupted.

Further studies yielded clues to how MPF was regulated. Initial experiments showed that newly fertilized frog eggs have stockpiles of the materials needed to replicate DNA and build the mitotic spindle, and so they do not produce those materials anew during the first several mitotic cycles after fertilization. Despite these stockpiles, the cells must make certain proteins in the cytoplasm during interphase if mitosis is to begin. Related experiments then showed that in cells arrested during interphase by the experimental inhibition of protein production, injection of a crude extract of active MPF could bypass the requirement for protein synthesis and trigger mitosis.

That last finding helped to confirm that MPF was the normal inducer of mitosis. It also suggested that one or another of the proteins made in the cytoplasm during interphase was essential to the activation of that factor.

While cell biologists were amassing evidence for the idea that the alternation of interphase and mitosis was driven by self-propelled chemical reactions in the cytoplasm, geneticists were gathering evidence for quite a different picture. Their data suggested that the cell cycle should be viewed as a carefully regulated assembly line. In such a linear system the completion of one event, such as DNA replication in the nucleus, would be required to trigger the next event, such as the initiation of mitosis, just as the fall of one domino in a series depends on the toppling of previous dominoes. The two views, sometimes called the clock theory and the domino theory, seemed incompatible, but eventually their contradictory findings would be explained.

Leland H. Hartwell of the University of Washington pioneered the genetic line of cell-cycle research roughly 20 years ago in experiments with brewer's yeast, *Saccharomyces cerevisiae*. The unicellular organism differs from many cells in that it does not divide by pinching in half. Instead, after starting to replicate its DNA in interphase, it sprouts a bud, thereby initiating mitosis. This bud grows continuously, as does the parent cell, and then separates, marking the end of the cycle in that yeast.

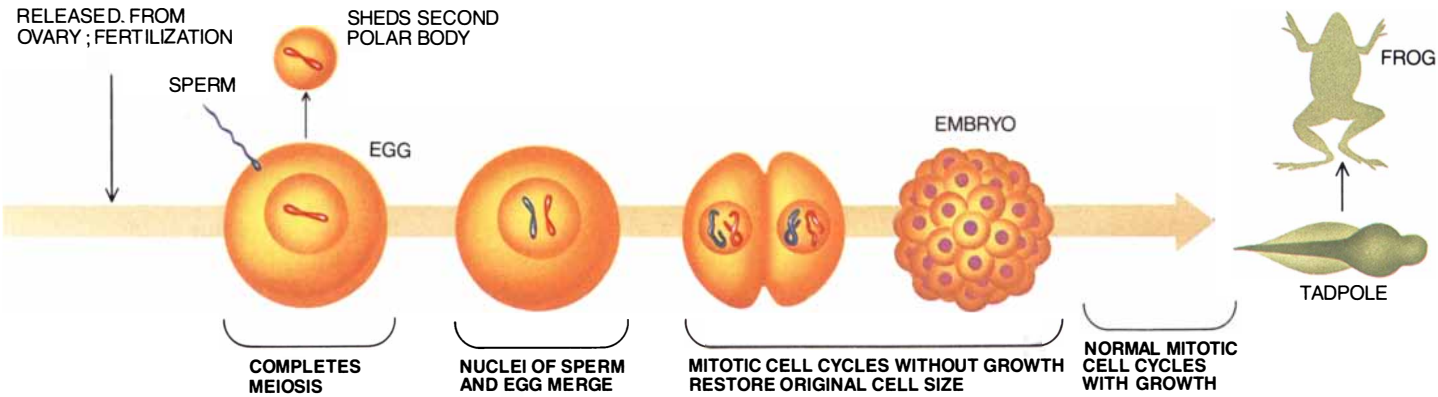
Hartwell began by identifying mutant forms of the yeast that became "stuck" at specific points in the cell cycle. He reasoned that the deranged cells each reflected an alteration in a gene whose product was critical to passing the point of arrest. (Each gene carries instructions for making a single protein.) Those crucial genes are now known collectively as cell-division cycle (*cdc*) genes.

By arranging the mutants according to the moment when their progress through the cell cycle was halted, Hartwell elucidated the normal sequence in which *cdc* genes must act. He also demonstrated that initiation of certain steps was dependent on the completion of one or more earlier steps. For instance, he found that completion of mitosis was dependent on assembly of the spindle.

Inspired by Hartwell's discoveries, Paul Nurse and his colleagues, then at the University of Edinburgh, did similar studies of fission yeast, *Schizosaccharomyces pombe,* which has a cell cycle more closely resembling that of mammalian somatic cells. During interphase, this cylindrical cell grows to twice its original length. Then, at the end of mitosis, it divides into two cells of equal size.

As Hartwell had done earlier, Nurse identified mutants that became stuck at specific parts of the cell cycle. Then he deciphered the normal sequence of activation of the *cdc* genes associated with the mutants.

One of those genes, *cdc2,* was particularly intriguing because its correct ac-



chromosomes are directed into a small cell called a polar body, which is discarded. Then the oocyte begins a second round of division and is released from the ovary as an egg. If it is fertilized, it completes meiosis, discarding a second polar body. Mitotic cycles follow, leading to creation of a frog. Mitosis and meiosis are controlled by the same molecules.

tivity seemed crucial for entry into mitosis. Certain mutations of the *cdc2* gene resulted in the production of an inactive version of the protein and thereby prevented cells from beginning mitosis. Other mutations led, in contrast, to production of a form of the protein that induced cells to undergo mitosis earlier than usual.

The *cdc2* gene product certainly seemed a good candidate for the prime regulator of mitosis—perhaps it was MPF itself. MPF had not yet been isolated, however, and so Nurse could not determine whether it and the cdc2 protein were the same substance. Still, he could ascertain whether the *cdc2* gene, like MPF, was important in other cells, which would suggest cdc2 could well be a universal regulator of mitosis.

He and David H. Beach, both then at the University of Sussex in England, began by screening the genes of budding yeast to see if any of them might "rescue" fission yeast that were locked in interphase by inactivation of the *cdc2* gene. Introduction of one of those genes did enable the fission yeast to undergo mitosis. The rescuer, it turned out, had been identified previously by Hartwell as a member of the *cdc* family in budding yeast.

Nurse then did an even more ambitious experiment, introducing segments of human DNA into cells of fission yeast that themselves carried inactive *cdc2* genes. Insertion of one particular piece of human DNA did induce mitosis, indicating that even human cells include a form of the *cdc2* gene. When the amino acid sequences of the human and yeast *cdc2* gene products were finally worked out in 1987, they turned out to be remarkably similar. A billion years of evolution had conserved this crucial protein, producing little change in its structure and none in its function.

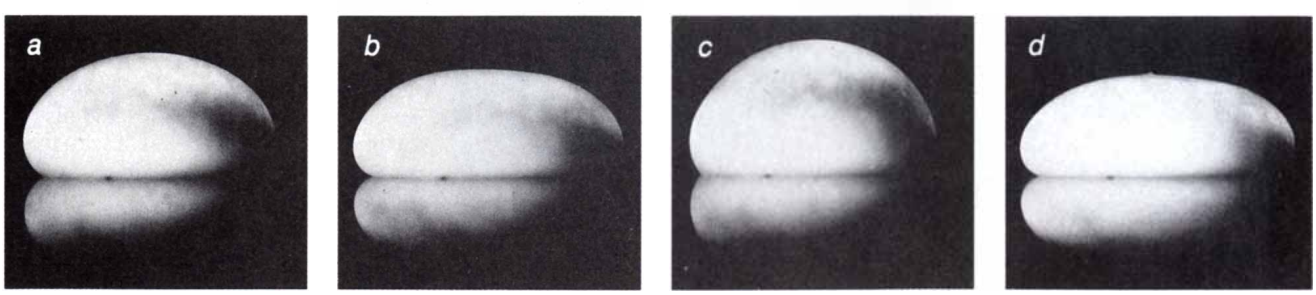
This protein is now known to be crucial to mitosis in all eukaryotes. All versions are called cdc2 proteins, regardless of the organisms from which they are derived.

From their chemical structure, cdc2 proteins have been identified as protein kinases: enzymes that transfer phosphate groups from ATP (adenosine triphosphate), a major energy carrier, to proteins. In recent years it has become clear that the addition and removal of phosphates is a major means of regulating the activity of cellular proteins. Removal is accomplished by the enzymes known as phosphatases.

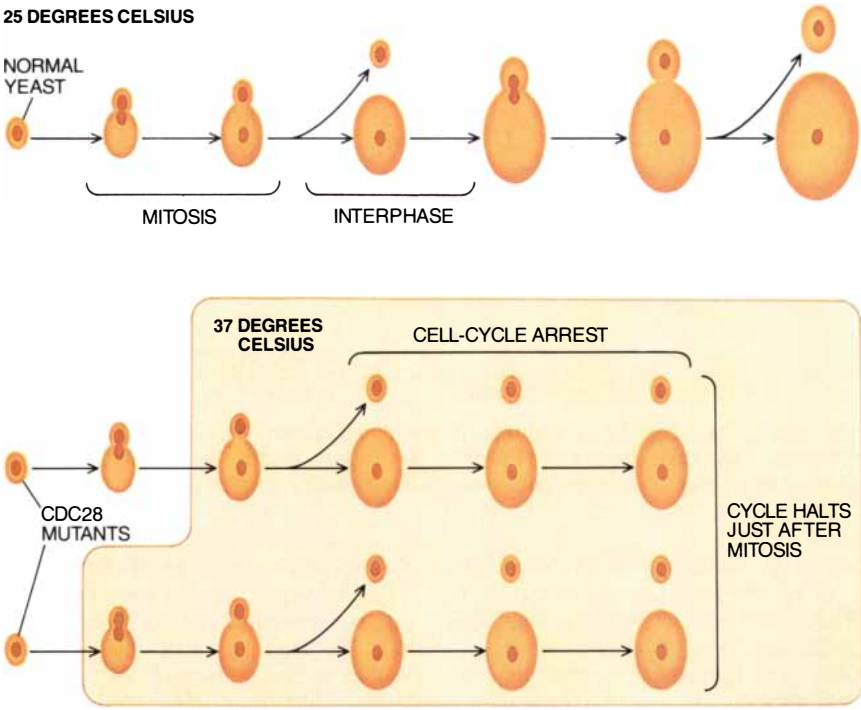
As the genetic studies were progressing, so were studies of MPF. In particular, Manfred J. Lohka and James L. Maller of the University of Colorado Medical School were busy trying to purify the factor. Many had failed before them, but in 1988 they managed to isolate a small amount and to ascertain that the substance consists of two protein molecules.

At that point, the amino acid sequence of the two proteins was not yet known, but several findings indicated that one of them was cdc2. For instance, the cdc2 protein seemed to have the same molecular weight as one of the MPF constituents. Moreover, that constituent was recognized by antibodies specific for yeast and human cdc2 proteins.

Around the same time, Beach and his colleagues showed that the cdc2 protein was active during mitosis in human cells in culture. Then several other teams, using a variety of methods, independently confirmed that the cdc2 protein was indeed a component of MPF. This last finding was the golden spike that united the frog and yeast studies and raised the possibility that the fundamental regulation of the cell



FROG EGG CONTRACTS, increasing in height, as mitosis begins (*a* and *c*); then the contraction disappears during interphase (*b* and *d*). The contraction recurs even if the nucleus is removed—evidence that, at least in certain kinds of eggs, the cell cycle is regulated by an autonomous oscillator: a series of self-perpetuating chemical reactions in the cytoplasm.



BREWER'S YEAST REPLICATES by budding (*top*). Certain temperature-sensitive mutants fail to complete a particular stage of the cell cycle after they are heated to 37 degrees Celsius, because they have a defect in a gene that is critical to passage through that stage. For instance, the mutant shown in the bottom two rows stalls at a specific point in interphase, regardless of when in the cell cycle the temperature is raised. Study of such mutants led to identification of the family of genes—called cell-division cycle (*cdc*) genes—that control progress through the cell cycle.

cycle was quite similar in all eukaryotic organisms.

The convergence was satisfying but not completely so. The discovery that the cdc2 protein was a part of MPF did not explain why MPF was active during mitosis but was not active during interphase.

In all cell types studied the concentration of the cdc2 molecule had been found to remain constant throughout the cell cycle. This constancy meant that something else—perhaps the second component of MPF—activated and inactivated cdc2 and thereby regulated the activity of MPF. Presumably this other substance was synthesized anew during each interphase; protein synthesis, it will be recalled, had earlier been found essential for activation of MPF.

This logic was certainly a rational basis for investigating the problem of MPF activation. But identification of the activating molecule actually emerged from a serendipitous observation made years before the cdc2 protein was found to be a component of MPF.

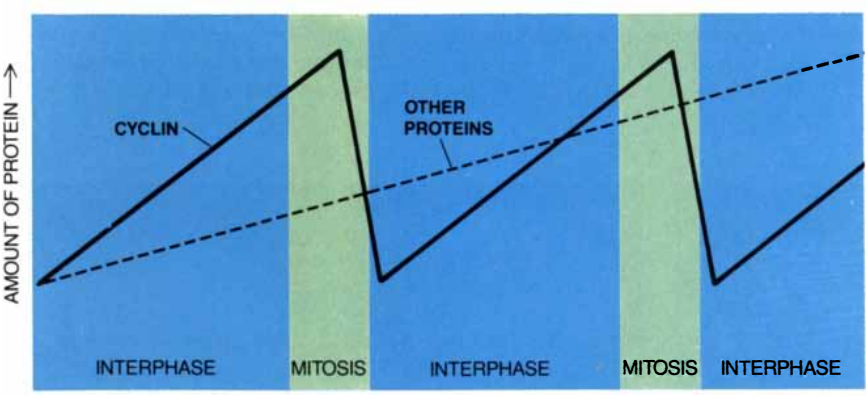
In the early 1980s Tim Hunt of the University of Cambridge was teaching the annual course in physiology at the Marine Biological Laboratory in Woods Hole, Mass. He and his students were investigating dramatic changes in the levels of protein synthesis that occur after sea urchin eggs are fertilized.

They found that the amount of virtually all newly synthesized proteins increased continuously after fertilization. One protein, however, abruptly disappeared at each mitosis, only to accumulate again during interphase. Hunt named the unusual substance cyclin.

The group went on to demonstrate that cyclin was produced at a constant rate throughout the cell cycle. It disappeared at the end of mitosis because it was rapidly degraded, and it accumulated in interphase because it was broken down much more slowly than it was produced. The pattern of fluctuation suggested that cyclin might be the molecule that regulated MPF activity.

Experiments in 1986 by Joan V. Ruderman of Harvard University lent credence to that notion. Working with surf clams, her group extracted messenger RNA for cyclin: RNA copies of the cyclin gene, which serve as the templates for the protein's production. Then they injected that messenger RNA into immature frog oocytes. The oocytes underwent meiosis, which meant both that the RNA was translated into cyclin and, more significantly, that the protein could indeed help regulate the cell cycle.

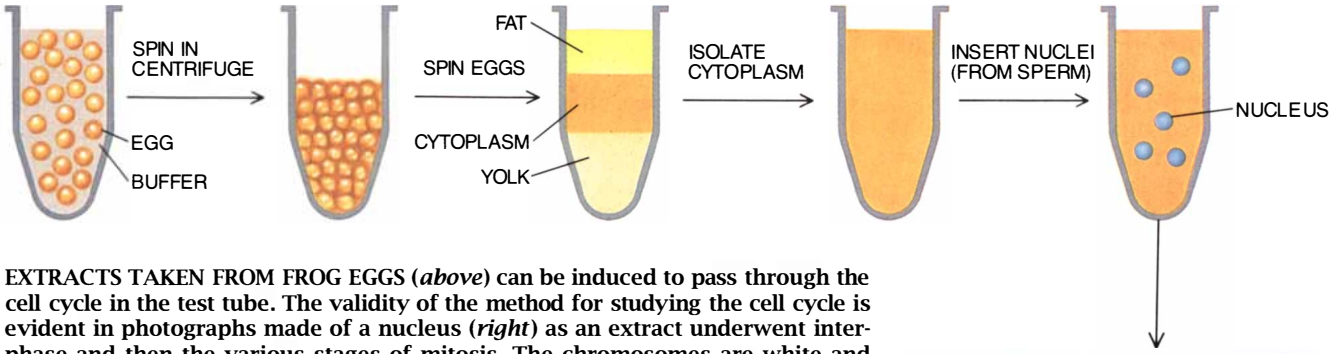
Today it is known that cyclin is the second component of MPF and participates in the activation of the cdc2 protein and thus MPF. At the same time, though, the exact role in the cell cycle had yet to be worked out.



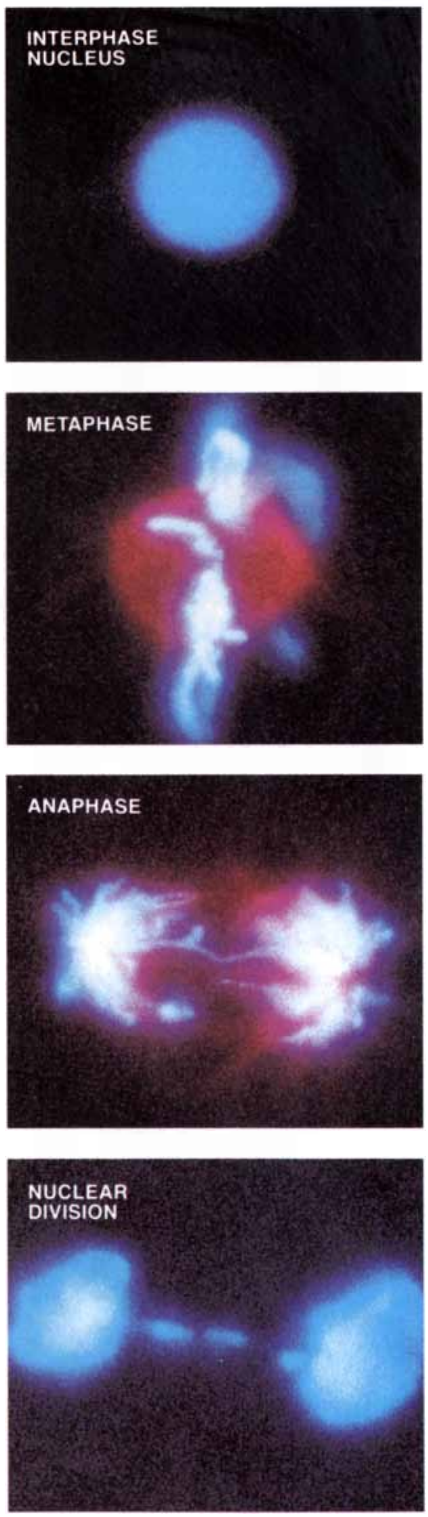
OSCILLATIONS in the level of the protein cyclin were identified in sea urchin eggs, where it rose during interphase and fell during mitosis. The discovery that cyclin was the only protein that fluctuated during the cell cycle suggested that it might help control the onset of mitosis. Cyclin is indeed a regulator: it influences the activity of the cdc2 protein, which together with cyclin guides cells into mitosis.

In order to advance research into cyclin, biologists first had to make the cell cycle more accessible to experimental manipulation. In about 1987 we and Christopher C. Ford and his colleagues at Sussex devised a way to do just that. The two groups independently produced extracts of frog eggs that could pass through several cell cycles in the test tube—complete with DNA replication, mitosis and the associated oscillations of MPF activity [*see illustration on opposite page*].

If the cell cycle was so simple that



EXTRACTS TAKEN FROM FROG EGGS (*above*) can be induced to pass through the cell cycle in the test tube. The validity of the method for studying the cell cycle is evident in photographs made of a nucleus (*right*) as an extract underwent interphase and then the various stages of mitosis. The chromosomes are white and blue; the mitotic spindle, which segregates chromosomes during mitosis, is red.



cyclin was the only oscillating protein that had to be produced anew in each cycle to keep the cycle running, proof of that simplicity would include confirming two predictions. One was that the cycle would continue to run even if the synthesis of all proteins except cyclin were blocked. The other was the converse: blockage of cyclin production alone would arrest the cell cycle in interphase.

We tested the first prediction by destroying all messenger RNA in frog egg extracts. Since proteins are made from these templates, the system no longer produced new proteins. It also failed to enter mitosis. Now we were ready to see if the restoration of only cyclin production would trigger mitosis.

We therefore introduced messenger RNA for sea urchin cyclin, a gift from Hunt. Sure enough, we could see the nuclei go through mitosis, indicating that the RNA had been translated into protein and that the protein had induced mitosis in the previously stalled extracts. When more cyclin RNA was added, the rate of cyclin synthesis increased and the duration of interphase decreased.

Hunt and his students evaluated the second prediction—that failure to synthesize cyclin would block mitosis. This proposition, too, was upheld. When they prevented the production of cyclin but no other protein in frog egg extracts, the extracts became stalled in interphase.

In our studies we found that, as was true for Hunt's sea urchin eggs, cyclin accumulates during interphase and is destroyed at the end of mitosis. The abrupt degradation led us to propose that cells might not be able to complete mitosis until cyclin is gone. Indeed, when we induced frog eggs or our extracts to make a truncated version of cyclin that could induce mitosis but could not be degraded, the eggs and extracts lost the power to complete nuclear division and remained arrested in mitosis.

Thus, by 1989 the collected experiments left little doubt that the degradation of cyclin is important to passage through mitosis and that the substance must be made anew in each interphase to activate MPF, induce mitosis and direct the cell cycle.

How does cyclin activate MPF or, more specifically, the cdc2 fraction of MPF? It turns out that the mere joining of cyclin and the cdc2 protein is not by itself enough to activate the complex. Other reactions must modify both cdc2 and cyclin before MPF becomes functional.

Proteins involved in controlling these modifications have been identified genetically and biochemically. One particularly interesting molecule, found by genetic methods, is named cdc25. It is intriguing because its accumulation, rather than that of cyclin, determines when mitosis occurs in certain cells, such as those of fly embryos late in development and fission yeast. The synthesis of cyclin is still required, but it is the rate of cdc25 accumulation, not cyclin accumulation, that determines when cdc2 becomes active and thus is the "rate-limiting factor" regulating when mitosis begins.

The finding raises an important point. Even though the cdc2 kinase is the central cell-cycle regulator in eukaryotic cells and even though the molecules that modify the cdc2 protein are apparently the same in all cells, the details of how the kinase is regulated can vary from organism to organism and from cell to cell within a single organism. In some cases, cdc25 may control the activation of the cyclin-cdc2 complex. In other cases, cyclin itself may control the activation; in still others, modulators that are still to be identified are probably key.

We cannot yet describe in detail the regulation of the cell cycle in all organisms, but we can at least propose a model for the simplest case: the newly fertilized frog egg. The cdc2 protein is

maintained at a constant level at all times. For its part, cyclin is made continuously, but its levels rise during interphase and decline during mitosis. As cyclin accumulates in interphase, it combines with the cdc2 molecule to form what may be called pre-MPF. This form of MPF is not yet active: it will not transfer phosphate groups to proteins and cannot induce mitosis.

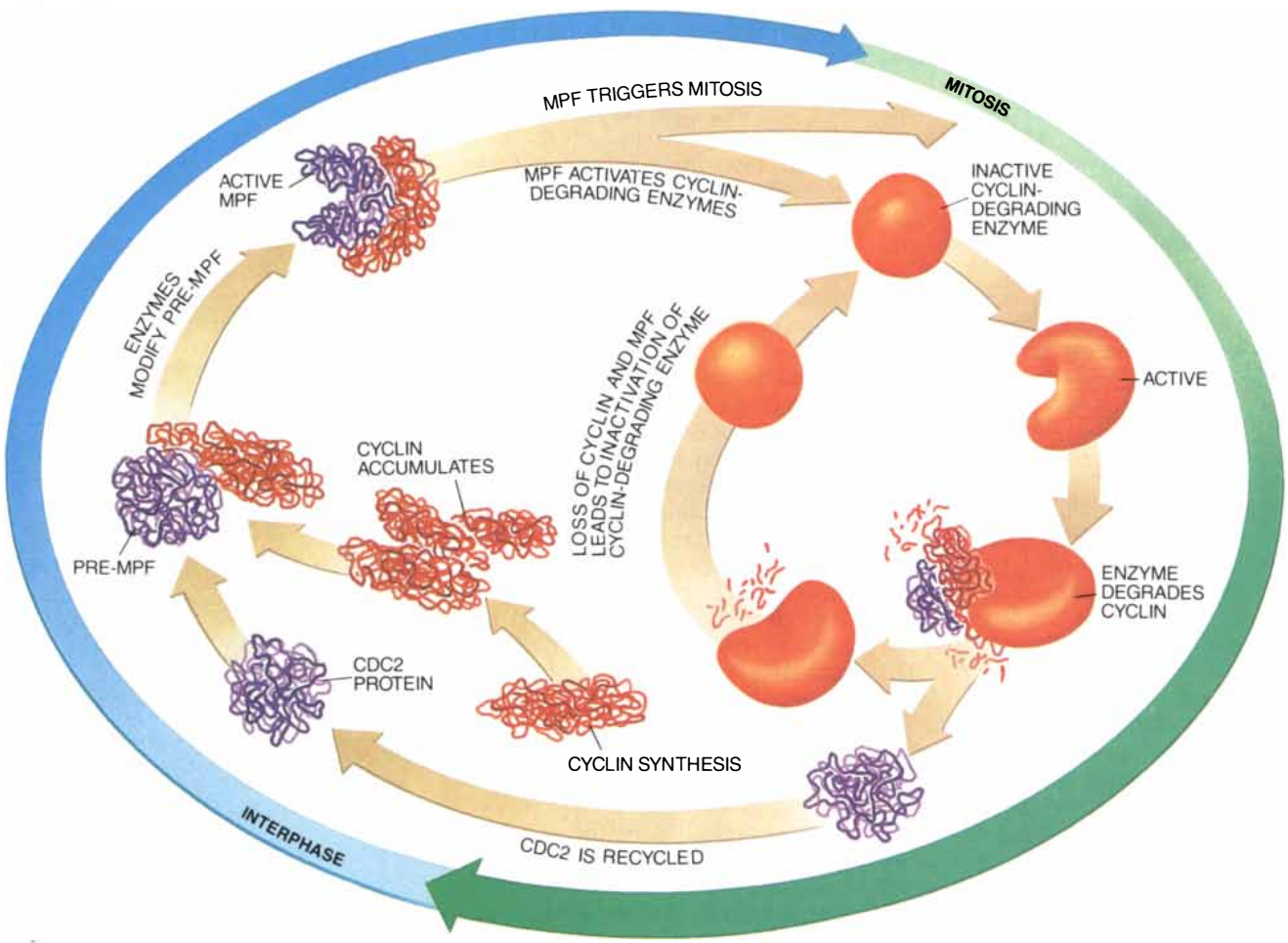
Pre-MPF is then converted to active MPF by enzymes, such as cdc25. Once activated, MPF serves as both a humble servant and a divine presence, directly and indirectly initiating all the events of mitosis. For instance, MPF has been found to initiate the breakdown of the nuclear envelope. As the servant, it directly phosphorylates envelope proteins known as lamins. As divinity, it orders other molecules to do its bidding: it triggers a cascade of molecular interactions that culminates in the further transfer of phosphate groups to the lamins. Phosphorylation causes the lamins to dissociate and thus leads to the disintegration of the envelope.

Active MPF not only controls the processes that result in the physical division of the nucleus and the rest of the cell—such as assembly of the spindle—it also activates enzymes that degrade cyclin. Mitosis ends when cyclin levels decline below some threshold. Without cyclin, the cdc2 protein (and thus MPF) cannot remain active.

As MPF loses effect, phosphatases gain the upper hand and remove any phosphate groups that MPF caused to be added to proteins during mitosis. In the case of the lamin proteins, the removal of the phosphates leads to the spontaneous reformation of the nuclear envelope. Phosphatases also inactivate enzymes that MPF had switched on, including enzymes that degrade cyclin. The combination of the silencing of those cyclin-destroying enzymes and the continued synthesis of cyclin enables cyclin to accumulate once again in interphase—and the cell cycle to begin anew.

In frog eggs, changes in cyclin levels occur independently of any events in the nucleus, and so the egg studies support the existence of an autonomous oscillator as the driving force behind the cell cycle. Yet, as the genetic studies suggested, in most other cells, nuclear events modulate the events of the cell cycle. Both yeast and the somatic cells of multicellular organisms have mechanisms for delaying the entry into mitosis until DNA has been replicated and any damage to DNA has been repaired. Similarly, such cells do not begin to segregate their chromosomes during mitosis until every chromosome has been correctly attached to and aligned on the mitotic spindle.

Thus, both the clock and the domino theories are correct, depending on which cell type one is examining. For somatic cells, the domino theory seems



MODEL of how mitosis is controlled in frog eggs holds that a form of cyclin accumulates during interphase and associates with the cdc2 protein to form pre-MPF, an inactive form of MPF (maturation promoting factor). Then enzymes convert the complex into active MPF, which triggers mitosis and activates enzymes that degrade cyclin. As cyclin is destroyed, MPF disappears and the cyclin-degrading enzymes become quiet. Thus, cyclin accumulates once again. In various other cell types, passage through START is highly regulated as well—by a complex consisting of cdc2 and a second form of cyclin.

more appropriate. In other words, the oscillator that by itself regulates the cell cycle in frog eggs has become subject to an elaborate system of checks and balances.

We can speculate about how nuclear events might influence MPF activity in such cells. For instance, incomplete replication of DNA in interphase could generate a signal that halts the accumulation of cyclin or cdc25 or a related cdc molecule. In the same vein, one would think that the improper attachment of chromosomes to the spindle during mitosis would result in production of a signal to stop the degradation of cyclin temporarily.

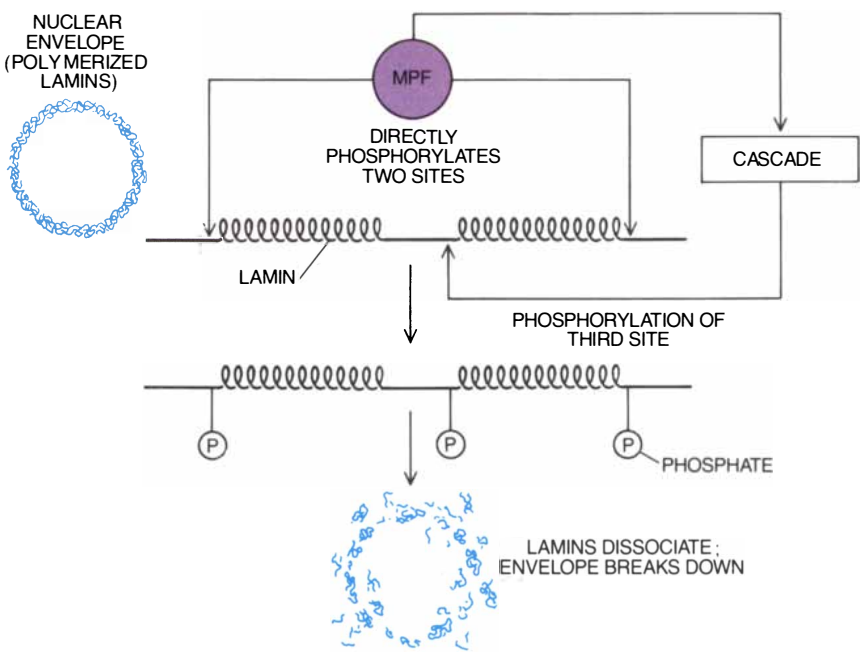
Such regulatory feedbacks and the biochemistry underlying them are not the only embellishments that have to be incorporated into a complete model of cell-cycle control. It is now known that in somatic cells and late embryos the decision to replicate DNA in interphase is as highly regulated as the decision to enter mitosis. The mechanism for making this second decision must be included in a full model.

This second checkpoint was first identified by Hartwell, who named it the START transition. He also showed in budding yeast that it is during this transition that the cell evaluates whether it has grown large enough to proceed safely to DNA replication and, from there, to mitosis. (When cells lack nutrients, they typically halt their progress through the cell cycle at START.)

Passage through START is controlled much as is the passage into mitosis. Once again progress depends on activation of the cdc2 protein, which is dependent on the accumulation of cyclin. But the cyclin involved in START is not the same one involved in mitosis. In fact, there are two classes of cyclin. One class regulates entry into mitosis and meiosis, and the other, structurally similar, class regulates the replication of DNA.

Movement through START is also controlled by nutrients, hormones and growth factors. These agents act by controlling the accumulation of cyclin prior to START. In contrast to the situation in frog eggs, where the "default" rule at the end of one mitotic cell cycle is to pass through another cycle of division, most cells automatically exit the cell cycle in interphase unless they receive specific external instructions to pass through the START checkpoint yet another time.

The existence of many layers of cell-cycle control in the majority of cells is not surprising. Multicellular organisms in particular must maintain checks and balances to coordinate cell-cycle events



MPF HELPS TO INITIATE MITOSIS in part by breaking up the nuclear envelope. It directly and indirectly adds phosphate groups to proteins called lamins that polymerize to form the envelope. The MPF phosphorylates two sites and triggers a cascade of reactions that ultimately induces another enzyme to phosphorylate a third site. The alteration of the lamin proteins causes them to dissociate.

both with one another and with the needs of the larger organism. The ability to regulate when cells will grow, divide and differentiate into specialized cells is critical to the orderly development of the embryo and to the health, and ultimately the survival, of mature organisms.

The progress made in research over the past 20 years, and especially over the past five years, is nothing less than extraordinary. The regulators of the cell cycle in frog eggs and yeast—cdc2, cyclin and such modulators as cdc25—appear to be the basic regulators of the cell cycle in all eukaryotic cells.

Yet the cells that have been the most informative are special cases in many ways. Frog eggs are virtually immune to extracellular controls that act on the cycles of other cells. And yeast are complete organisms in themselves. Now investigations will have to move beyond those simple systems to gain a better understanding of how cdc2, cyclin and their modulators interact with extracellular signals in multicellular organisms. Only then will it be possible to understand such diseases as cancer, in which regulation of the regulators somehow fails.

Another priority on the research agenda is to learn much more about how the cyclin-cdc2 complex participates in the various events of cell division: How exactly does it, say, help to initiate spindle assembly or the condensation of chromosomes? Which enzymes does the complex act on, and what exactly do those enzymes do during mitosis? What are the signals that mediate the activity of the complex when something goes awry in the nucleus during mitosis? With a little luck, such questions will be answered satisfactorily in the next round of cell-cycle research.

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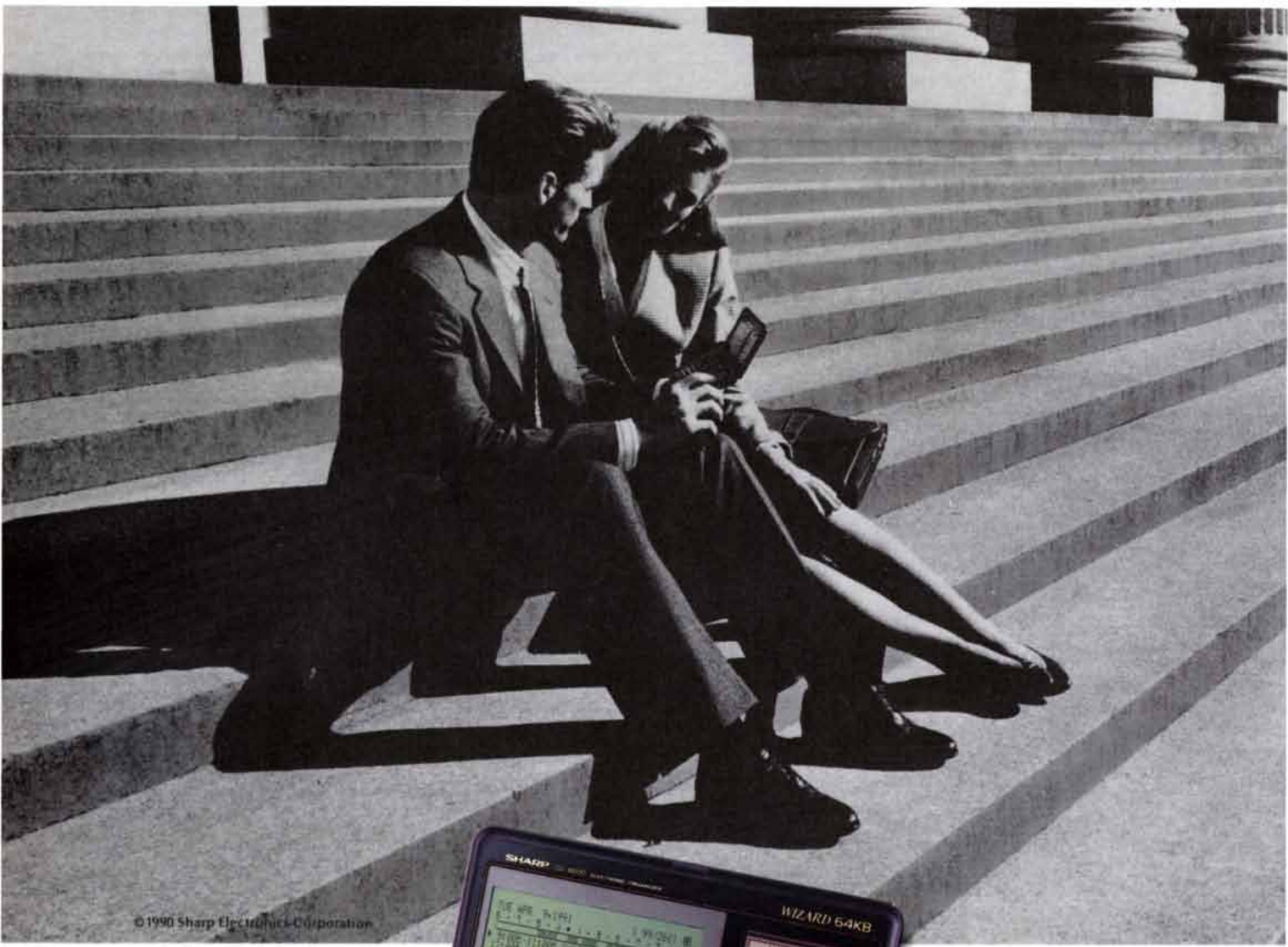

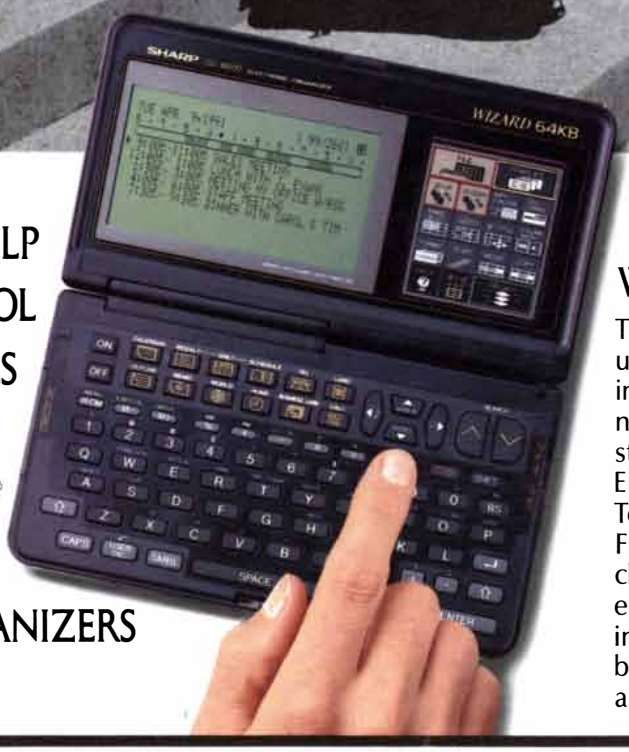

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Plateau Uplift and Climatic Change

The formation of giant plateaus in Tibet and the American West may explain why the earth's climate has grown markedly cooler and more regionally diverse in the past 40 million years

by William F. Ruddiman and John E. Kutzbach

The world climate that humans consider normal is in fact a geologically recent development. Prior to 40 million years ago most of the world was warmer and wetter than it is now. Rainfall tended to be evenly distributed throughout the year, and evergreen and warm deciduous forests covered much of the globe. Many types of climate and vegetation common today were almost entirely lacking. Because of the absence of strong seasonal and annual aridity, grasslands and deserts were rare. Because of the lack of extreme cold, northern spruce forests and tundra regions were small or nonexistent. The sea ice that now covers the Arctic Ocean was either limited in extent or completely absent, and immense glaciers, like the one now covering Greenland, did not exist.

During the past 40 million years, and particularly during the past 15 million years, this warm, wet climate largely disappeared. It persists today only in limited regions, such as southeast Asia, the Gulf Coast of the U.S. and the tropics. Colder climates and much greater regional extremes of precipitation have developed. Approximately three million years ago the earth grew so cool that it began to experience periodic ice ages, during which ice sheets covered much of the Northern Hemisphere. All of recorded history has taken place during a brief, mild interlude in what is essentially a glacial era.

What caused this cooling and diversification of climate and vegetation into a complex mosaic of many regionally distinctive types? Recent evidence points toward a particularly significant culprit: a spasm of geologic upheaval that resulted in the development of huge elevated plateaus in several regions, particularly southern Asia and western North America. Our research indicates that dramatic increases in elevation of these plateaus have had significant physical and chemical effects on the atmosphere that have helped shape modern-day climatic trends.

Over the course of tens of millions of years, a broad array of processes influence the earth's climate. No single factor can plausibly explain the whole panoply of climatic change. Even allowing for the complexity of the problem, however, the explanations previously available for the progressive changes have not proved entirely satisfactory.

One school of thought focuses on the changing positions of the earth's continents and oceans. The Atlantic Ocean has expanded at the expense of the Pacific Ocean, whereas an ancient equatorial sea that extended across much of Eurasia (called the Tethys Sea) has shrunk to become the modern, much smaller Mediterranean Sea. In addition, the fraction of continents flooded by shallow inland seas has slowly decreased, exposing large amounts of land and creating climates less moderated by the temperature-stabilizing effects of oceans. Computer model simulations show that changes in the arrangement of the continents and the size of inland seas can have important effects on global climate over very long intervals of geologic time. But they are significantly less convincing as sole explanations for the dramatic changes of the past 40 million years.

Some researchers theorize that the opening and closing of isthmuses could create critical "gateways" for altering oceanic circulation and hence climate. For example, the eastern end of the Mediterranean closed around 23 million years ago, and the Isthmus of Panama closed shortly before the glacial era that began three million years ago. No one has yet explained, however, how such relatively abrupt topographical changes could account for the observed substantial, progressive climate changes.

Another possibility is a long-term decline in the concentration of carbon dioxide in the atmosphere, which would lessen the amount of heat trapped by the atmosphere and lead to "greenhouse cooling." The amount of carbon dioxide in the earth's atmosphere over

WILLIAM F. RUDDIMAN and JOHN E. KUTZBACH have collaborated since 1986 to learn about the effect of plateau uplift on global climate. Ruddiman is a researcher at the Lamont-Doherty Geological Observatory of Columbia University and adjunct professor of geology at the university. His research initially focused on the interaction between ice sheets and the North Atlantic Ocean during the most recent ice ages; he has since concentrated on the link between longer-term tectonic and climatic change. Kutzbach is professor in the department of meteorology and the Institute for Environmental Studies at the University of Wisconsin at Madison. He also directs the university's Center for Climatic Research. He has extensively utilized quantitative computer models to study climate changes associated with periodic shifts in the earth's orbit, the uplift of plateaus, and the evolving configurations of the continents.

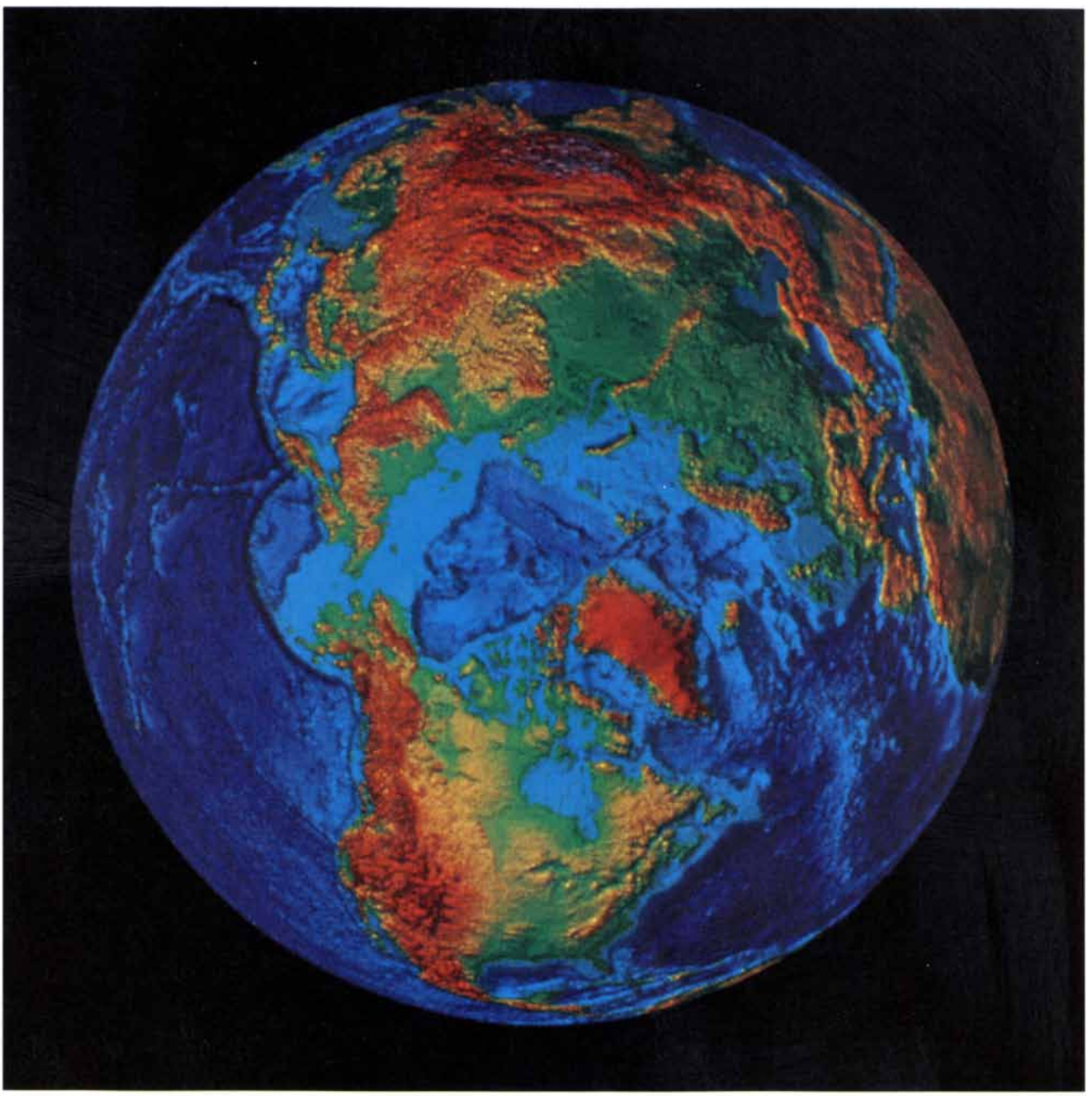
POLE-ON VIEW of the earth's Northern Hemisphere shows the huge Tibetan Plateau and extensive elevated territory in the American West. The uplift of these regions in the past 40 million years has altered atmospheric circulation and climate. Red depicts the highest elevations and blue the lowest in this map prepared at the National Geophysical Data Center in Boulder, Colo.

million-year time scales is controlled by two major processes. Chemical weathering of continental rocks removes carbon dioxide from the atmosphere and carries it in dissolved chemical form to the ocean, where it is taken in by marine biota and deposited in sediments on the seafloor. Tectonic activity eventually frees this trapped carbon dioxide, in the following manner. The motion of the earth's lithospheric plates transports the seafloor to ocean trenches, where subduction carries old crust and sediments down toward the earth's hot interior. At great depths, the sediments melt, releasing carbon dioxide, which emerges from the volcanic islands that overlie the buried crust and rejoins the atmosphere, completing the cycle [see "Modeling the Geochemical Carbon Cycle," by Robert A. Berner and Antonio C. Lasaga; SCIENTIFIC AMERICAN, March 1989].

If the pace of seafloor spreading (and hence of subduction) slowed significantly, less carbon dioxide would be vented to the atmosphere, the atmosphere would become relatively depleted of carbon dioxide and temperatures would fall. In fact, globally averaged seafloor spreading rates show little or no net change in the past 40 million years. Nevertheless, we will describe later how enhanced removal of carbon dioxide from the atmosphere by chemical weathering may have played a significant role in global cooling.

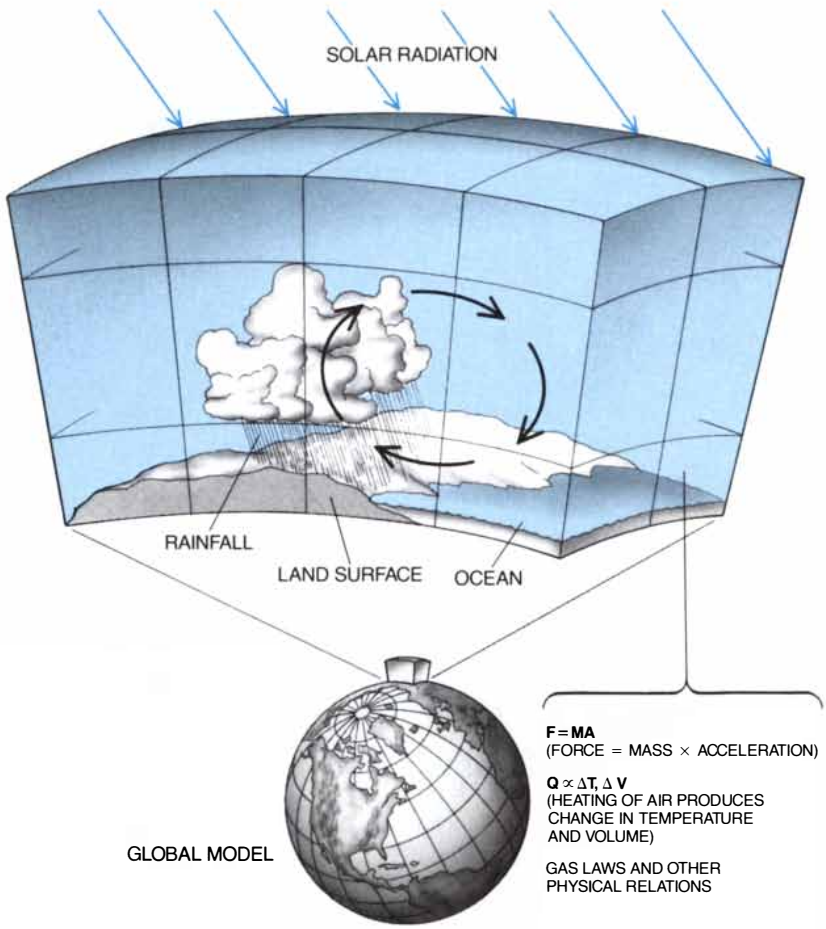
The limitations of the various explanations of the worldwide cooling led us to search for another. A convincing explanation would involve some process or factor that has changed in unison with the earth's climate and that affects climate in physically plausible ways.

As long ago as the 19th century, geologists proposed that mountain building can cause climatic change. Mountain uplift cools the high-altitude crests and divides precipita-



How Global Climate Is Modeled

In the global climate model, a system of equations calculates time-dependent changes in wind as well as temperature and moisture changes in the atmosphere and on the land. The model also predicts alterations in the temperature of the ocean's surface. The globe is divided into thousands of boxes whose sides typically extend several hundred kilometers in latitude and longitude and a few kilometers in altitude. The computer treats each box as one element as it calculates the evolving global climate. The model imposes seasonal and latitudinal changes of incoming solar radiation, the height and shape of continents, and other external conditions that affect the atmosphere's behavior. The equations must be solved in hourly increments over at least 20 years of simulated time to generate accurate statistics. For this massive effort, we used a CRAY supercomputer at the National Center for Atmospheric Research.



tion patterns into heavy rainfall or snowfall areas on the upwind side and areas of so-called rainshadow drying (produced by air that has shed most of its moisture) on the downwind side. Critics have noted, however, that these effects are relatively local in scale.

Our recent work suggests that a more subtle, yet more fundamental, kind of uplift could influence climate over much broader regions, indeed across virtually the entire Northern Hemisphere. This uplift consists of the gradual rising of certain continental areas into broad plateaus.

The two largest masses of high, rocky terrain in the Northern Hemisphere today are the area encompassing the Tibetan Plateau and Himalaya Mountains in southern Asia and the broad region of the American West centered on the Colorado Plateau, extending from the Sierra to the Rocky mountains. A wide variety of geologic evidence indicates that these regions rose substantially during the past 40 million years. We therefore focused our research on these plateaus.

The Tibetan Plateau covers a region of more than two million square kilometers, nearly one third the size of the continental U.S. Its average elevation exceeds 4.5 kilometers (about 15,000 feet), comparable to the elevation of the highest individual mountain peaks in the American West. The Himalayan mountain range forms a narrow rampart along the southern margin of this massive plateau.

Fossil plants and pollen found in valley deposits testify to the changing climate of Tibet. Today vegetation on the Tibetan Plateau consists mostly of grass, herbs and scrub vegetation adapted to the harsh steppe climate, which involves severe winters and seasonal drying. Some five to 10 million years ago the vegetation was very different: pollen deposited then indicates the presence of deciduous trees comparable to those in modern temperate forests. Prior to 30 million years ago tropical and subtropical forests similar to those in the southeastern U.S. existed in Tibet. These changes suggest the region has cooled considerably.

Increasing elevation is the most plausible explanation for the drop in temperature. Near the surface the atmosphere cools about 6.5 degrees Celsius for every kilometer gain in altitude. The vegetation changes, along with assorted tectonic and sedimentary evidence, imply that the Tibetan Plateau has risen more than four kilometers, roughly two kilometers of which may have occurred within the past 10 million years. Lower-lying regions of southern China and southeast Asia to the east and southeast of Tibet have harbored much the same warm-adapted vegetation for more than 40 million years. Even more definitively, uplift accounts for the presence of oceanic sediments in late Cretaceous (approximately 70 million years old) strata in Tibet.

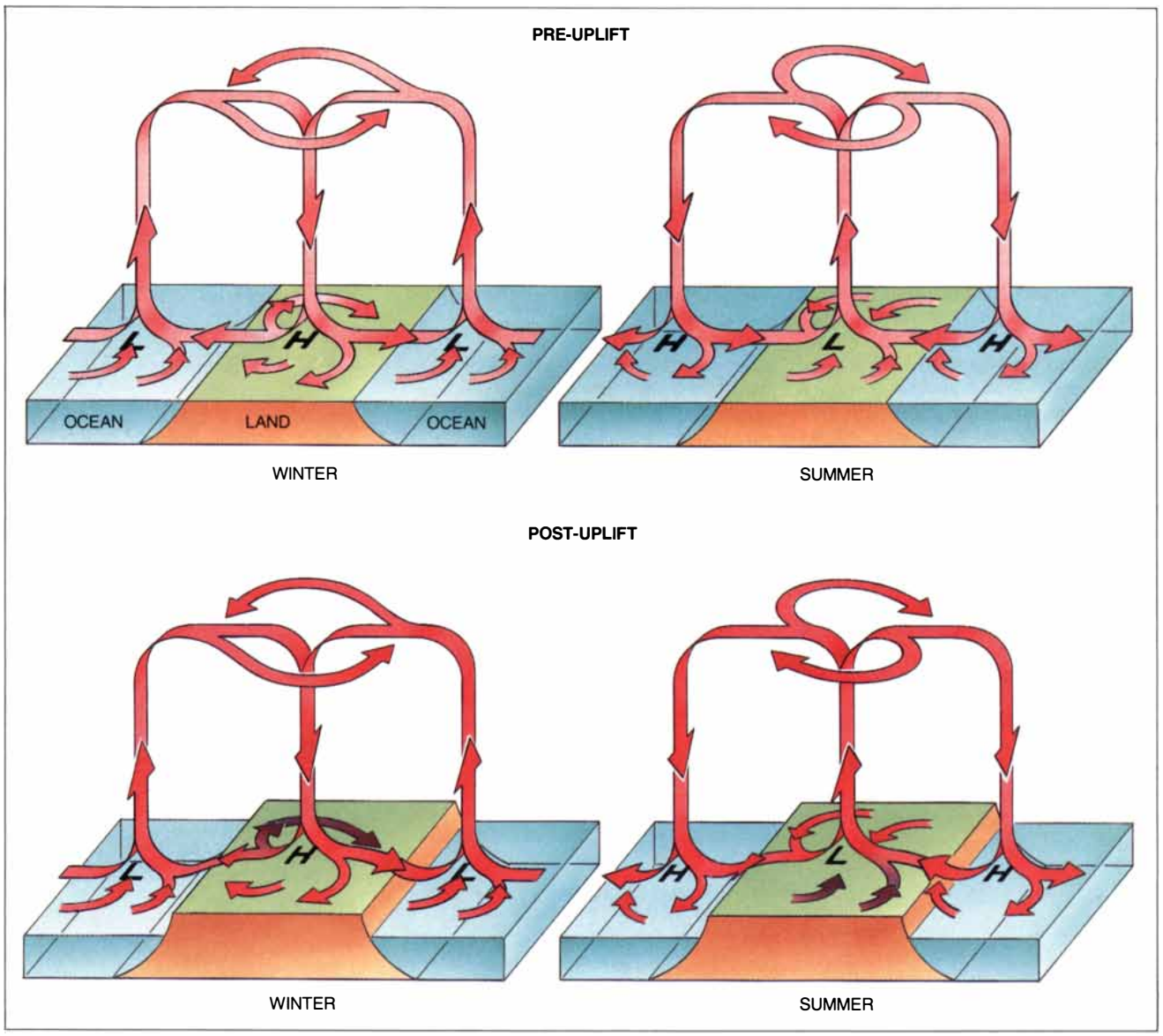
The reasons for the Tibetan uplift appear to be connected to the tectonic motions of the continents. India separated from Antarctica about 130 million years ago, drifted northward and collided with Asia around 40 million years ago. The compressive stresses that built up after the two continents collided somehow forced Tibet upward, although the exact mechanism responsible for the uplift is still being debated.

The broad upward bulge in North America that extends from the Sierra range in California to the plains of Colorado and Nebraska east of the Rockies also has strongly influenced climate in the Northern Hemisphere. In the mid-

dle of the bulge lie the Colorado Plateau and the basin and range provinces at mean altitudes of 1.5 to 2.5 kilometers above sea level. At the eastern end of the bulge, the so-called Great Plains actually form a tilted ramp that falls gradually from Denver (the "Mile-High City"), just east of the Rockies, to low elevations (less than 300 meters above sea level) at the Missouri River in the middle of the continent.

A widely cited but still controversial chronology of uplift in the American West resembles that of uplift in Tibet. In this view, elevations through most of this area were very low (on average, well under a kilometer above sea level) 40 million years ago, when upward motion of the land began. Large sections of the region rose to about half of the modern value sometime between 10 and five million years ago and subsequently attained present-day altitudes.

Plant fossil evidence of uplift is more difficult to interpret for the American West than it is for Tibet. Another kind of geologic evidence—the history of sedimentation and erosion recorded in the rocks—offers a stronger indication of the changing American topography. Forty to 30 million years ago eastward-flowing rivers on the High Plains, such as the Arkansas and Platte rivers, deposited mainly clay and fine silt. Much of the sediment coarsened to sand by 20 to 15 million years ago and then to pebbles and cobbles by 10 to five million years ago. Similar changes in river sedimentation have also occurred at the other end of the uplifted bulge on the western flanks of the Sierra. These have taken place mostly within the past 10 million years. In the past five million years, parts of the Arkansas and Platte rivers on the westernmost High Plains near the Rockies have cut into their beds by several hundred meters. Massive downcutting of the Grand Canyon



CIRCULATION of the atmosphere at mid-latitudes is driven partly by temperature differences. In summer, heated air rises over the land and flows outward, creating a low-pressure area at the surface and a compensating inflow from the cooler, high-pressure centers over the water. In winter the oceans are warmer than the land, and the flow reverses, as descending air results in high pressure over land surfaces. After uplift, the thin air over high plateaus amplifies temperature-driven atmospheric flows, particularly the seasonally reversing low-level monsoon winds that form around the plateaus. In addition, the earth's rotation diverts low-level and jet-stream winds northward around plateaus (in the Northern Hemisphere).

by the Colorado River, along the southern margin of the Colorado Plateau, has also occurred within the past 10 million years.

The above evidence implies that river velocities in western North America have increased markedly. Faster rivers carry coarser sediment and erode their beds more rapidly. One change that could have caused rivers to run faster is the steepening of river gradients resulting from uplift of the western end of the plains and adjacent Rocky Mountains. (An opposing view holds that shifts in climate could have produced the observed sedimentation changes.)

The reason for uplift in the American West is less clear-cut than in Asia. Various theories hold that changes in rate or direction of seafloor spreading in the Pacific Ocean, along with the burial of an older mid-ocean ridge that previously existed in the East Pacific, led to the accumulation of hot, low-density material under the North American continent, causing it to rise. As yet, no one theory is widely accepted.

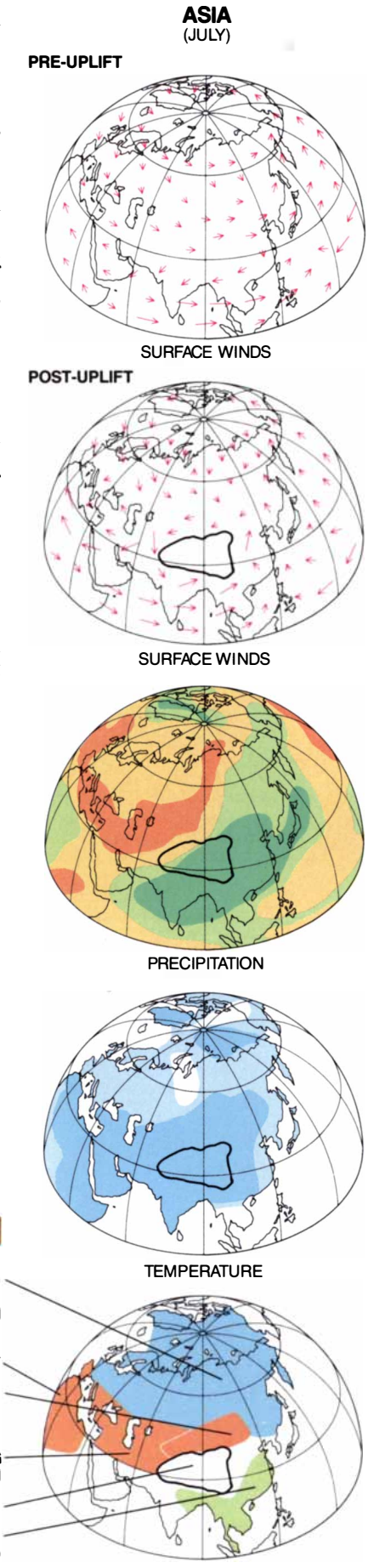
Noting that the timing of these inferred plateau uplift histories roughly matches that of global cooling, we sought to understand the link between plateau uplift and climatic change in the Northern Hemisphere. To this end, we ran several computer experiments in cooperation with Warren Prell of Brown University, assisted by Peter Guetter of the University of Wisconsin at Madison. We used a sophisticated climate-simulating computer program known as a general circulation model (GCM), which was run at the National Center for Atmospheric Research in Boulder, Colo.

This kind of model provides the most complete representation available of the physics of the circulation of the atmosphere. It incorporates equations that describe atmospheric flow in terms of momentum, energy and heat [*see box on page 68*]. Because GCMs must process an extraordinary amount of information, they require the use of powerful, high-speed supercomputers.

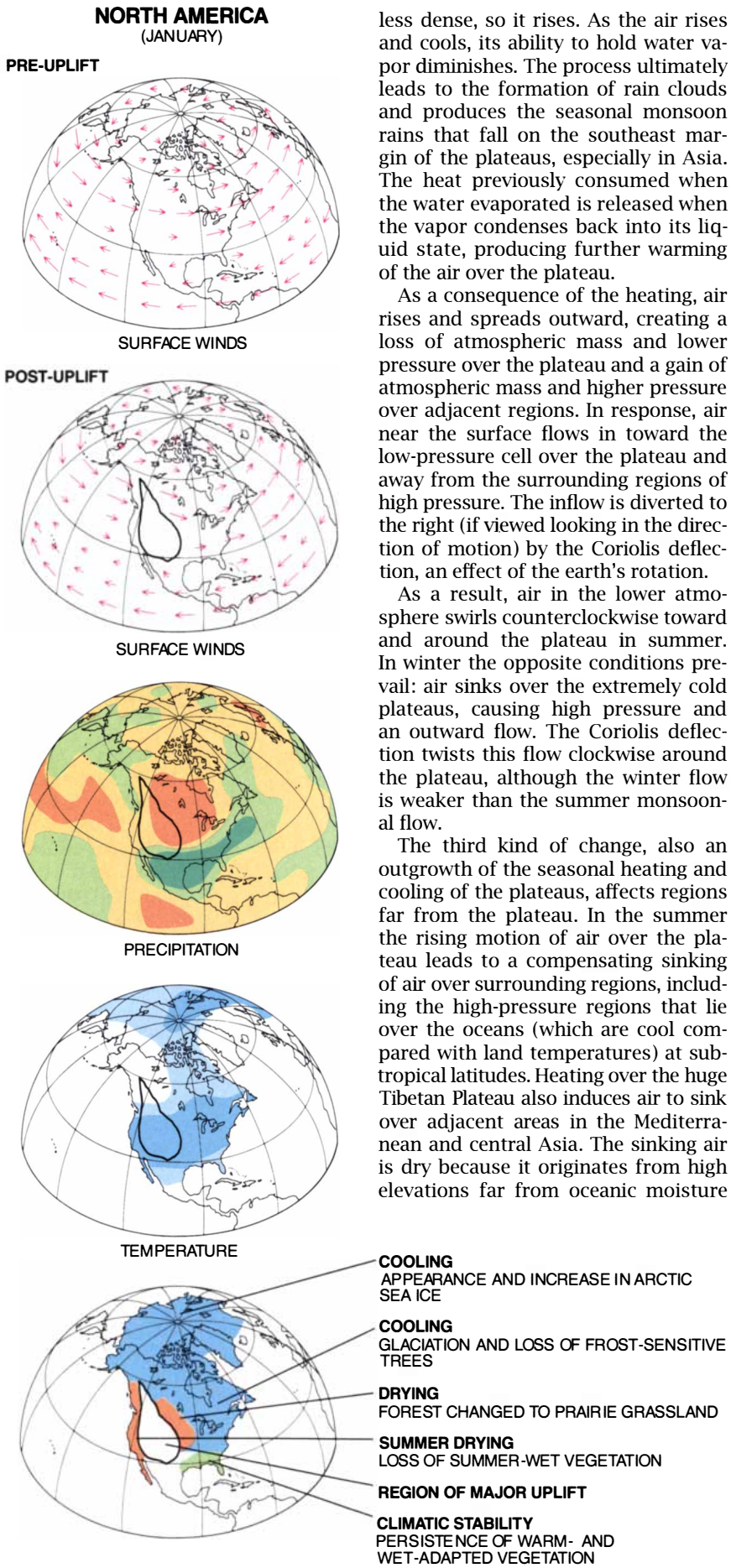
These models are especially useful for conducting sensitivity tests, wherein a single parameter—plateau elevation, in this instance—is changed to determine its unique effect on the overall atmospheric flow. We ran computer experiments representing three cases, chosen so as to simulate crudely three of the stages of uplift deduced from geologic evidence. One simulation contained no plateaus or mountains, a highly oversimplified representation of the earth's topography 40 million years ago. The second contained plateaus at half their present elevation, similar to the half-completed uplift that may have prevailed about 10 million years ago. The third simulation incorporated plateaus and mountains at their modern heights. Although the climate model used can simulate the general shape of the broad high plateaus, its spatial resolution is too coarse to depict accurately the narrower mountain ranges and valleys.

The experiments showed that elevated plateaus affect atmospheric circulation in three ways. First, rising terrain progressively blocks the west-to-east airflow that typically occurs both near the surface and higher up in the atmosphere (the jet stream) in middle latitudes. Because of the earth's rotation, the eastward flow is diverted northward around the plateau, whereas a large southward return flow, or meander, occurs just downstream. In all the cases described here, the changes refer to the long-term average atmospheric flow, not to short-term weather patterns that move across the globe.

A second kind of change in atmospheric circulation derives from summer heating and winter cooling of air over the uplifted terrain. In the summer the sun heats the high plateaus, which in turn rapidly warm the thin overlying atmosphere. The warm air is



COMPUTER MODEL SIMULATION of climate over Asia (*this page*) and North America (*opposite page*) shows the orderly west-to-east flow of the mid-latitude winds that would take place in the absence of plateaus (*top*). Flow patterns altered by uplift effect changes in precipitation and temperature. These changes are in accord with the climatic trends inferred from the geologic record (*bottom*). The model simulated summer and winter conditions; one of each is shown.



less dense, so it rises. As the air rises and cools, its ability to hold water vapor diminishes. The process ultimately leads to the formation of rain clouds and produces the seasonal monsoon rains that fall on the southeast margin of the plateaus, especially in Asia. The heat previously consumed when the water evaporated is released when the vapor condenses back into its liquid state, producing further warming of the air over the plateau.

As a consequence of the heating, air rises and spreads outward, creating a loss of atmospheric mass and lower pressure over the plateau and a gain of atmospheric mass and higher pressure over adjacent regions. In response, air near the surface flows in toward the low-pressure cell over the plateau and away from the surrounding regions of high pressure. The inflow is diverted to the right (if viewed looking in the direction of motion) by the Coriolis deflection, an effect of the earth's rotation.

As a result, air in the lower atmosphere swirls counterclockwise toward and around the plateau in summer. In winter the opposite conditions prevail: air sinks over the extremely cold plateaus, causing high pressure and an outward flow. The Coriolis deflection twists this flow clockwise around the plateau, although the winter flow is weaker than the summer monsoonal flow.

The third kind of change, also an outgrowth of the seasonal heating and cooling of the plateaus, affects regions far from the plateau. In the summer the rising motion of air over the plateau leads to a compensating sinking of air over surrounding regions, including the high-pressure regions that lie over the oceans (which are cool compared with land temperatures) at subtropical latitudes. Heating over the huge Tibetan Plateau also induces air to sink over adjacent areas in the Mediterranean and central Asia. The sinking air is dry because it originates from high elevations far from oceanic moisture sources. Compressional heating, which takes place as the air sinks, also lowers the relative humidity.

In winter the process reverses. The general sinking of air over the plateaus is compensated for by a rising motion in the low-pressure systems over the oceans (now warm compared with land temperatures) at subpolar latitudes. Through these large-scale circulation patterns, the climatic effects of plateaus can make themselves felt in distant lands and oceans.

Our next goal was to see if the regional climate changes simulated by the computer model agreed with climatic histories found in the geologic record. We focused on specific areas and compared the simulated changes in surface temperature, precipitation and wind direction against geologic evidence, primarily fossil remains of ancient vegetation.

Along the west coast of North America, the uplift experiment indicates a shift in low-level summer winds from westerly to northerly and an increase in subsidence of dry air. As a result, summers become drier and slightly cooler along the coast. In agreement, fossil evidence shows that vegetation needing sustained summer rains, such as magnolia trees, gradually disappeared in California over the past 15 million years. At about the same time, the wind-driven transport of surface waters offshore and the associated upwelling of cool waters from below appear to have intensified. This change makes sense because the most favorable winds for upwelling along this coast flow from the north and northwest.

Around the northern plains states, such as Nebraska and the Dakotas, the computer model predicts drier winters, mainly because air masses coming from the more northerly directions contain less moisture. Botanical evidence shows that prairie grasses and herbs, which need relatively little water, have spread widely across these states in the past 15 million years, replacing trees, which require more water. The change in vegetation also encouraged the flourishing of grazing mammals such as horses and bison across the plains.

Over much of east central North America (downstream from the uplifted region), the model shows colder winters and cooler summers caused by more northerly wind directions. This agrees with botanical fossil evidence of a progressive change from relatively warm-adapted broad-leaved trees in the far northern Arctic to cold-adapted trees, spruce forest and finally tundra. In the southeastern U.S. the simulat-

ed climatic effects of uplift are inconsequential, and, in fact, the vegetation there has changed relatively little.

The same computer run simulated uplift-related changes for Asia. The interior of the continent north and west of the Tibetan Plateau becomes drier as summer surface winds switch from westerly (and relatively moist) to northeasterly (and dry). The plateau causes air to sink and blocks the flow of moisture in from the Indian Ocean. This simulated change agrees with the flora, which evolved from forest to steppe and even to desert vegetation, as shown by the fossil record of the past 20 million years. In northern Asia the climate model simulates colder winters and cooler summers. Such changes are consistent with the gradual transformation of local vegetation from warm deciduous forest to taiga (subarctic forest) and to tundra in the far north.

The model shows southeastern Asia and India remaining warm and becoming wetter as a result of uplift. Alterations in atmospheric circulation cause the summer monsoon to grow stronger on the southeast flank of the plateau. Vegetation adapted to a warm, wet climate has persisted in this region up to the present.

We also looked at the effects of plateau uplift on the European climate. In Europe, winters become cooler in the computer model because of increased wind flow from the northeast, and summers grow cooler because of greater north-to-south airflow. These changes are mirrored by the gradual loss of subtropical vegetation during the past 20 million years.

Around the Mediterranean and in northwest Africa, the model predicts drier summers resulting from stronger winds from the northeast and increased subsidence of dry air. A reduction in precipitation would explain the appearance and spread of summer-dry "Mediterranean" vegetation that has taken place during the past several million years.

Although this global climate model did not represent the deep ocean, it simulated three uplift-induced atmospheric changes that could significantly affect the Atlantic Ocean. Drier summers over the Mediterranean and eastern Atlantic lead to higher evaporation rates, which should produce saltier Atlantic waters. Winds over the west central Atlantic acquire a stronger component of flow from the south, which should drive the salty water farther northward. Finally, colder winters over the northern continents generate colder air masses that would chill the ocean surface, making the salty surface water denser. The cumulative result should be an increased sinking of cold, salty surface waters into the deep North Atlantic. This sinking flow would carry oxygen and so help to ventilate the deep ocean. Marine geologic data confirm that ventilation of the Atlantic from the north increased substantially during the past 15 to 10 million years.

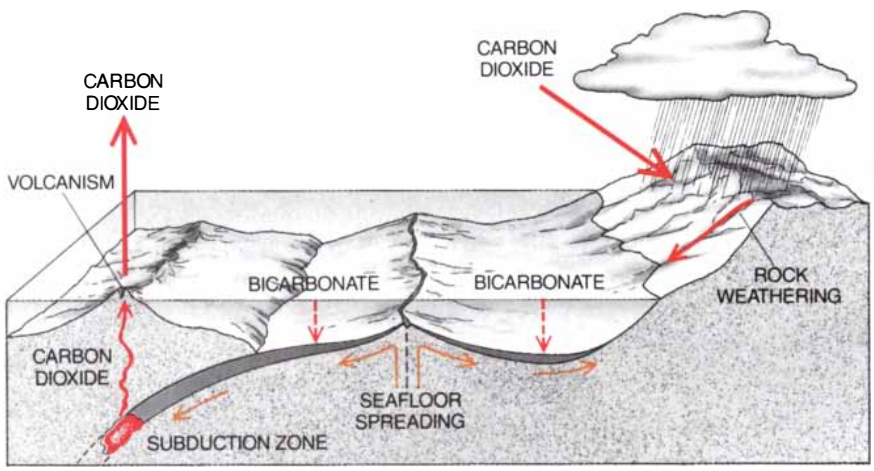
The computer model results do not agree with geologic evidence in all regions. The model simulates warmer winters and only slightly cooler summers in Alaska, for example. Botanical evidence, however, points toward a major cooling of the climate there. The model also simulates wetter winters and summers over the southern Rockies and southern Great Plains. Fossil evidence traces a more complicated trend, involving increased precipitation in high-altitude mountain ranges but also drying in low-lying basins. These inconsistencies may stem in part from the fact that the model is insufficiently detailed to simulate the effects of narrow mountain ranges. Such features can cause local rainshadow effects and blockage of low-altitude airflow.

The broad success of the simulation in explaining the comprehensive alterations in the regional climate and ecology during the past 40 million years confirms that plateau uplift has significantly influenced climate. In general, the simulations indicate that plateau uplift can explain the fundamental trend toward increasing regional differentiation of seasonal and annual climate changes (colder or warmer, drier or wetter) and away from the more equable, moist and temperate climates of earlier times.

Still, the simulated effects of uplift do not account for the full amplitude of the observed temperature changes. Temperatures at high latitudes have fallen by 10 degrees C or more during the past 40 million years, ultimately leading to the development of a sea-ice cover over the Arctic Ocean and to the growth of terrestrial ice sheets that repeatedly covered North America and Eurasia not long after three million years ago. Compared with this inferred cooling, the direct temperature changes from uplift in our model simulation are modest, especially in summer.

Our initial simulations did not, however, yield a full evaluation of the effects of uplift. For simplicity, the model we first used held certain key components of the climatic system (for example, snow cover, sea-ice cover and ocean temperature) at fixed, modern values rather than allowing them to vary in response to changes in the circulation of the atmosphere.

We recently repeated the uplift experiments using a revised model that allows these components to interact with the evolving atmospheric flows. The new results show climatic responses similar in pattern to but greater in intensity than those previously described. Some different features also appear, such as thicker and more extensive Arctic sea ice and expanded winter snow cover caused by uplift. A definitive ex-



CHEMICAL WEATHERING occurs when atmospheric carbon dioxide dissolved in groundwater attacks silicate and other rocks to form bicarbonate, which is carried into the ocean and incorporated into the shells of marine biota. The carbon dioxide reenters the atmosphere many millions of years later in the cycle of subduction and seafloor spreading. Plateau uplift in the past 40 million years could have accelerated the chemical weathering cycle by creating monsoon rains and rapid runoff on freshly faulted slopes. These changes may have significantly decreased atmospheric carbon dioxide levels, lessened the greenhouse effect and cooled the climate worldwide.

"Vision is the art of seeing things invisible."

Jonathan Swift

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ploration of uplift effects on atmospheric and oceanic circulation will require still more comprehensive models with even greater resolution.

In addition to causing physical changes in circulation, plateau uplift may alter climate by increasing chemical weathering of rocks, thereby reducing atmospheric carbon dioxide concentrations. Carbon dioxide combines with rainwater and groundwater to form carbonic acid, which reacts with silicate minerals in rocks during weathering. The resulting bicarbonate ions drain into the oceans, where they are taken up by marine animals such as plankton and corals and eventually deposited on the seafloor. The net effect is that chemical weathering removes carbon dioxide from the atmosphere and locks it away at the bottom of the oceans. As described earlier, subduction and volcanism eventually return the carbon dioxide to the atmosphere, but this process requires a long time (tens to hundreds of millions of years) to complete.

Maureen Raymo, while a student at Lamont-Doherty Geological Observatory of Columbia University in 1986, proposed that uplift of plateaus and mountain ranges has increased the rate of chemical erosion of continental rock on a globally averaged basis. Uplift could enhance chemical weathering in several ways. Heavy monsoons, which develop at the margins of plateaus, unleash particularly intense rainfall. In these regions, uplift-related faulting and folding also expose fresh rock to the weathering process. Moreover, the steeper slopes created by plateau uplift cause faster runoff, which removes erosion products and intensifies the chemical attack on the rock.

Mountain chains like the southern Himalayas and eastern Andes, where heavy monsoon rains fall on steep slopes, should experience particularly rapid weathering. The Himalayas rose along with the uplifting of the Tibetan Plateau; the Andes are associated with a smaller tableland plateau in South America. Significantly, the three rivers that currently carry the highest loads of dissolved chemicals into the ocean—the Yellow River in China, the Ganges-Brahmaputra river system in India and the Amazon in Brazil—all drain regions that have been uplifted in the past 40 million years. Changes in several geochemical indices in ocean sediments are consistent with increased erosion rates.

Raymo suggests that long-term uplift in Tibet and other regions may have increased the rate at which carbon dioxide is removed from the atmosphere. In this way, concentrations would have fallen even though the amount of carbon dioxide exhaled by volcanoes (as inferred from seafloor spreading rates) remained nearly constant. Falling carbon dioxide levels would reduce the ability of the atmosphere to retain heat, thereby amplifying the global cooling.

Plateau uplift, acting via physical and geochemical mechanisms, may have been a major factor influencing the initial appearance of large continental ice sheets roughly three million years ago. By that time, the Northern Hemisphere had grown sufficiently cool that it began to experience periodic ice ages. Each ice age cycle has been marked by the appearance of plateaulike sheets of ice several thousand kilometers wide and one to three kilometers high, comparable in size to the Tibetan or Colorado plateau. Such icy plateaus developed over large parts of the northern continents, especially east central North America. During the peak of each ice age (such as the most recent glaciation 18,000 years ago), so much water was locked up in ice that average worldwide sea levels dropped at least 120 meters below the present shorelines.

Unlike the rock plateaus, the ice sheets not only grew but also melted away over relatively short periods. In the early 1900s Serbian astronomer Milutin Milankovitch refined an earlier idea that the cycle of ice ages and warmer, interglacial epochs is controlled by regular variations in the size and shape of the earth's orbit. These variations operate on 20,000-year, 40,000-year and 100,000-year periods. These rhythmic changes in the earth's orbit have always occurred, but prior to three million years ago the Northern Hemisphere was too warm for them to set the tempo of glacial cycles.

Plateaulike domes of ice, growing and melting according to the pacemaker of variations in the earth's orbit, have rearranged circulation patterns in a rhythmically fluctuating manner. The largest effects have been concentrated at middle and high latitudes, where ice sheets form. Global climate model experiments show that the large North American ice sheet of 18,000 years ago split the jet stream into two bands, one to the north and the other to the south of the ice. Beneath the jet-stream limb crossing the northern flanks of the North American ice sheet, strong winds developed that carried cold air from northern Canada out across the North Atlantic. These winds chilled and even froze the ocean surface as far south as

50 degrees north, the latitude of France. The glacial freezing of the ocean surface in some way suppressed the sinking of surface waters in the North Atlantic, which today helps to ventilate the world's deep ocean.

The climate of the modern world represents the warm extreme of a cycle of glaciation. In the Northern Hemisphere, large ice sheets now exist only on Greenland; the North Atlantic has warm surface waters and experiences vigorous deep-water mixing. From a longer perspective, however, the uplifted plateaus that set off the recent ice ages are still in place.

Barring outside factors, the cycle of ice ages will presumably continue. Human activities have added such a factor in the form of greenhouse gases. The effects of these activities on global climate are still disputed. If greenhouse warming does indeed occur, it will operate under circumstances quite different from those that produced the global cooling of the past 40 million years. In the past, significant climate changes have followed from large-scale alterations in the earth's topography and the configuration of the continents. At present, carbon dioxide levels are rising without any corresponding major geographic changes.

Predicting the future course of the earth's climate will require a profound understanding of how the atmosphere responds to various kinds of disturbances. Unraveling the relation between plateau uplift and climatic change may prove to be one important avenue toward achieving that goal.

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Nonimaging Optics

Nonimaging concentrators—"funnels" for light—collect and intensify radiation far better than lenses and mirrors do. The devices are used in fields ranging from high-energy physics to solar energy

by Roland Winston

Many of us first learned about concentrating light when we were children. Lazy summer afternoons were perfect for burning initials into wood, using nothing more than sunlight and a household magnifying glass. Who can forget the wonder of discovering that an ordinary piece of glass can focus sunlight to a tiny spot? Most of us have carried this lesson into adulthood. If someone were to ask how to attain the highest possible concentration of sunlight, most people would say with a magnifying glass, or some combination of lenses, or perhaps a telescope mirror.

It turns out that the lesson we learned as children is not quite right. Although lenses and mirrors can be used to concentrate light, they are not the best tools for the job. In fact, any optical device that concentrates light by forming an image will fall far short of the theoretical limit. The reason is simple: although lenses and mirrors produce almost perfect images at the focal point, they blur and broaden the images away from the focus. As a consequence, maximum concentrations of light can be attained only by dispensing with image-forming requirements, a fact that has been applied most successfully only within the past 20 years or so. Devices designed in such a fashion are called nonimaging concentrators.

ROLAND WINSTON is professor of physics at the University of Chicago, where he obtained his Ph.D. in 1963. A pioneer in the field of nonimaging optics, Winston discovered the nonimaging concentrator now called the compound parabolic concentrator while designing Čerenkov radiation detectors for a high-energy physics experiment in 1965. With the late Walter T. Welford of Imperial College, London, he has published two books on nonimaging optics: *Optics of Nonimaging Concentrators: Light and Solar Energy* and *High Collection Nonimaging Optics*.

A nonimaging concentrator is essentially a funnel. Light entering the concentrator over a large area is reflected so that it passes through a much smaller area. The process destroys any image of the light source, but when only concentration is desired, it is unnecessary to form an image anyway. The high concentrations of light attained with nonimaging devices have already found extensive applications in a variety of fields, ranging from high-energy physics to solar energy. A solar furnace, for example, does not care about receiving a picture-perfect image of the sun; all it cares about is receiving the maximum intensity of sunlight per unit area.

Workers all over the world continue to find new uses for nonimaging concentrators, wherever the need is simply to make high intensities of light without the necessity of preserving images. Recently my colleagues and I at the University of Chicago have even used the devices to produce the highest intensity of sunlight anywhere in the solar system, including that at the surface of the sun itself.

Nonimaging optics was born in the mid-1960s, when a Soviet, V. K. Baranov, a German, Martin Ploke, and I independently designed the first compound parabolic concentrators. The name is a bit of a misnomer, because the walls of such concentrators are usually not parabolic. The term simply refers to a class of devices that concentrate light to the highest possible limit.

My initial work in nonimaging optics grew out of high-energy physics. As a young faculty member at Chicago, still in my twenties, I collaborated with T. A. Romanowski of Ohio State University on an experiment to detect a rare decay of a particle called the lambda. A lambda belongs to a class of unstable particles known as hyperons,

NONIMAGING CONCENTRATORS called compound parabolic concentrators collect sunlight atop the Illinois Department of Agriculture Building in Springfield. Each reflector in the array is designed to maximize the concentration of light on an evacuated tube, which retains heat in a manner similar to a thermos bottle. Total area of the array, used to heat and cool the building, is 12,000 square feet.

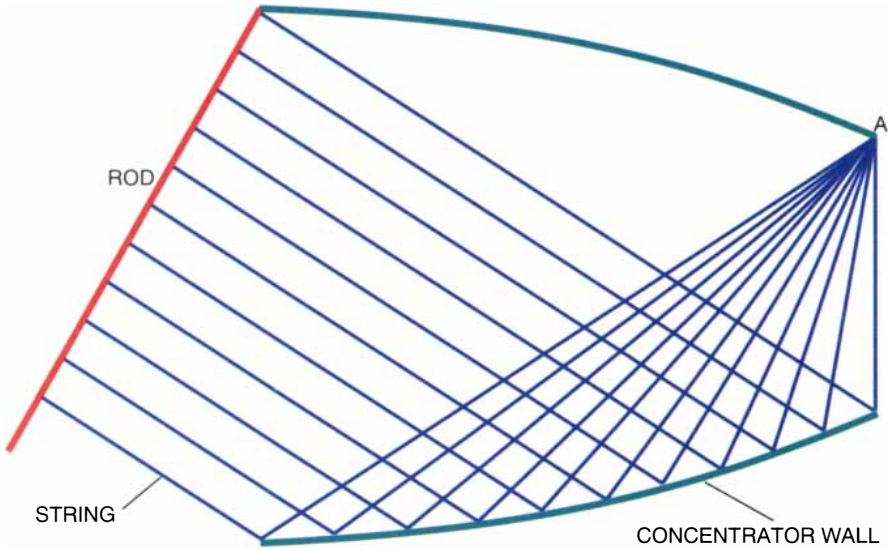
which resemble the neutrons and protons of ordinary matter but which are somewhat heavier. A lambda most frequently decays into either a proton or a neutron and a particle called the pion, but one time out of every 1,000 or so decays the lambda will eject an electron. My colleagues and I sought to investigate this rare decay of the lambda as an important step in verifying a theory known as the Cabibbo-Kobayashi-Maskawa model. Our job was to fish out the rare electron decay from the dominant pion mode.

We planned to detect the ejected electrons by exploiting an effect called Čerenkov radiation, named after its Soviet discoverer. Čerenkov radiation is an optical analogue of the "sonic boom." Just as a jet plane traveling faster than the speed of sound emits a shock wave of sound, a particle traveling in a gas or liquid faster than the speed of light will emit a shock wave of light. (Readers who know about Einstein's postulate that nothing can travel faster than the speed of light in a vacuum can rest assured; the particle is moving faster than the speed of light in the gas or liquid but slower than the speed of light in a vacuum.) Since pions are nearly 300 times more massive than electrons, they move more slowly, and in a fluorocarbon gas only the electrons move fast enough to produce Čerenkov radiation.

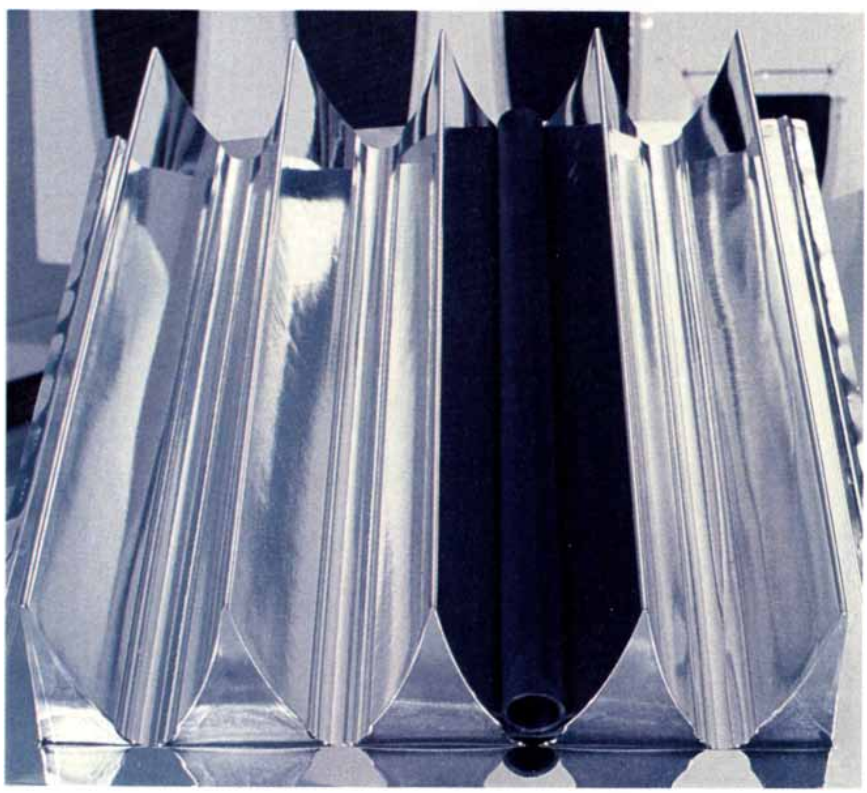
We needed to collect the weak light and pipe it to phototubes so that the appearance of each electron could be registered. But the emitted light is faint and distributed over a large area and over many angles, and so collecting the light by conventional imaging methods would have required well over 100 large, five-inch-diameter phototubes. Such a large number was costly and impractical. Clearly, this was a problem begging for a novel approach. After all, a phototube does not require receiving a perfect image of a light source to function properly; the tube needs only to receive the light.

At the time we were faced with this problem, I knew it should be possible to collect light more efficiently than with conventional imaging devices. A simple calculation convinced me that it should be possible to collect light four times more efficiently and reduce the number of phototubes to a couple of dozen. I enlisted the assistance of a talented mechanical engineer, Henry Hinterberger, and we began a productive collaboration. Several months of long, hard work later, we had designed and built the first compound parabolic concentrator, a funnel-shaped reflector. The year was 1965.

Besides solving our problem, I had also helped start the field of nonimaging optics, although I did not know it at the time. Yet little happened until the mid-1970s, when other investigators began to realize the enormous potential for nonimaging concentrators in astronomy and in solar energy. It was only then that I learned about Baranov's and Ploke's independent discov-



EDGE-RAY METHOD is one of two known techniques for designing nonimaging concentrators. The concentrator is made so that all light rays entering the device at a maximum angle are directed, after one reflection at most, to the rim of the exit aperture. One can visualize the approach as sliding a piece of string (*blue line*) along a rod (*red line*). The diagram shows the string in various stages of the sliding process. At each stage, the string is held taut and parallel to the incoming light rays. The string is then bent abruptly to meet the rim of the exit aperture (*point A*) in such a way that the total length of the string remains the same. The points at which the string is bent define the wall of the concentrator (*green curve*).



COMPOUND PARABOLIC CONCENTRATOR troughs use the edge-ray method to concentrate the sun's energy onto absorber tubes. The fact that the tube here is black indicates it has absorbed all rays within the angular field of view of the concentrator. This configuration allows maximum absorption of the sun's rays without expensive tracking equipment. It was the basis for a number of commercial solar-concentrating collectors in the U.S. in the early 1980s. With the ebbing of the oil crisis, much research shifted to Japan, where an advanced version is being developed.

eries, nearly 10 years after they had made them.

At present there are two known ways to design nonimaging concentrators. The first is called the edge-ray method. Light typically enters a concentrator over a range of angles from head-on, or zero degrees, to some maximum angle, say, 20 degrees. In the edge-ray method, all light rays entering at the maximum angle are directed, after one reflection at most, to the rim of the exit aperture [*see illustration at left*]. The remaining rays, at intermediate angles, should therefore be reflected within the exit aperture itself, a phenomenon that is intuitively appealing and works perfectly in two dimensions (trough-shaped concentrators) and nearly perfectly in three dimensions (cone-shaped concentrators). The beauty of the edge-ray method is its simplicity.

The second approach is conceptually more abstract and bears little resemblance to the edge-ray method. Among the investigators who have made contributions to this second, so-called geometric vector-flux approach, I would like to mention my principal collaborator, the late Walter T. Welford of Imperial College, London, and my former student Xiaohui Ning. In the geometric vector-flux approach, one imagines the aggregate of optical rays traversing an optical system as a kind of fluid flow. But instead of traversing space in the usual sense, the rays traverse an abstract region called phase space: the space of ray positions and ray directions. A quantity called the geometric vector flux can be constructed from the positions and directions. One designs a concentrator for a given application in a way that conserves the flux or leaves it undisturbed.

The language of the last paragraph may have been daunting, but an example should make it clear. Imagine a flexible sheet of high-reflecting film about the size of this magazine and a round object, say, an orange. Suppose the film is rolled to form a cone, shiny side in, so that a hole about the size of a nickel is left at the tip [*see illustration on opposite page*]. The hole is positioned on the orange and the sides of the cone adjusted until the entire orange appears to be visible to the person looking through the large end of the cone. At this point the concentrator (the reflecting cone) does not disturb the geometric vector flux associated with the orange; the lines of flow emanating from the orange are radial because of symmetry, and the cone simply follows those lines. As a consequence, the en-

tire orange seems to be visible, even though all but a small part is hidden from the eye.

The effect is much more than a clever optical illusion. The cone reflects rays of light from the small patch of orange in such a way that the entire orange seems to come into view. Now imagine reversing the direction of all the rays. Rays coming into the cone and heading toward the edge of the orange will be reflected to the nickel-size hole. In other words, rays that would otherwise strike the surface of the orange instead pass through the hole: the light is concentrated.

In most applications, of course, one is interested in concentrating light on a flat rather than a spherical surface. The flat-surface solution is more complicated, but the basic principles are unchanged. Each flow line is now a hyperbola, and hence the concentrator must be designed with hyperbolic walls. When such a concentrator is placed at the focus of a telescope or a solar furnace, for instance, the instrument is "fooled" into having a larger target area for incoming light, which is to say that once again the light is concentrated.

The proliferation of nonimaging optical devices grew out of the desire to design solar concentrators that do not need to track the sun. For both efficiency and economy, solar-energy devices must concentrate the sunlight. A solar heater delivers higher temperatures at higher concentrations of light, and it is often cheaper to concentrate light from a given area onto a smaller area of solar cells than it is to fill the entire area with them. But a tracking system is a cumbersome and inconvenient piece of machinery. The effort to install and maintain it adds to the cost of solar-derived energy.

When the oil crisis hit the U.S. in the 1970s and the government became interested in developing alternative energy sources, a drive was started to make solar energy a more attractive option. There was interest in making solar concentrators more cost-effective by mitigating tracking requirements. Robert G. Sachs, then director of Argonne National Laboratory and a professor emeritus at Chicago, knew about my work with funny-shaped, nonfocusing concentrators and thought I could help.

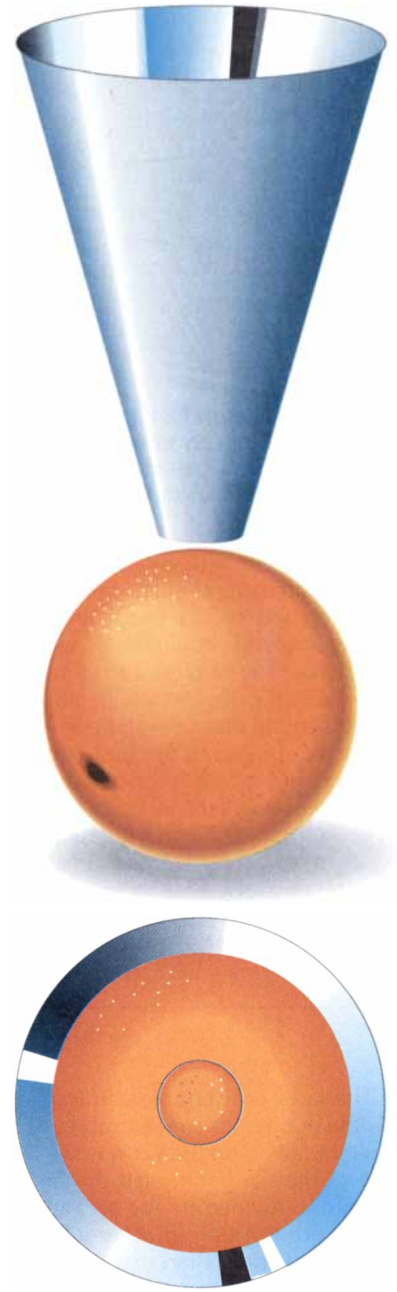
Nonimaging devices are well suited to the job, as shown by early research done in collaboration with William W. Schertz and Ari Rabl at Argonne. Working with Joseph J. O'Gallagher (my colleague on solar research at Chicago since 1976) and my former students Manuel Collares-Pereira and Keith A. Snail, we showed that nonimaging concentrators can be designed to focus sunlight efficiently throughout most of the day without ever moving. Almost any reasonable geometry can be accommodated.

We saw our work lead to the large-scale deployment of nontracking solar concentrators by such U.S. manufacturers as General Electric, Energy Designs and Sunmaster. As the oil crisis ebbed, however, much of the interest shifted to Europe, Israel and Japan. Recent events in the Persian Gulf may renew interest in solar energy in the U.S.

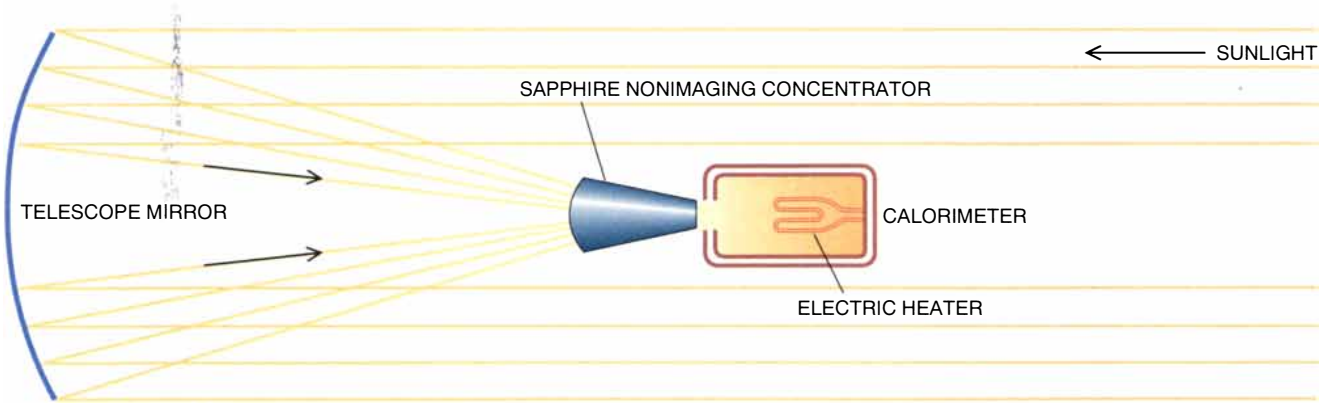
In the past few years my research group, with the support of the Solar Energy Research Institute in Golden, Colo., has set out to show that nonimaging devices can concentrate sunlight at or near the theoretical limit implied by thermodynamics. According to the second law of thermodynamics, no device can concentrate sunlight to an intensity corresponding to a temperature that exceeds the temperature at the surface of the sun. If such an intensity were obtained, it would be possible to make a heat engine running between the sun and the concentrator that would extract energy at no cost: the engine would be a perpetual motion machine. The upper limit of concentration turns out to be about 46,000 times the intensity of sunlight at the surface of the earth. (Historically, I first obtained the upper limit from phase-space conservation arguments, but I shall not delve into them here.)

Actually, there is a loophole for producing concentrations that exceed 46,000. If the concentrator is made of a material that has an index of refraction n, the upper limit for concentration is increased by a factor of n^2. (The index of refraction of a material is the ratio of the speed of light in a vacuum to the speed of light in the substance; the slower the speed, the higher the index.) The index of refraction of glass, for example, is 1.5, which boosts the theoretical maximum for a glass concentrator to about 100,000. Higher index materials increase concentration because they can bend light rays from wider angles to a desired angle. The phenomenon, a manifestation of Snell's law, is familiar to anyone who has observed the apparent bending of a stick projecting out of water. Thermodynamics is not violated by the n^2 increase in concentration, because an object also radiates energy in proportion to n^2, and the two factors cancel each other.

To chase after the thermodynamic limit, we placed a nonimaging concentrator at the focus of a parabolic telescope mirror. In principle it would be



GEOMETRIC VECTOR-FLUX approach is currently the only other known way of designing nonimaging concentrators. One can think of the aggregate of optical rays traversing an optical system as a kind of fluid flow. For a round object, say, an orange, the lines of flow are radial. If a flexible sheet of high reflecting film is rolled to form a cone, shiny side in, so that a hole about the size of a nickel is formed at the narrow end (*top*), the cone can be positioned on the orange in such a way that when viewed through the large part of the cone, the entire orange appears to become visible (*bottom*). The concentrator (the reflecting cone) does not disturb the geometric vector flux associated with the orange. The cone simply follows the lines of flow, and the entire orange seems to become visible, even though all but a small part is hidden from the eye.



TO MEASURE HIGH INTENSITIES of sunlight, light is passed through a sapphire concentrator into a thermos bottle filled with liquid—a calorimeter. The change in temperature of the liquid before the sun was turned "on" and after it was turned "off" is recorded. An electric heater is used to calibrate the change. Workers relied on calorimetry, a 19th-century technique, because the high intensities of sunlight being measured would have destroyed conventional power meters.

possible to obtain high concentrations with the nonimaging element alone, but in practice such an element would be extremely long and prohibitively expensive to make. The mirror, 40 centimeters in diameter, forms a spot about one centimeter in diameter and one meter from the mirror. In the first round of experiments, which became part of the thesis research done by Philip Gleckman, one of my graduate students, we designed a silver funnel and filled it with an oil of index 1.53 to "squeeze" the one centimeter spot to approximately one millimeter. We attained concentrations 56,000 times higher than the intensity of sunlight at the surface of the earth, or roughly 70 percent of the solar-surface intensity. We fell short of the 100,000 limit primarily because of losses from reflection and blocking of light by the measuring equipment.

In the latest round of experiments, done in collaboration with my current student, David Cooke, and also Gleckman, Helmut Krebs, O'Gallagher and Dan Sagie, we made the nonimaging concentrator out of sapphire, which has an even higher index, 1.76. The design was more daring, and the theoretical limit was boosted to about 140,000. We attained a concentration of 84,000, which actually exceeds the intensity at the solar surface by 15 percent. So if someone asks where to find the highest intensity of sunlight in the solar system, the answer is on our rooftop laboratory at the University of Chicago.

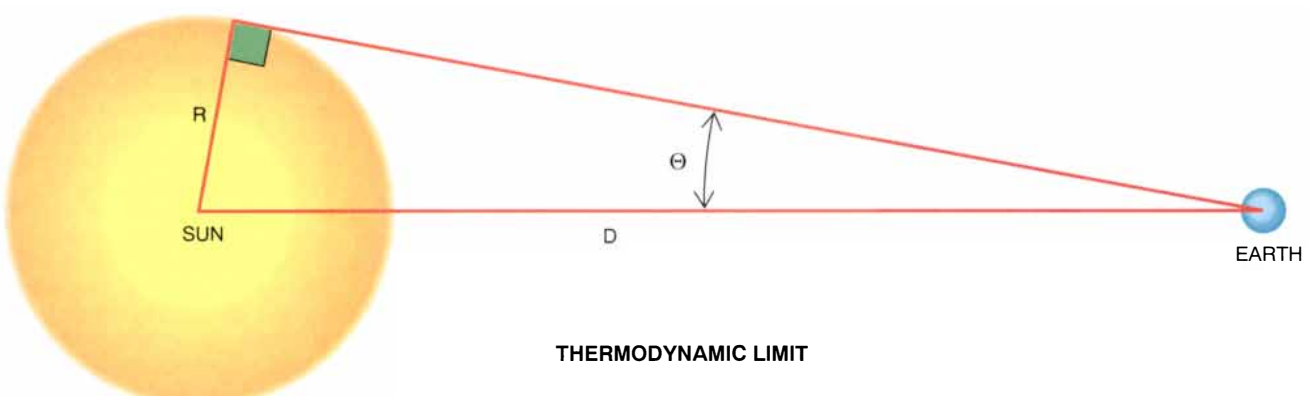
One of the applications for the high intensities of sunlight we have generated is the construction of a solar-pumped, or solar-energized, laser. Such a device would have obvious applications in space, for sat-

How Nonimaging Concentrators Perform at the Thermodynamic Limit

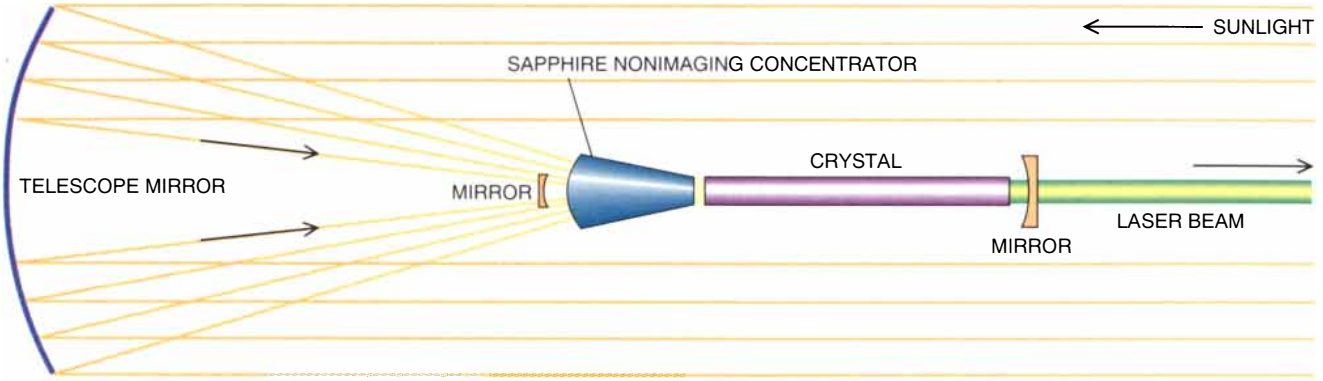
The laws of thermodynamics place a theoretical limit on the maximum concentration of sunlight. The intensity of sunlight falling on the earth is the intensity of light at the surface of the sun multiplied by the area of the sun's surface, $4\pi R^2$, and divided by the area of the sphere defined by the earth's orbit, $4\pi D^2$. In other words, the intensity of light at the sun is greater than that at the earth by a factor of $(D/R)^2$, which from trigonometry is $1/\sin^2\Theta$, where Θ is the semiangle subtended by the sun, 0.267 degree. Substituting this value into the expression yields 46,000.

According to thermodynamics, no device can concentrate sunlight on the earth to a higher value. If such a higher value were obtained, it would be possible to make a heat engine running between the sun and the device that would extract energy at no cost: the engine would be a perpetual motion machine. A loophole is allowed if the concentrating device is made of a substance having an index of refraction n greater than one; the maximum concentration is boosted by a factor of n^2 to $n^2/\sin^2\Theta$. (The index of refraction of a substance is the ratio of the speed of light in a vacuum to the speed of light in the substance.)

Conventional imaging devices fall short of the theoretical concentration limit by a factor of four. A parabolic mirror produces an image of the sun at its focus having an area of $\pi R^2\sin^2\Theta/\cos^2\phi$, where R is the length indicated in the drawing, Θ is the semiangle subtended by the sun and ϕ



THERMODYNAMIC LIMIT



SOLAR LASER is one of the potential applications for the high intensities of sunlight produced with nonimaging optics. The concentrated sunlight enters a laser crystal at one end and induces atoms in the crystal to emit light of a certain frequency or frequencies. The emitted light bounces back and forth between two mirrors positioned outside the crystal. Some of the intensity "leaks" through one of the mirrors, forming a laser beam that propagates out into space.

ellite communications. Another motivation for building a solar-pumped laser is to produce an intense source of ultraviolet light. Such a source, it is believed, could be used to destroy hazardous industrial wastes. (If situated in a desert, the device could be operated for virtually the cost of sunlight.) We are certainly not the first in building solar-pumped lasers. Amnon Yogev and his group at the Weizmann Institute have pioneered their development, exploiting nonimaging optics to produce output powers of hundreds of watts.

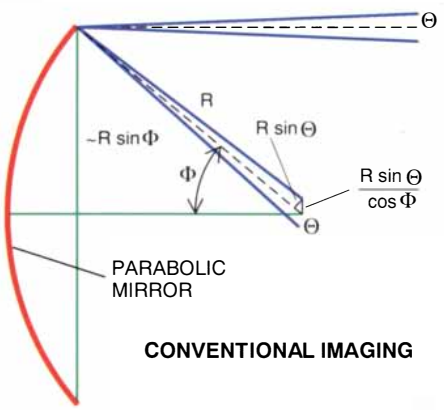
Applications for nonimaging devices have spread from high-energy physics and solar energy. Energy can be transported to conventional lasers by means of nonimaging optics, as John D. Kuppenheimer, Jr., and his colleagues at Sanders Associates have shown. A team of workers led by Roger H. Hildebrand and Doyal A. Harper at Chicago has exploited nonimaging devices for infrared radiation detectors in astrophysics. The *Cosmic Background Explorer* (*COBE*) satellite that recently measured the black body radiation remnant from the big bang with exquisite accuracy also relied on nonimaging optics [see "The Cosmic Background Explorer," by Samuel Gulkis, Philip M. Lubin, Stephan S. Meyer and Robert F. Silverberg; SCIENTIFIC AMERICAN, January 1990]. A group of investigators at the University of Utah has incorporated nonimaging devices in a large array of Čerenkov detectors. The array, called the fly's eye, was built to detect and understand better high-energy cosmic rays.

Illumination systems are another area of interest. A fluorescent light, for instance, throws a large fraction of the light in unwanted directions. An ideal nonimaging concentrator creates a uniform beam of light and could be designed to project all of the light to precisely where it is needed. Even vision itself seems to involve nonimaging optics. The cone cells in the retina concentrate light and have shapes resembling compound parabolic concentrators.

Although the number of investigators working in nonimaging optics is growing, it is still small enough to constitute a rather exclusive club. Centers of intense interest have grown up: in Australia, Ian M. Bassett of Sydney University; in Israel, Jeffrey M. Gordon of Ben Gurion University; and in Spain, Antonio Luque of Polytechnic University in Madrid. An indication of rekindled interest is the second international conference on nonimaging optics, to be held in San Diego in July of this year under the auspices of SPIE, the International Society for Optical Engineering. In 1988 ARCH, an umbrella organization run by Argonne and the University of Chicago, helped to launch NiOptics, a company dedicated to applying nonimaging optics. Headed by Robert L. Holman, the company seeks to integrate nonimaging elements into optical systems that have been the exclusive province of imaging devices.

Perhaps one of the most interesting frontiers in nonimaging optics concerns the possibility of new approaches for designing concentrators. I have described the two methods known at this time, the edge-ray and the geometric vector-flux approaches. It is reasonable to expect that more techniques can be developed. With support from the Department of Energy, we have systematically been searching for new designs over the past decade. The fact that only two methods have been uncovered indicates it is probably time for others to join the hunt.

is the rim angle of the mirror. From geometry, the collecting area of the mirror can be expressed as $\pi R^2 \sin^2\phi$. The concentration of the mirror is the ratio of the area of the mirror to the area of the spot: $\sin^2\phi\cos^2\phi/\sin^2\Theta$, which can be written as $(1/4)\sin^2 2\phi/\sin^2\Theta$. The expression clearly has a maximum value of $(1/4)1/\sin^2\Theta$, which is equal to a quarter of the thermodynamic limit. When blocking by the focal target is included, the concentration is of course even less.



CONVENTIONAL IMAGING

FURTHER READING

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Tumbleweed

This enduring symbol of the American frontier was actually an import from southern Russia that exploited the ecology of the Great Plains, becoming a major agricultural pest in the late 19th century

by James A. Young

In 1881 U.S. Secretary of Agriculture James M. Rusk reported that a troublesome, new weed was spreading across farms on the northern Great Plains. Unlike other weeds, this species did not spend its life rooted to the soil; instead it tumbled and bounced across fields with every gust of wind. The weed had sharp, spiny leaves that frequently lacerated the flesh of both horse and rancher. The plant was exploiting the vast areas of the plains quickly, thriving in regions too barren to support any other flora. Its destructive spines and ability to generate and disseminate numerous seeds were prompting many panic-stricken farmers to abandon their houses and fields. Equipped with such biological adaptations, the tumbleweed became the scourge of the frontier.

To present-day Americans, the tumbleweed evokes wistful visions of the Old West. In novels by Zane Grey, tumbleweeds drift against sagging barbed wire fences in the stark western landscape. In movies, they serve as background props, sharing scenes with cowboys and covered wagons. Indeed, the plant is so thoroughly entrenched in the folklore of the American frontier that it is difficult to conjure any other vision. Yet just over a century ago the tumbleweed was a newcomer to the flora of the region, one that wreaked sudden agricultural havoc, growing uncontrollably throughout the plains.

The first signs of the impending invasion occurred in the Dakotas in the late 1870s. Local farmers had noticed the sudden appearance of a new weed. To members of one immigrant group, it bore a strong resemblance to a weed in their native country. In a letter to the Department of Agriculture, Norm S. French, a farmer from North Dakota, wrote, "Intelligent Russians have told me that the weed grows abundantly in southern Russia, in the vicinity of Odessa, where it is locally known as Tarter [sic] thistle, and it is supposed to have been brought to America by Russians in some manner not known."

Frontier settlers described the plant with various names, including saltwort, Russian cactus and wind witch. But Russian thistle became the common designation preferred by botanists from the Department of Agriculture. The botanists there, however, had a much harder time agreeing on a scientific name for the plant. Plant taxonomy compares the morphology of a plant to published accounts of other plants or to those kept as specimens. Unfortunately, no taxonomic book described the weed, and no samples existed in herbaria in the U.S.

The department botanists placed the new weed in the chenopod, or goosefoot, family, under the genus *Salsola*, and speculated that it was related to a poorly understood form of a native sea blight found in brackish waters along the eastern seaboard. They settled on the scientific name of *Salsola kali*, with a related variety, *targus*.

Other botanists, however, did not

TUMBLEWEED, or the Russian thistle, breaks away from its roots in late fall. Its rolling action often presents a threat to motorists, especially in violent weather.

use the name to describe the plant. Disagreement arose when researchers discovered new populations of the Russian thistle scattered across the country. Thinking that the plant was native to the region and unaware as well that it was the *Salsola kali* described by the Department of Agriculture, botanists proposed different species names. Many of these names worked themselves into the literature, and even today one can find the plant classified under various scientific taxa.

Only recently have most botanists agreed that the weed should be called *Salsola australis*. This was the name given in 1810 by Robert Brown of the British Museum, who discovered the plant in Australia. Although his work went unnoticed until about a decade ago, plant scientists now realize that Brown was the first to classify the weed as a distinct species of *Salsola*.

Why did so much confusion over the plant's name persist for so long? After all, it seems obvious how to determine the weed's taxon: because the plant came from Russia, it would seem reasonable to find out what the Russians called it. Unfortunately, Russian botanists have been as confused as U.S. scientists in classifying the thistle. Apparently, the native population of plants from which the tumbleweed arose no longer exists in Eurasia. Comparative morphology is impossible even in the plant's former native habitat.

Botanists, of course, were not the only ones frustrated by the weed's physiology. Farmers, too, were troubled by its morphological characteristics—in particular, the leaves, which were modified to form strong, sharp spines. These spines frequently penetrated the heavy leather gloves worn by threshermen; consequently, many refused to process bundles of grain they thought might be infested with Russian thistle. But most important, the spines lacerated the legs of horses running in infested pastures. Because the horse was the basic source of power for preparing fields and harvesting and transporting grain on prairie farms, any threat to the horses was a threat to the existence of homestead agriculture.

To complicate matters, the weed burned easily in the arid landscape. The rolling action of the tumbleweed spread prairie wildfires quickly; flaming thistle bounced across fire lines and set houses and crops ablaze.

As the weed spread through South Dakota, farmers began shipping a steady supply to the Agriculture Department in Washington, D.C., along with complaints and demands of some action to combat the pest. Sarajag W. Narregang, president of the Dakota Irrigation Company, wrote to the secretary of agriculture on October 28, 1891: "We first saw it three years ago. Since that time, it has steadily increased, until at present the greater portion of South Dakota east of the Missouri River is infested.... This obnoxious weed has become so formidable in some portions of the state,... that many farmers are driven from their homes on account of it." So frightening was the

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RUSSIAN THISTLE exploits land too barren to support other flora. Adult plants appear dark green in the summer, making the desert landscape seem productive.

weed's spread in South Dakota that Edward T. Kearney, a North Dakota farmer and legislator, suggested a wire fence be built around his state to protect it from the onslaught.

Russian thistle did not restrict its spread to farms. The Fargo, N.D., *Daily Argus* reported: "The vanguard of the invader is already north of Sheldon; with the fall winds it will make its appearance in our neighborhood.... In [Oakes], the chinks of the sidewalks are fringed with it, the yards and vacant lots are matted with it."

Politicians tried to relieve some of the economic burden caused by the Russian thistle. The North Dakota legislature passed a special tax to compensate farmers. But by the 1890s the infestation was so extensive that the value of wheat production lost because of Russian thistle exceeded the taxes collected by the state.

As the complaints of the invasion mounted, the secretary of agriculture dispatched assistant botanist Lyster H. Dewey to investigate the biology of the plant and find a means to eradicate it. Through interviews with farmers and inspections of thistle fields, Dewey showed that the weed was first introduced in about 1877 on a farm in Bon Homme County, S.D. Thistle seeds were apparently mixed in with flax seed imported from Europe.

The tumbleweed invasion carried an ugly social undertone: many believed that Russian Mennonites had deliberately introduced the weed. Most of the frontier people discriminated against the Mennonite religion and social customs. The introduction of the weed was supposedly a retaliation for the derision. But Dewey found no evidence to substantiate anything but accidental contamination.

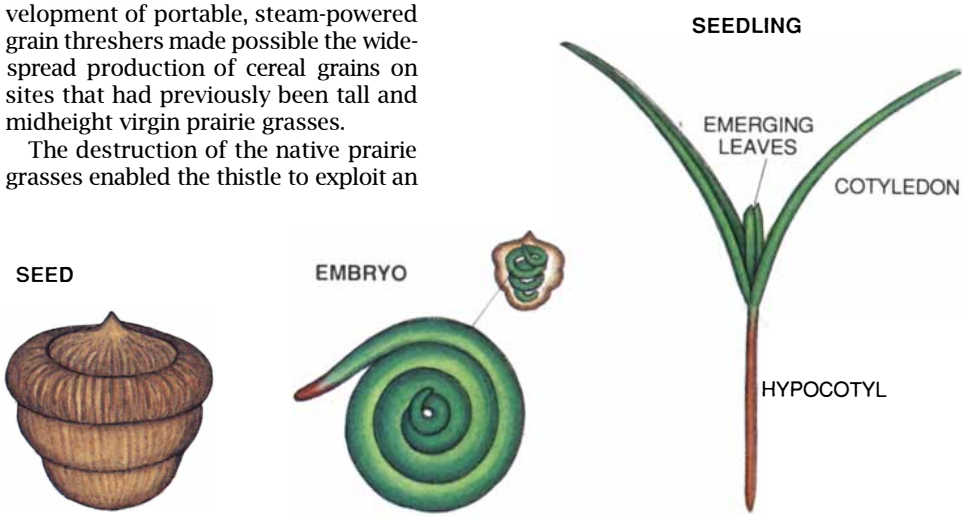
Once Russian thistle reached the U.S., it thrived on the open plains. According to Dewey, the farming practices of the pioneers gave the plant the opportunity to establish itself. During the last decades of the 19th century, wheat farming rapidly spread across the eastern portion of the northern Great Plains. In particular, the expansion of railroad networks and the development of portable, steam-powered grain threshers made possible the widespread production of cereal grains on sites that had previously been tall and midheight virgin prairie grasses.

The destruction of the native prairie grasses enabled the thistle to exploit an ecological niche. Russian thistle competes poorly with established vegetation. It cannot tolerate shade or excessive moisture for long periods, and it is not aggressive enough to supplant dense native populations. Instead, like many weeds, Russian thistle benefits from such agricultural practices as irrigation and fertilization, which are devised to reduce environmental stresses on crops.

Human activity not only created a suitable habitat for the thistle, it also was largely responsible for the plant's dissemination. Often farmers unwittingly sowed Russian thistle seeds along with their crop seeds, and thistle seeds contaminated grain shipments transported by railroad. In addition, the same steam threshermen who so disliked the spiny weed frequently did not thoroughly clean their machines and so dispersed the seeds as they traveled from farm to farm.

Such an extensive infestation made the weed virtually impossible to control, and early attempts at eradication met with failure. For instance, in the early 1890s Charles V. Piper of Washington State Agriculture College enlisted railroad section hands to find infestations along the railroad rights-of-way in Washington. The rail workers individually uprooted and destroyed numerous plants, leaving few populations near the railroad embankments.

But while Piper waged war on one front, the Russian thistle launched an offensive on another—in particular, along irrigation ditches. On July 26, 1897, Piper received a letter from Walter N. Granger, manager of the Yakima Investment Company. A survey of the irrigation district had disclosed a solid, 25-acre patch of Russian thistle. Apparently, one of the irrigation canal excavation contractors for the district



LIFE CYCLE of the Russian thistle begins with a coiled embryonic plant inside the seed. In the spring the embryo germinates, forming a seedling characterized by two cotyledons. Juvenile plants tend to be soft and gray-green in color. The flowers, in the axil between the spiny leaves and the branch stem, develop in the summer. An adult plant may reach two meters in diameter.

had purchased tainted feed grain grown in North Dakota for his draft horses.

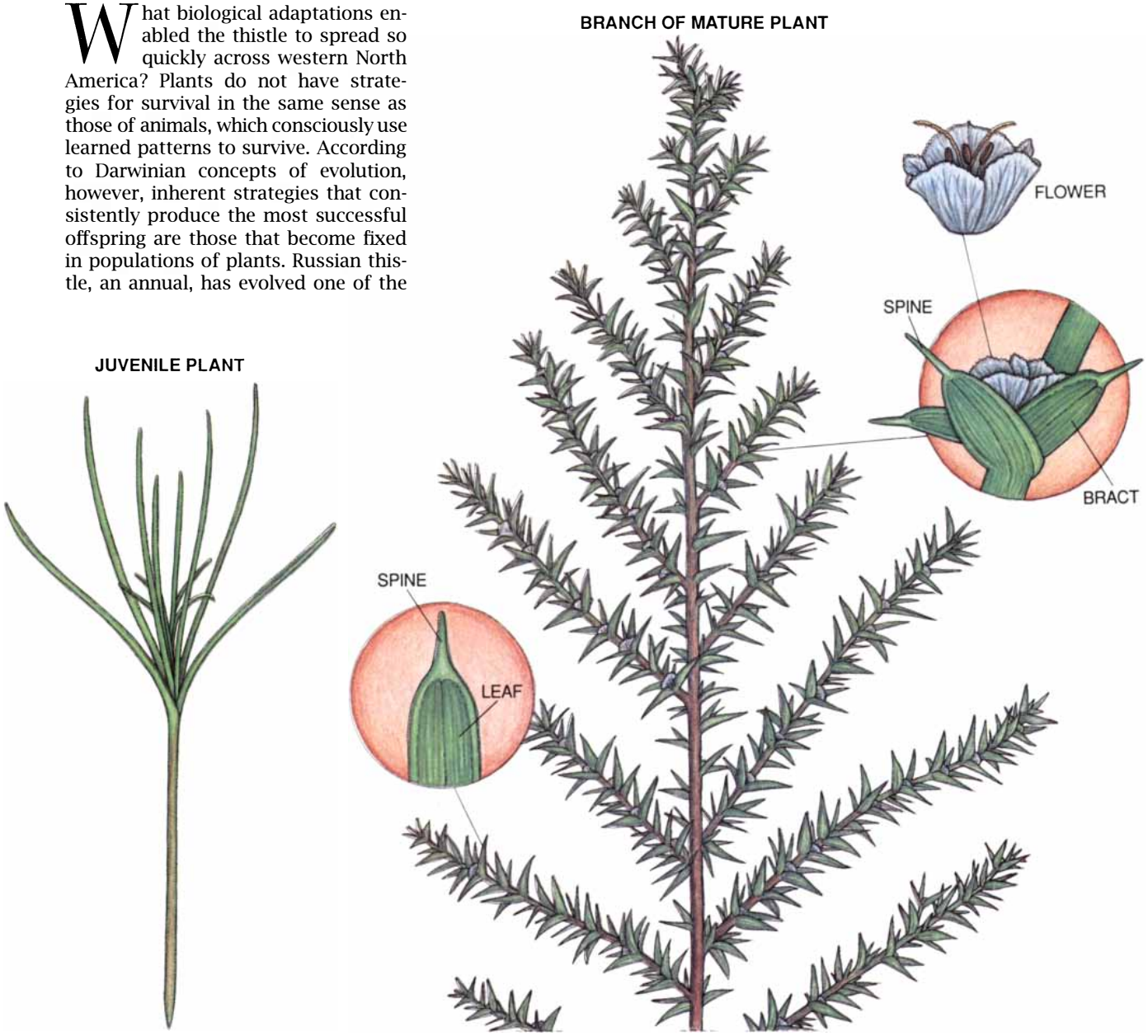
By about the turn of the century, Russian thistle had tumbled from the Dakotas to the Pacific coast. The weed found a home in the sagebrush desert that occupies much of the area between the Sierra Nevada–Cascade and the Rocky mountains. Not surprisingly, excessive grazing had severely depleted many of these ranges of their natural flora. And in the lower elevations of the Great Basin, where large amounts of soluble salts accumulated in the soil, the thistle has thrived in the native environment occupied by other members of its family. Although found primarily in the central and western U.S., the plant today has established limited populations along waste areas and railroad tracks east of the Mississippi.

What biological adaptations enabled the thistle to spread so quickly across western North America? Plants do not have strategies for survival in the same sense as those of animals, which consciously use learned patterns to survive. According to Darwinian concepts of evolution, however, inherent strategies that consistently produce the most successful offspring are those that become fixed in populations of plants. Russian thistle, an annual, has evolved one of the most well-developed strategies of producing viable offspring: it tumbles to disperse seeds.

For an ideal tumbler, the outline of the canopy, or the above-ground portion of the plant, must be nearly round to offer minimum resistance to the soil surface. To increase the range of seed dispersal, flowers and the seeds they produce must be well within the plant canopy. This kind of plant structure ensures that the seeds are not lost through abrasion the first time the canopy tumbles. In addition, a timed mechanism must release the aerial part of the plant from the anchoring roots only after the seeds mature.

Russian thistle is nearly perfect on all three aspects of ideal tumbling design. Although the outline of the canopy is usually not completely round, especially in larger plants, it may represent a trade-off with the plant's metabolic needs. A flattened globe or hemispheric outline appears to promote more efficient interception of light by the leaves within the canopy. The position of the flowers—in the axil between the leaves and stem—protects the seeds from damage and also ensures that only vigorous tumbling will release the seeds.

In addition, a specialized layer of cells in the stem that holds the weed to its roots also enables the thistle to break smoothly away. The nature of these cells is not well understood. Many plants have cell layers that release fruits and deciduous leaves, but such layers do not commonly occur in stems. The stems of other, less familiar tumbling plants, such as the tumble



mustard (*Sisymbrium*) and flixweed (*Descurainia*), break in a jagged manner, apparently because of the wind.

The destruction of the cells in the stem most likely developed as an adaptive advantage: it coincides with seed maturity. Both the active separation of the thistle from its roots and the maturity of the seeds in the mother plant occur in the late fall as a response to the shorter days. Consequently, the seeds are ready for dispersal the moment the thistle breaks off and tumbles.

Seed dispersal is not completely random. A plant cannot tumble if it occupies a site covered by significant residual vegetation. A dense stand of shrubbery or ungrazed tall grass prairies will stop most tumbling thistle plants, leaving them lodged in windrows where birds and small mammals can consume the mature seeds. Seeds survive only a few months, and so unless a change in the wind sets the weed tumbling to a suitable habitat, the seeds will die. Hence, successful germination, establishment of seedlings and flowering depend on dispersal to sites where competition is minimal: Russian thistle would rather tumble than fight.

Russian thistle plants can produce huge numbers of seeds; typically one plant contains about 250,000. To accomplish this high productivity, the thistle produces simple seeds that lack stored energy reserves and complex coverings such as large fruit or thick seed coats. Instead the mature seed consists of a slightly immature, coiled embryonic plant covered by a thin membrane that forms the utricle, or the highly specialized "fruit" of the tumbleweed. Small, papery leaves called bracts protect and cover the utricle. Bracts, which are disseminated with the seeds during tumbling, apparently serve as aerodynamic wings to aid further dispersal and may also help the seeds absorb moisture from the soil.

For temperate-zone plants whose seeds mature in the fall, frost represents a threat. Most seeds remain dormant until the danger of frost damage passes. Such a strategy, however, requires the seed to commit a great many resources to complex growth regulator compounds. These compounds enable the seed to germinate only under suitable conditions. They must be attuned to environmental stimuli such as temperature, light, moisture and soil fertility.

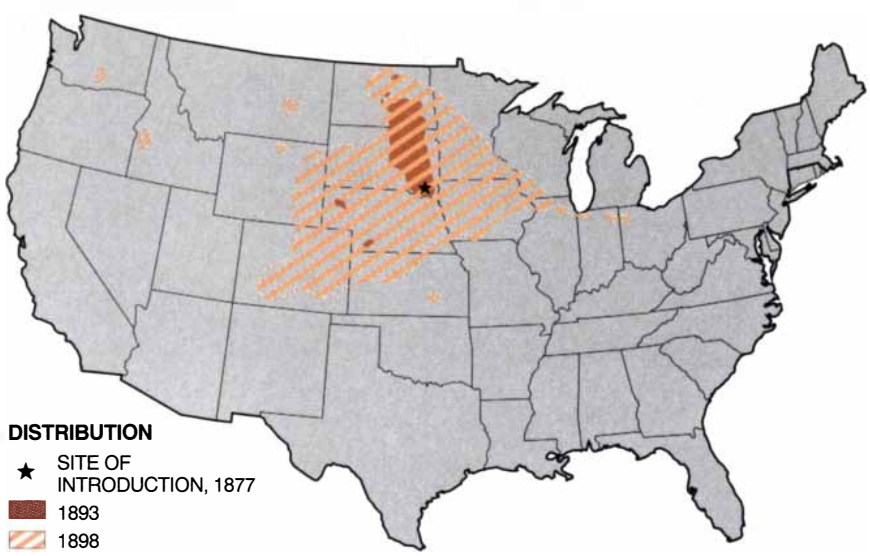
But with its very simple seeds, Russian thistle cannot afford such an expensive strategy. Virtually all its resources are devoted to the coiled embryo and utricle. Instead of a complex regulator system, the thistle evolved a less complicated system of afterripening. This system is a form of delayed seed germination that, for the Russian thistle, depends only on temperature.

Afterripening is thought to be caused by the immaturity of the embryo. Once the embryos gradually complete their development, the seeds are able to germinate at constant incubation temperatures between 24 and 27 degrees Celsius (75 and 80 degrees Fahrenheit). Of course, such temperatures are rare in northern environments during the late autumn and early winter. Over time, the seed relaxes the internal, temperature-related germination controls. By late spring, when the danger of frost is slight, Russian thistle will germinate at various temperatures that do not have to remain constant. The embryos sprout almost instantaneously between –2 and 43 degrees C (28 and 110 degrees F), even if such extreme temperatures occur within a single day. Consequently, a more or less universal genotype can adapt to vast ranges in latitude.

The Russian thistle does not undergo germination in the normal sense, whereby cell division results in the growth of the juvenile root or radicle. Rather the embryo uncoils. This process can occur in earth whose salt content is high enough to draw water from most other plants. If, after uncoiling, the radicle finds sufficient moisture—in the form of thin films coating soil particles—it quickly spreads cotyledons, or seed leaves, and begins growing through cell division.

Such a germination system is acutely sensitive to the microenvironment of the soil. One square meter of land can generate thousands of seedlings, whereas in the adjacent square meter a majority of seeds may fail to germinate because of slightly drier conditions.

Two hairlike cotyledons, each about one inch long and gray-green in color, characterize the Russian thistle seedling. The hypocotyl, or stem, is often bright red. From a distance the seedlings are virtually invisible. Dense stands of young plants will give a greenish cast to the landscape. Adult foliage is often dark green, making the landscape appear to be flourishing. The development of flowers and the change from soft juvenile to spiny adult foliage occurs during the summer. As the plants mature, they display a vivid variety of plant pigmentation—from straw tan to shocking purplish red. In size, too, they vary widely; a single plant can range from the size of a baseball to that of a compact automobile.



SPREAD OF RUSSIAN THISTLE began in 1877 in Bon Homme County, S.D. Its seeds were apparently imported with grain from Russia. Farm and railroad activity were primarily responsible for the rapid dispersal of the thistle seeds. During the 20 years or so after its introduction, the plant spread to more than a dozen states.

Although Russian thistle may have the most well-developed system of tumbling for seed dispersal among all plant species, tumbling is not characteristic of the Chenopodiaceae family, to which the Russian thistle belongs. In fact, the mustard family (Cruciferae) contains a greater number of tumbling species. Many of the tumbleweed's *Salsola* relatives are semiwoody perennials that use the wind and animals to disperse seeds.

Why the Russian thistle "chose" to

tumble to disperse its seeds may lie in its long association with agriculture—especially cereal grain production. Cereal grains require annual planting, a practice that tends to drain the soil of its nutrients. The constant soil disturbance eventually leads to barren tracts of land. Without flora to impede motion, such areas become perfect for tumbling. Further distribution of the Russian thistle occurred through mimicry, which has great adaptive advantages for agricultural weeds. The seeds of Russian thistle, once free from their papery bracts, are similar in size to cereal grains, making mechanical separation difficult. As humans moved, they unwittingly carried Russian thistle seeds with their cereal grains and seeds.

Evidently the marriage between farming and the tumbleweed has continued for some time. Archaeologists have found carbonized seeds of the weed in excavations of some of the world's oldest agricultural sites in southern Eurasia. Were it not for agriculture, the Russian thistle would have remained innocuous, exploiting only naturally occurring denuded areas. Instead the weed has become the unwanted shadow of cereal grain production in temperate zones worldwide.

Today the tumbleweed presents less threat to cereal grain production than it did a century ago. Scientists finally brought the weed under control when they developed phenoxy herbicides during World War II. These chemicals act by disrupting the maturation process of the plant; the weed essentially grows itself to death. But the cost of herbicides and their application adds to the production costs of cereal grains.

The weed now proves meddlesome in other areas. Irrigation districts and highway departments spend millions of dollars each year cleaning up and disposing of accumulations of Russian thistle. The plants clog canals and are a hazard on the road. Many a motorist, intent on outracing a tumbleweed, has instead ended up in the hospital.

In addition, Russian thistle growing in abandoned waste areas acts as a host for the curly top virus, which infects and rapidly kills crops. Leaf-hopping insects transmit the virus to susceptible plants, which include sugar beets, field-grown tomatoes and most flora in suburban gardens. Tumbleweed pollen is also a potent allergen, creating misery for millions in the western part of the country.

The hardiness and prolific abilities of the Russian thistle do not always make it a pest. As a last resort, it can be used for feed. In the 1930s, for instance, a severe drought limited hay production in the Canadian prairie provinces. By 1937, the last year of the drought, so little forage existed that what little was left of the breeding stock would have perished in the next winter. A late rain suddenly transformed barren grain fields into lush green fields of Russian thistle seedlings. Farmers harvested the seedlings for hay and silage. As a hay species, Russian thistle leaves much to be desired, but the juvenile plants saved the Canadian livestock industry on the plains.

MATURE RUSSIAN THISTLE tumbles to disperse seeds. But when the thistle lodges against fences or windrows, the seeds remain in the plant and die within months.

The ability of the thistle to produce numerous plants under adverse conditions has given scientists the opportunity to exploit its characteristics. At New Mexico State University, researchers determined that the plant is one of the most efficient in the world at creating biomass per unit of water used.

Workers from the Agricultural Research Service in Phoenix, Ariz., also investigated the thistle's potential as fuelwood. They grew the thistle on cropland where the water had been withdrawn for domestic use in urban areas and compacted the plants into logs for burning. Unfortunately, the bulkiness of the thistle does not yield much energy per unit volume and thus presents a barrier to widespread use.

At Utah State University, scientists found Russian thistle plants growing on raw soils from strip-mine reclamation projects have a root exudate that seems to make soil nutrients more available for other plants. After researchers uprooted the thistle, other species, including grasses, grew in the soil during subsequent seasons.

Throughout history, Russian thistle has followed human activities—even atomic-weapon testing. On sites in southern Nevada, where many warheads were detonated, Russian thistle was the first plant to reestablish a population at ground zero. Such tenacity would perhaps be unsurprising to a plowman tilling frontier land in the Dakotas or a muzhik sowing seeds on the Russian steppes. As long as humans disturb the earth, Russian thistle will find a home.

FURTHER READING

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Surveying Ancient Cities

A ground-level search of abandoned settlements yields enough artifacts to reconstruct urban history. It even turns up evidence that sharply focused excavation would miss

by Anthony M. Snodgrass and John L. Bintliff

In August 1981, near the end of our season in Greece, we discovered Askra, the home village of the early Greek poet Hesiod. Archaeologists had sought its location intermittently for a century. The 15-hectare site in the Boeotian highlands of central Greece was important for its literary associations and for the window it offered on rural Greek life. It was also far beyond our resources for full excavation.

The approach we took to investigating Askra—a surface survey—is not merely a low-budget alternative to traditional archaeological methods based on excavation. Surveys embody a fundamentally different approach to the study of how communities are born, grow and eventually die. They offer a broad sample of life throughout a given site rather than a statistically dubious (albeit exhaustive) slice of a few small plots. In some cases, surveys can give evidence that contradicts historical accounts. We found, for example, that rural Greece, commonly thought to have been deserted during the later stages of the Roman Empire, was in fact a thriving mix of diminished towns and intensively cultivated farmsteads.

Survey archaeology was first conceived as a technique for rural areas, and so we had to modify it for application to an urban site containing potentially unmanageable numbers of artifacts. Since investigating Askra, we have applied the methods we derived there to two larger Boeotian cities, Haliartos and Thespiai. In the meantime the technique has also been adapted to a small coastal township on the Cycladic island of Keos, a major Minoan city in Crete, a town in Etruria and an inland city in the Peloponnese.

The modern ground surface, as long as it is accessible and has not been altered, yields material representative of every period during which the site has been occupied. Potsherds and roof tiles are most common, followed by stone implements and building fragments, bronze coins and terra-cotta objects. By systematically covering the entire accessible area of a former city, picking up all distinctive material, recording its location and determining its identity, it is possible to construct a plot of the city's periods of occupation, growth, shrinkage and shifts in location.

To be sure, urban surveys are effective only under certain prescribed conditions. The site must be largely free of modern construction, and it must have been subjected to cultivation (the more intensive the better) at least intermittently since the abandonment of the city. The processes that bring pottery and other artifacts to the surface from the buried layers underneath are as yet understood only in a general way, but it is clear that they work. Cultivation plays a vital role in bringing material to the surface, as does the gradual erosion of topsoil. Material from the most recent periods is generally overrepresented in the surface layer, whereas ancient items are underrepresented.

Although they may be highly effective, surveys will never supplant excavation entirely. After all, the dating of artifacts found on the surface is possible in large part only thanks to decades of painstaking research by excavators, who have noted the sequences and associations of each class of material in their stratified deposits.

Moreover, there are many questions about the history of a city that surface surveys cannot answer. Unless the surface archaeologist is lucky enough to find the foundations of recognizable buildings—fortification walls, monumental public structures and the like—there is little the method can contribute to tracing changes in political power and independence, for example. (The relative abundance of imported pottery and similar items can furnish only indeterminate clues.)

Even when it was clear we had to survey Askra rather than trying to excavate it, the site still posed problems. Surface survey is a well-established archaeological practice, but surveys of areas that include urban centers had seldom been attempted because of the huge range in the concentration of artifacts. In Mediterranean lands the barren mountain slopes yield a handful of pieces per hectare, whereas the densest urban areas display 20 or even 200 artifacts per square meter.

Anyone but a Mediterranean archaeologist may find such figures hard to believe, but they are real enough. Furthermore, artifacts are not distributed in neat, discrete packets corresponding to ancient sites. Instead the nearly millionfold variation in artifact density takes the form of a gradual distribution extending hundreds or even thousands of meters from "primary" sites. The surveyor faces an extraordinarily rich body of data.

This embarrassment of riches poses problems, however, in devising collection strategies and determining what constitutes surface evidence for a site. Only after the highs and lows of the local distribution are known is it possible to place all the evidence in context. A concentration of artifacts that might pass for a rural farmstead at one site could represent only part of the gen-

ANTHONY M. SNODGRASS and JOHN L. BINTLIFF directed the survey investigations of the ancient Greek towns of Haliartos and Thespiai and the village of Askra. Snodgrass holds the Laurence Chair of Classical Archaeology at the University of Cambridge; he graduated from the University of Oxford with a degree in classics in 1959 and embarked on a career in archaeology, earning his doctorate with a study of Greek armor and weapons. From 1961 to 1976 he taught at the University of Edinburgh. Bintliff, Reader in Archaeology at Durham University in England, has particular interests in European social evolution, spatial archaeology and landscape evolution. He received his Ph.D. from Cambridge and taught at the University of Bradford from 1977 to 1990.

eral surface scatter at another. At the same time, there are limits to the amount of material from a single site that archaeologists can fruitfully catalogue and study. Early traverses of Askra yielded 10 or more artifacts per square meter, implying that a complete survey might yield 1.5 million artifacts.

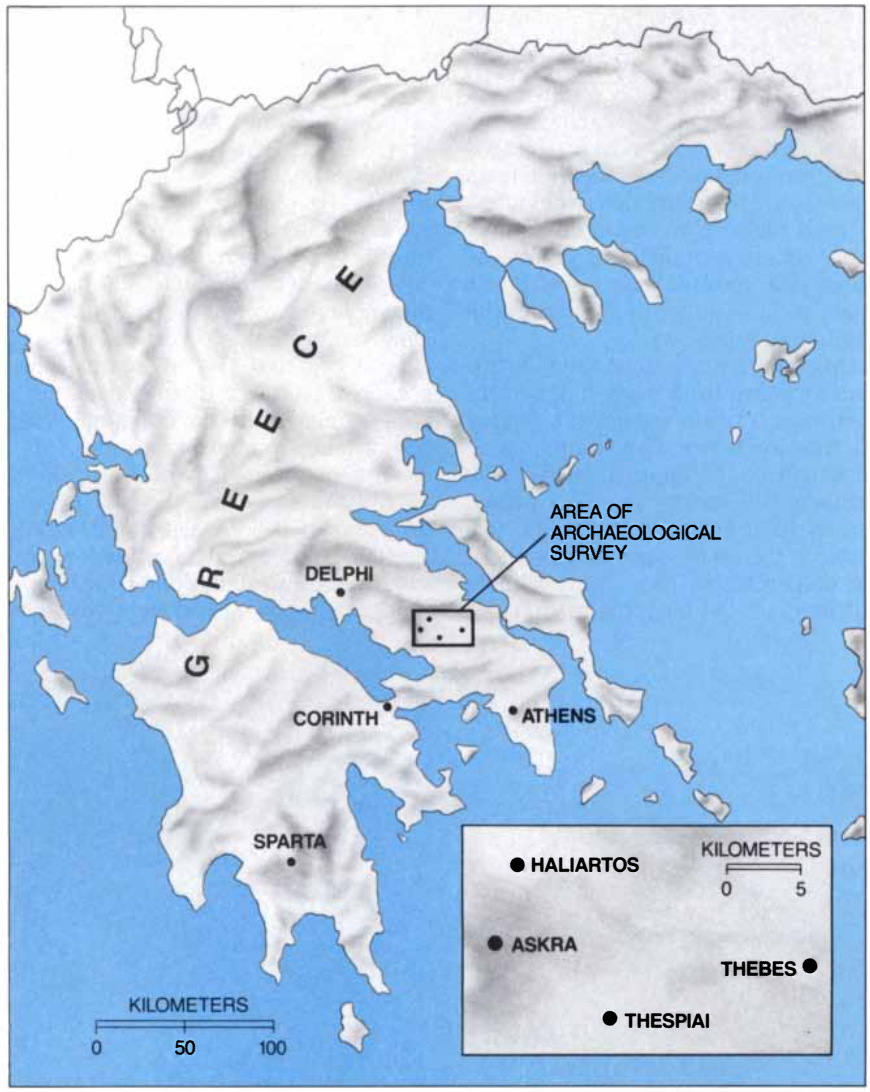
We devised a sampling method that has since served well for larger sites in subsequent seasons. The work is done in two stages. The first stage covers the entire accessible surface area so that the site can reveal all its distinctive artifacts and so that its phases of occupation can be dated. (Askra, for example, proved to have been occupied intermittently for more than 4,000 years.) The second stage is a more precise examination that provides an accurate measure of the total density of artifacts and helps substantiate dates derived from the initial pass.

We divided Askra into a series of transects less than half a hectare in area and surveyed each in its entirety. Walkers 15 meters apart counted visible artifacts in a strip five meters wide and picked up any material they judged likely to provide a date. Then the team scoured a 300-square-meter subsection of each transect. Workers picked over every square centimeter of ground by hand and counted all the artifacts, again picking up items that appeared useful for dating.

On average, we retained about 20 distinctive pieces from the first walking of each transect, and we added a further 15 from each intensive sample. More than half of the approximately 2,000 artifacts collected from Askra turned out to have chronological value, vindicating the on-the-spot judgments of the walking teams. As a result, we could substantiate the mapping of times of occupation of even such a relatively small site by hundreds of accurately dated pieces for each period.

From the very start of our survey, we had noted that virtually every site, however small, was surrounded by a halo of finds whose density decreased as we moved away from the site itself. The most widely accepted explanation for such halos is the time-honored ancient practice of fertilizing the ground with the manure of animals kept in the vicinity of domestic premises. Pieces of discarded pottery became mixed with the dung; the density of items in a given location is indicative of the density of cultivation. This hypothesis received striking confirmation in 1986, when Brian E. Davies and Andrew Waters of the University of Bradford found that concentration patterns of heavy metals in the

SURFACE-SURVEY ARCHAEOLOGISTS comb a modern vineyard in central Greece for artifacts left behind by millennia of human activity. Sites of abandoned cities may yield more than 100 objects per square meter. By dating the objects they find, archaeologists can determine the periods during which an area was occupied and estimate its changing boundaries.



soil across our sites matched the density patterns of ancient pottery.

It has long been known that heavy metals are deposited where people live and work. Davies and Waters's findings suggest that the refuse-deposition activities of 2,500 years ago have left clearly graded and quantifiable traces in both the form of visible potsherds and invisible pollutants. This reinforces our hypothesis that the rural sites were nuclei of intensive agricultural activity. On a vastly larger scale, the cities that we investigated have their own much broader and denser pottery halos. As economic historians have long maintained, Boeotian towns were occupied by cultivators.

Our technique had taken time to evolve, but it was ready by the time our survey carried us up to the walls of Thespiai and Haliartos, the two main cities in whose territory we were working. In particular, we were prepared to test the results of our surveys against written history. Whereas an obscure village like Askra, for all its literary associations, had no connected documentary history, these two towns had both been members of the Boeotian League and virtually independent political entities.

Thespiai earned a certain fame for its long opposition to Thebes, the most powerful city of the league. In 480 B.C., when Thebes prudently sided with the Persians invading Greece, Thespiai enjoyed its greatest moment of glory as it sent 700 soldiers (from a total population of perhaps 10,000) to die with Leonidas of Sparta in the attempt to hold the pass of Thermopylae.

In 424 B.C. Thespiai for once fought side by side with Thebes, winning a victory over the Athenians at Delion. The city again suffered heavy losses, however, and the following year the Thebans were able to exploit this weakness and compel Thespiai to dismantle its fortification walls. Not surprisingly, when Thebes achieved its military and political zenith by an unprecedented victory over Sparta in 371 B.C.—a battle actually fought on Thespian territory—Thespiai supported Sparta. The loss put an end to the city's heyday.

In the meantime Thespiai had produced its most famous daughter, the beautiful courtesan Phryne, who became the mistress of the sculptor Praxiteles and posed for his most famous statue, a nude Aphrodite. She dedicated in her native city another of his works, a statue of Love that made Thespiai a tourist attraction for the rest of antiquity.

Haliartos was by comparison a smaller and less famous town. Its population numbered no more than 5,000 at its peak. It came to notice in 395 B.C. as the scene of a minor skirmish in which a force of Thebans and Athenians ambushed a group of Spartans. The Spartan General Lysander, then the most powerful individual in Greece, was among the few killed. The most memorable event in the city's official history was also the last: in 171 B.C. Haliartos backed the Macedonians and other enemies of Rome in a war fought on Greek soil. The town was razed, its inhabitants killed or sold into slavery and its land apportioned among the citizens of Athens, which had taken care to join the Roman side. The territory of both Thespiai and Haliartos is now entirely free of permanent human habitation. The land is cultivated from villages some distances away.

This official history furnished some crude guidelines for our work, even though some episodes were of the kind that a surface survey cannot expect to trace or illuminate. The story also left open many questions we hoped to illuminate. We hoped to establish, for example, how changes in total urban population affected the distribution of occupied farmsteads in the surrounding countryside—and how the extreme case of city destruction influenced the exploitation of the surrounding land. One important issue, of course, was whether the rural and urban sectors grew simultaneously or at each other's expense. We also wondered how the boundary between two states might be reflected in the surface evidence.

The picture that we were eventually able to construct was, in this and other ways, much more detailed than any available from documentary sources. For Askra, of course, there was hardly any documentary information, so any new knowledge was pure gain.

Askra gave clear indications of a long but interrupted occupation and a pro-

gressive shift of several hundred meters in the nucleus of the settlement over time. A small area of the site was first inhabited for a period around 2500 B.C. After a very long break, the same locale was first reoccupied and then enlarged into a substantial village of 1,000 people or more between about 900 B.C. and A.D. 100. A second, much shorter break seems to have intervened before the final period of settlement between about A.D. 300 and 1600; since then the site has reverted to open farmland.

The two breaks are inferred only from negative evidence: we found no material whose date fell within those time spans. The first interruption, however, is so long that there can be no doubt of it; furthermore, for part of the time, a neighboring hilltop site was inhabited, suggesting an alternative focus of local settlement. And the second break is corroborated by the Greek travel writer Pausanias, who visited the area around A.D. 170 and described it as deserted.

There is little to say about the first period of occupation. The second, 1,000 years long, embraces the life of the poet Hesiod (circa 700 B.C.) in the village's earlier stages, when Askra was no more than a few scattered dwellings. Ensuing centuries saw first a steady growth and filling in of the settlement, then a marked shrinkage of population and inhabited area.

Throughout the period, the nucleus of the settlement shifted to the south. When the site was reoccupied in the fourth century A.D., the shift resumed until, by the final phases of Askra's occupation in Late Byzantine and Turkish times, the settlement had no overlap at all with the original nucleus of prehistoric and early historical times.

Like Askra, Haliartos had a prehistoric forerunner, sited on the highest ground in the area. And a phase of apparent abandonment, although much shorter than that of Askra, preceded the establishment of the core of the historical city. Classical Haliartos spread progressively down the slopes to the south and north until it attained a population of 5,000 or more and an area approaching 30 hectares. The easternmost extremity is lost under the houses of the modern town that shares the same name.

One interesting discovery was that although by about 400 B.C. the territory of the more populous Thespiai was more densely covered with permanent structures than that of Haliartos, the reverse had been true three centuries earlier at the beginning of the historical period. Apparently the smaller town was faster to colonize its rural territory with independent farmsteads.

During the classical period, the ancient city was surrounded by walls whose foundations are still partially visible. The original nucleus on high ground became the city's acropolis and had an inner fortification of its own. (All these walls were most probably torn down in 171 B.C.)

As predicted from the official history, there is an abrupt break in the sequence of dated pottery in the second century B.C., and for the rest of antiquity the greater part of the site was entirely deserted. A short distance to the east, however, on the outer fringes of the classical city, a new settlement grew up in Byzantine and early Turkish times. From that point onward, in an unbroken cycle, the decline and desertion of one location has been accompanied by the simultaneous growth of an alternative center of population not far away. Two such shifts are traceable between the 17th and 19th centuries A.D., before the foundation of the modern town and the revival of the name "Haliartos" around 1900.

The unique feature of the story of Haliartos is the ruthlessness and thoroughness of the Roman sack of 171 B.C. More gradual shifts, in contrast, are typical of all the major settlements in the area we study. These shifts explain why the modern villages with the official names of Askraia, Thespiai and Haliartos all lie at a certain remove from their ancient forerunners.

Thespiai proved the most daunting of the urban surveys we undertook. We had expected it would be larger than Haliartos, but we were hardly prepared for a city that had exceeded 120 hectares—more than a square kilometer—in area during the period of its greatest extent in the fifth and fourth centuries B.C.

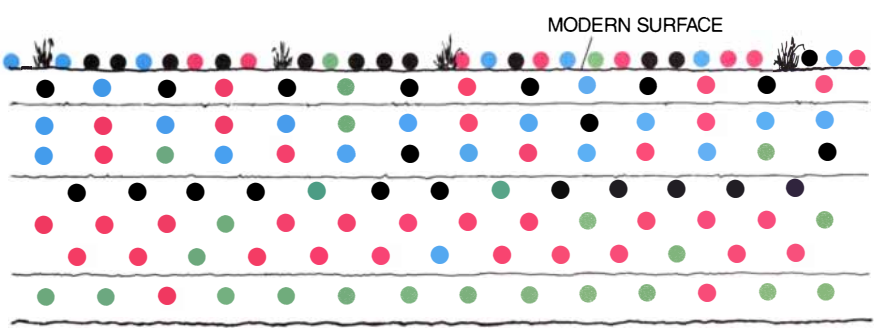
The two-stage procedure of observation and counting had to be repeated 598 times in all. It turned up well over 10,000 datable artifacts. We were able to draw up seven successive plans of the town's occupation and desertion over a span of some 7,000 years.

Unlike Haliartos, Thespiai did not grow from a single compact nucleus sited on top of a prehistoric settlement. The material of the eighth, seventh and sixth centuries B.C. is grouped in half a dozen separate clusters, suggesting a scatter of hamlets only welded into a single urban complex by the growth of the high classical era in the fifth and fourth centuries.

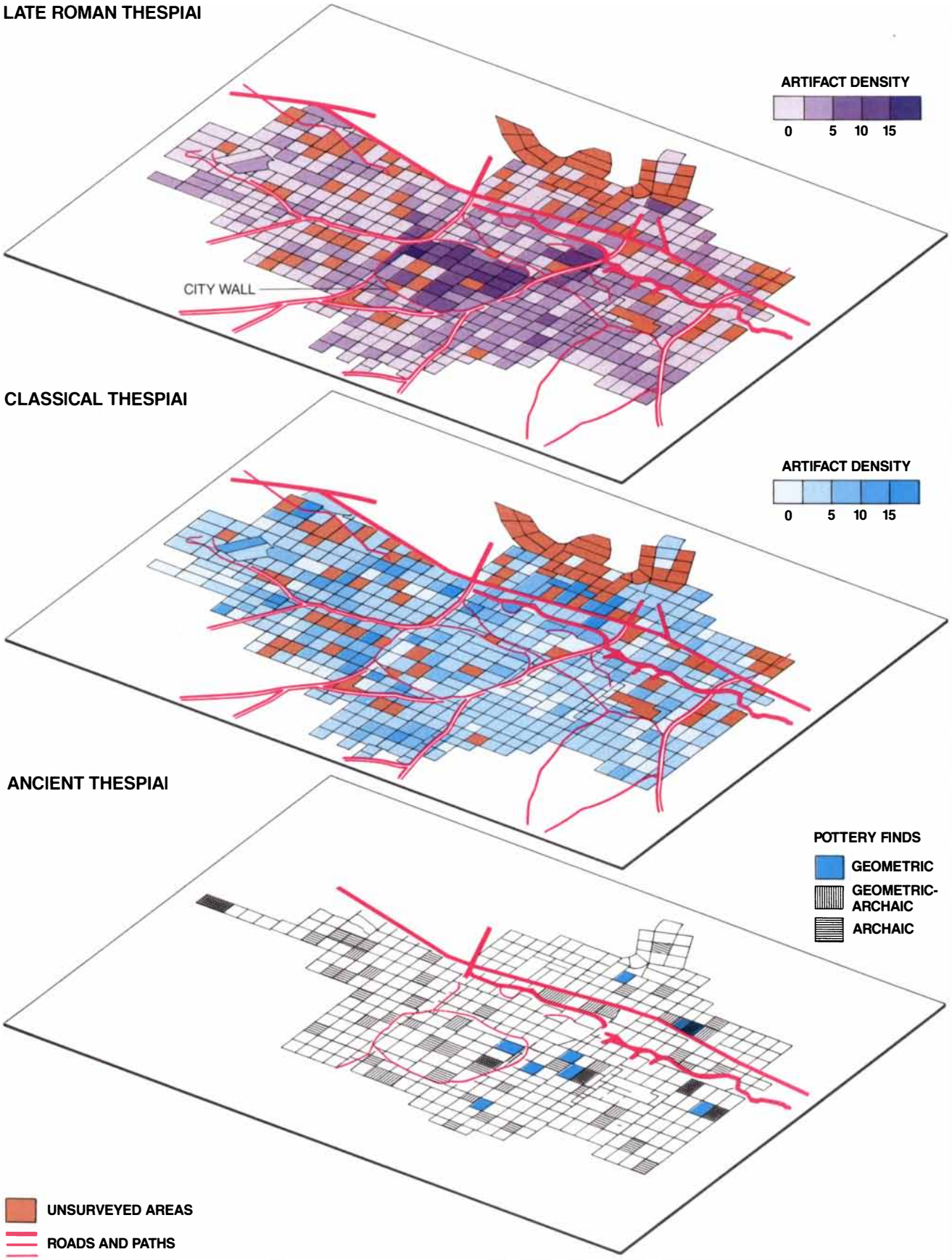
The inevitable sequel was a decline in size and, once again, a shift in the nucleus of occupation. One later phase stands out with special clarity: in the middle of the Roman Imperial period (between A.D. 30 and 300), Thespiai's inhabitants found it expedient to build a new fortification, enclosing a drastically reduced area of 12 hectares.

This polygonal circuit incorporated many blocks of classical stone; it stood until the late 19th century, when, ironically, it was destroyed by a classical epigraphist eager to get at its inscribed stones. Its outline is still faintly visible today. Not surprisingly, we found that material of the later Roman period (from about A.D. 300 to 600) was very heavily concentrated within and around this enclosure. Of the 32 transects that produced more than six later Roman pieces, 25 lay inside the fortified polygon and the rest immediately to the east and northeast.

Although late Roman Thespiai was much reduced in size, the large number of farmsteads we found in the surrounding countryside indicate that it lay at the center of a thriving rural economy. After the classical period, the late Roman is the most intensive period of rural settlement in the entire history of the central Grecian landscape—it was also the time of the reoccupation of Askra. This late Roman recovery is now



ANCIENT ARTIFACTS are brought to the surface by a continuous process of cultivation, erosion of topsoil and other geologic effects that are not yet fully understood. Older objects, from lower strata, are typically underrepresented at the surface.

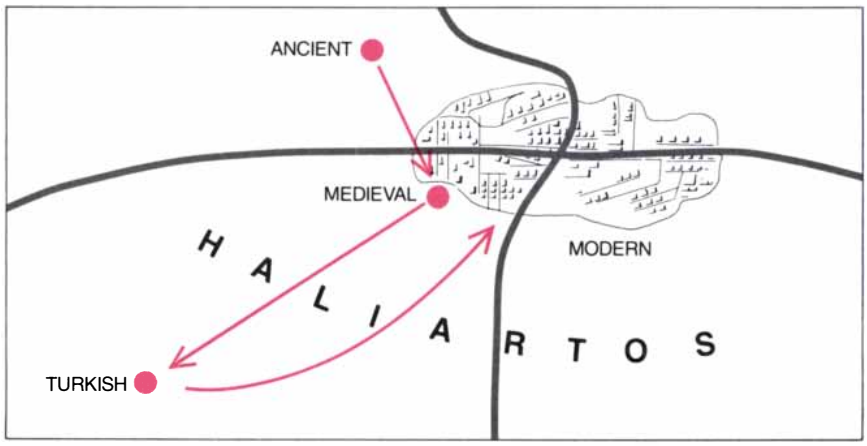


ANCIENT CITY of Thespiai was explored by surface survey. Dates of items found show that the settlement was occupied for more than 7,000 years. Archaeologists marked the site off into transects (*areas shown by black lines*), which were then examined. A specified part of each transect was painstakingly searched to verify the conclusions of the broad survey.

being revealed by surveys elsewhere in Greece. It is a good example of a development for which the documentary sources, with their gloomy picture of the age, had done nothing to prepare us.

Thespiai also provides a corrective to widely held views of postclassical decline for later periods. A settlement survived there in Byzantine times, entirely to the east of the polygonal enclosure; the ruins of several churches bear witness to continued vitality.

In the end, although the city outlasted all its contemporaries, large and small, it died. When the British traveler Colonel Leake visited Thespiai in 1802, he found a few inhabited houses still standing on the eastern part of the site. A few years later the last inhabitants moved to the hilltop village just to the north, where their descendants still flourish. The ancient city on the plain was given over entirely to cultivation for the first time in nearly 3,000 years—a near-perfect condition for archaeological survey.



ODYSSEY OF HALIARTOS shows how towns migrate as well as growing or shrinking. The city encompassed nearly 30 hectares before it was razed by Roman troops. Subsequent settlements skirted the edges of the old city for two millennia; a new Haliartos was built to the east of the ancient site just under a century ago.

The results of our surveys in Boeotia cast light not only on the conditions there but also on the nature of the questions that archaeologists and historians attempt to answer. Official history presents events in a form that is memorable and, as far as the facts allow, gratifying to those who read it. Individuals and organizations appear to formulate consistent policies and carry them through either more or less successfully—as was once said of the *Times of London,* official history describes what ought to have happened rather than what did happen.

Additional constraints affect the case of ancient cities: the written sources that survived were chosen mostly for their literary quality rather than their faithfulness to events. Some ancient historians did share the modern desire for objective truth, and other kinds of documentary sources such as coins and inscriptions also survive. But all such records are vulnerable to distortions, and all too often the sum total of historical evidence yields a portrait of a city that begins with a foundation legend and ends with a visitation of the punishment of the gods. It is significant that some modern authorities have turned as often to poets and philosophers such as Homer, Plato or Aristotle as they have relied on the prose historians.

Conventional archaeology offers only limited help in augmenting the historical picture. Financial and political exigencies usually combine to prevent the excavation of more than a limited part of an ancient urban complex (in contrast with the potentially complete unearthing of small prehistoric settlements). Digs must be sited on land free of existing buildings and available for purchase or expropriation. Only by the rarest good fortune does excavation result in a valid cross section of urban life. Indeed, many investigators would openly disavow such a mundane objective. Better by far to locate the civic center or the main sanctuaries, where they may be able to make some spectacular finds and have a virtual certainty of forging some kind of link with the official history.

Furthermore, even with the best of intentions, the small samples of material and the peculiar nature of preserved deposits makes "commonsense" inferences from excavation notoriously unreliable. The contents of graves, for example, may present a poor picture of the structure of a society and its attitudes toward the living. The goods interred with a corpse may or may not correlate with social or economic standing. Implements found in a grave or scenes depicted in it may or may not match those in everyday life.

Conventional archaeology, then, runs the risk of tautology if excavations proceed only in areas designated by historical accounts. And it can yield a thoroughly skewed sample of ancient life if researchers rely on the contents of rare caches of well-preserved material. Surface survey, in contrast, extracts a limited but valid picture from the detritus and other evidence that human habitation cannot help leaving on the ground.

Those inside and outside archaeology have often asked us whether the results of surface investigation should not be put to the test by excavation. Ideally, perhaps they should. But even excavation yields findings that are often inconclusive, and they are only valid for the area actually dug. Furthermore, resources seldom extend to both survey and excavation, so the choice of one means excluding the other.

Our surface survey of Thespiai covered 99 percent of the city's maximum area in the initial transects and about 13 percent in the regularly spaced intensive samples. For the same cost, we could have excavated perhaps two or three trenches five meters square down to virgin soil: a total of about 0.005 percent of the city's area. Even if the excavation uncovered an equivalent body of dated material, there is no question which method produces a better statistical sample of the physical traces of a city's past.

FURTHER READING

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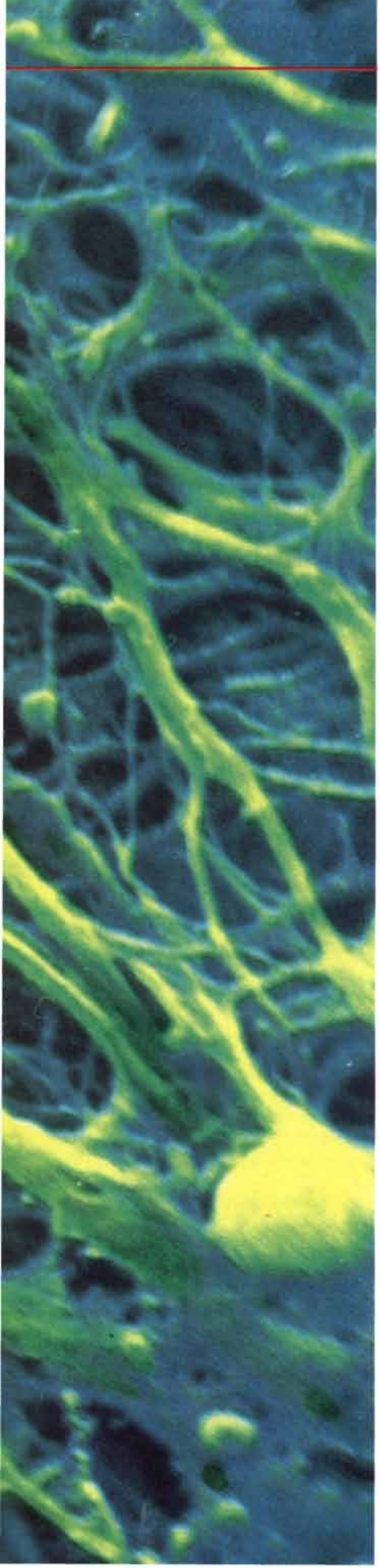
Rx FOR ADDICTION

by Marguerite Holloway, *staff writer*



NERVE CELLS form an intricate web that makes up the most complicated and imposing organ in the body: the brain. These neurons, just several of the trillions that orchestrate human activity, pose some of the greatest challenges for drug developers. Like a fortress, the brain is encircled by a moat—the blood brain barrier—which often prevents medications from entering. Additionally, nerve cells cannot reproduce once they are mature, so healing them remains very difficult. Despite these challenges, researchers are beginning to understand the changes brought about in neurons by drug addiction.

Probing the mysteries of drug addiction is revealing basic knowledge about the brain and may yield a new generation of pharmaceuticals.

Patches over both eyes, his scalp studded with electrodes to record brain waves, a cocaine addict from Baltimore describes how it feels to be high on cocaine—in real time. For half an hour, while the drug produces feelings of intense pleasure, researcher Edythe D. London asks him whether he agrees or disagrees with a series of statements: I would be happy all the time if I felt as I do now? I feel more clear-headed than dreamy?

The addict's brain activity is later recorded by a positron emission tomographic (PET) scanner. It creates images from the stream of high-energy particles released during the decay of short-lived radioactive isotopes that were injected into the drug user at the outset of the session. Because the brain absorbs more of the isotope in areas where levels of glucose metabolism are high, the images show active regions in bright red; slower areas light up as yellow or blue.

When London, chief of the neuropharmacology laboratory at the Addiction Research Center of the National Institute on Drug Abuse (NIDA), correlates what she sees with what the addict has said, she can create one of the most complete pictures yet obtained of the way cocaine acts in the living brain. Using formulas and readings of the blood levels of isotopes, London can retrospectively develop PET images for the 30 minutes of the experiment. "It is very exciting—you can watch what is happening chemically at the same time that someone talks about his or her subjective state," says London, a pioneer in the use of PET scans to study the acute effects of drugs of abuse.

London's research puts her at the forefront of a small group of investigators who are beginning to make headway against the intractable and

devastating problem of addiction. Some 5.5 million people in the U.S. are addicted to illegal drugs, according to the Institute of Medicine—that figure does not include people addicted to legal substances such as barbituates or amphetamines. Another 59 million or more are dependent on alcohol and nicotine, according to the National Institute on Alcohol Abuse and Alcoholism and the American Lung Association. Drug abuse remains disproportionately more prevalent among minorities, who often have less access to health care. The toll in terms of lives, health cost, crime and productivity cannot be measured.

Ironically, these often destructive, and illegal, substances provide valuable scientific information. And addiction researchers are using these insights to pioneer a frontier in pharmacology. In the past, drug developers randomly screened for chemicals that had therapeutic benefits—relying in large part on serendipity. Indeed, vacationing employees of some drug companies still return with bags of soil that are analyzed for microbial substances with biological activity. The way these drugs worked was usually uncovered years later, often yielding important clues about the systems in which they intervened. Now that process also works in reverse. The advent of modern biology has begun to make the understanding of how an organism functions an important source of potential therapeutic opportunities.

The promise of this approach is especially bright in the pharmacology of the central nervous system (CNS). Over the past decade scientists armed with molecular biology and powerful imaging technologies such as PET have gleaned new knowledge of the brain. Those discoveries have begun to illuminate how abused substances affect neurochemistry. Scientists are beginning to design highly targeted drugs that may soon be used to treat addiction on a chemical and even a genetic level.

The research being conducted in the most recent, and controversial, pharmacological offensive in "the war on drugs" may have wide application. Scientists searching for the biological foundation of addiction are making important contributions to the understanding of the basic machinery of the most protected and mysterious organ, the brain. At the same time, they are illuminating aspects of mental illness and neurological disorders. Clinicians testing medications already on the market—including those for depression, anxiety and schizophrenia—are observing that a few of them seem surprisingly helpful in treating addiction.

Eventually, if the overlap between mental illness and drug addiction becomes more clear, medications developed to treat addiction may be used to combat aspects of mental illnesses. In biological terms, drugs that are abused can create states that are very similar to some mental disorders. "The diseases of brain cells, or the perturbations of brain cells, that are associated with drug, alcohol and probably tobacco use and with mental illness may involve similar brain processes," says William E. Bunney, professor of psychiatry at the University of California at Irvine, one of the first scientists to probe the connections between mental disease and addiction.

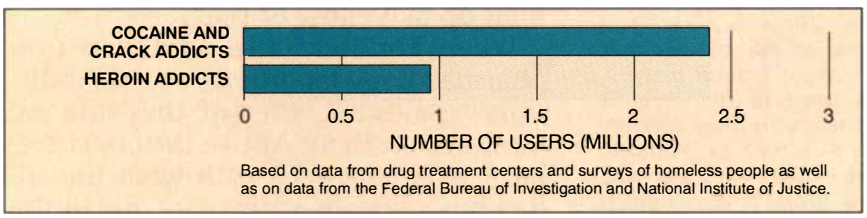
PET Probes

Developing drugs to treat drug addiction has recently become a major research focus at NIDA, amounting to some $36 million in 1990, partly because of the risk of spreading AIDS through intravenous drug use. Although that amount is hardly impressive, especially when compared with the estimated $6.5 billion the U.S. government spent on drug law enforcement and criminal justice last year, NIDA is hoping to catalyze joint research efforts with pharmaceutical companies. Many drugmakers have steered away from developing drugs for the CNS because they believe that neuroscience is too young—and too complex—to translate into products. The CNS field, particularly in the U.S., has been largely the province of venture capitalists, who over the past decade funded several neuroscience start-up companies, including Nova Pharmaceuticals, Athena Neurosciences and Alkermes, Inc.

Now, however, some major drug companies, including Glaxo, Du Pont and Bristol-Myers Squibb, are becoming more interested as NIDA courts them—and as London and others report a wave of findings. "Fifteen years ago we couldn't see any of this," whispered Michael J. Kuhar, chief of neuroscience at NIDA's Addiction Research Center (ARC), during London's presentation at a December 1990 meeting of the American College of Neuropsychopharmacology in San Juan, Puerto Rico.

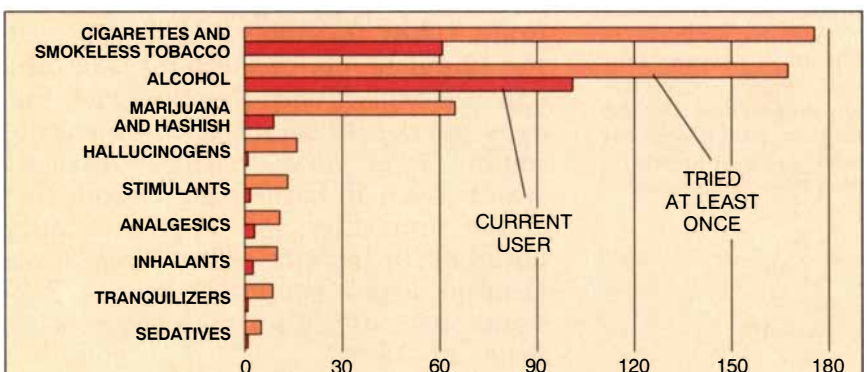
What London showed with her brightly colored slides was that cocaine caused glucose metabolism to plummet in the cortex (the outer region of the brain) in 16 male cocaine addicts. She also observed that this metabolism fell in the amygdala, which lies in the mesolimbic system, an inner brain region governing emotion and such drives as hunger, thirst and sex. The lower the metabolic activity, the more the addicts felt the effects of cocaine, London noted. This observation held true for amphetamines, barbituates,

Cocaine and Heroin Use



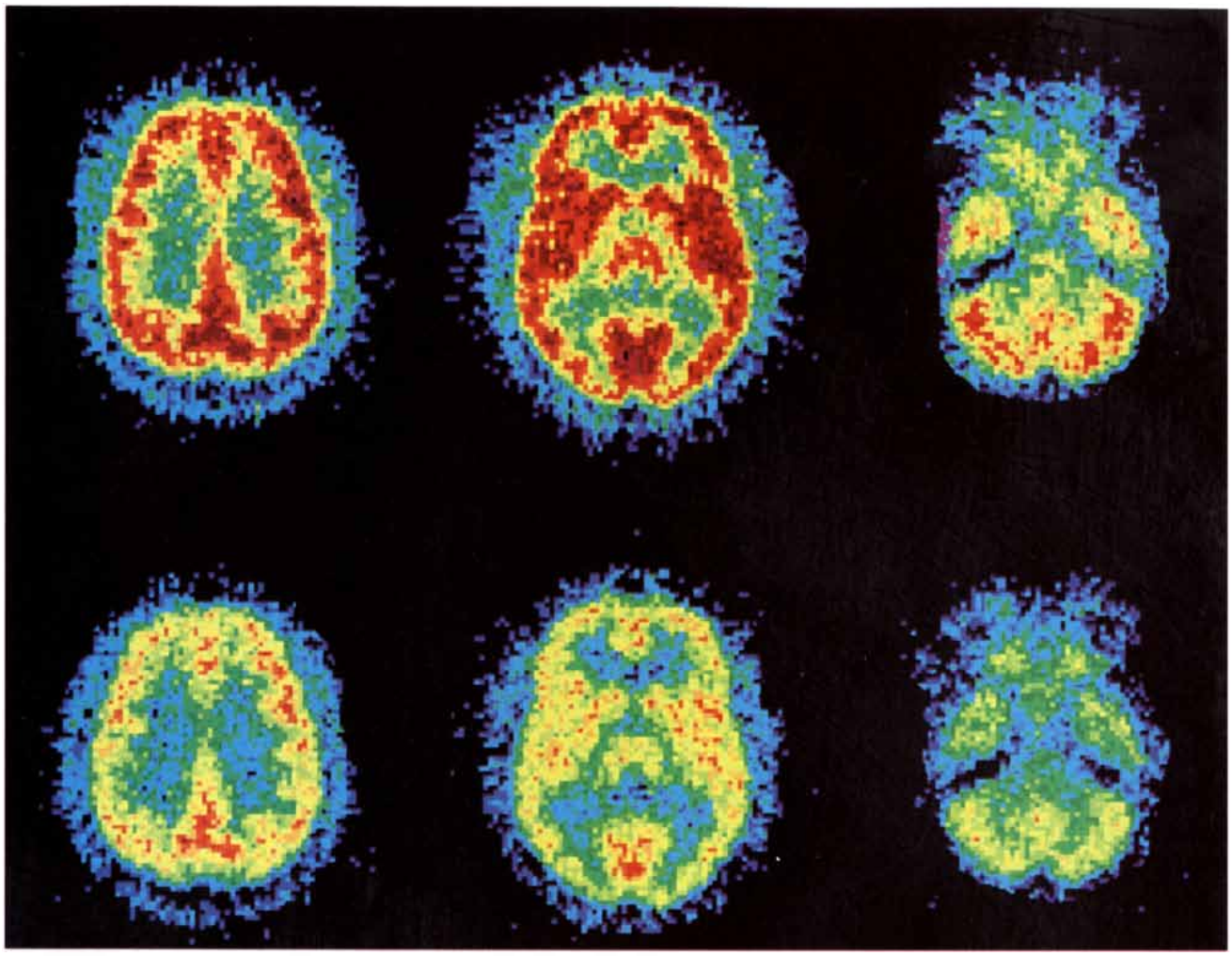
Based on data from drug treatment centers and surveys of homeless people as well as on data from the Federal Bureau of Investigation and National Institute of Justice.

Other Drug Use



Based on a household survey of 9,259 people, aged 12 and older. The survey does not include homeless people or those living in jails or military installations.

SOURCE: Senate Judiciary Committee, 1990 (top); *National Institute on Drug Abuse, 1990* (bottom).



COCAINE causes glucose metabolism to fall in certain regions of the brain as shown by the blue areas in these PET scans (*bottom*). But in a person who has not taken cocaine (*top*), activity in these areas remains high, as shown in red.

benzodiazepines and morphine, she added, but not for marijuana, which caused a surge of glucose metabolism.

On a molecular level, the activity shown in London's PET scans reflects the complex interplay of chemical messengers, called neurotransmitters, that carry nerve impulses from one cell to another. Neurotransmitters travel across a synapse, the junction between two nerve cells, where they bind to proteins—receptors—on the other side, triggering activity in the next cell. Scientists have found that most drugs of abuse interfere with this normal transmission. They have also hypothesized that forms of mental illness, such as schizophrenia and major depression, could be characterized by abnormalities in the neurotransmitter systems.

The discovery of some of these neurotransmitters gave neuroscience a big push in the early 1970s. A team led by Solomon H. Snyder, a neurobiologist at Johns Hopkins University, explored the way narcotics bind to receptors in the brain and discovered an opiate receptor. Snyder, who later founded Nova Pharmaceuticals, presumed that receptors existed to bind with some biologically important chemical. He and two other scientists—John Hughes of Parke-Davis in England and Hans W. Kosterlitz of the University of Aberdeen—discovered within a few months of one another that the body does make its own opiatelike compounds. These neurotransmitters, called endorphins, bind to opioid receptors, producing sensations of pleasure as well as serving to kill pain.

By the mid-1980s a number of other opioid receptors had been identified, and the number of receptors that accept drugs continues to proliferate. For instance, a receptor for marijuana was recently discovered by researchers at the National Institute of Mental Health (NIMH).

The existence of this cannabinoid receptor may mean that there is another, as yet undiscovered, neurotransmitter that normally binds to it. Nicotine also has receptors, which may be identical to those for the neurotransmitter acetylcholine. Alcohol, however, has not been found to bind to any one identified receptor, although it appears to influence many of them.

Cocaine may work differently. Kuhar, who is using PET to study cocaine addiction, has found that this stimulant interferes with the neurotransmitter dopamine (although it also affects other neurotransmitters and opioid-producing neurons). Cocaine, it turns out, hooks up with a protein called the dopamine reuptake transporter.

The intricacies of dopamine's actions remain unclear, but the neurotransmitter seems to work in part by turning a neuron on and leaving it on, causing feelings of pleasure. It does this until the transporter shuttles it back to its home neuron for storage. Dopamine acts much like a light switch, as Kuhar energetically demonstrates in his ARC office, where a yellow and red PET scan

Courting the Industry

Drugs to treat addiction are not popular in the pharmaceutical industry. In addition to the challenge and high cost of developing medications for the central nervous system (CNS), many companies worry about what they consider the stigma of addiction. They insist, for example, that buyers of a well-known drug for depression would no longer want to take it if they learned that it was being used to treat cocaine addiction. "It would be the kiss of death," says Salvatore Enna, senior vice president of research at Nova Pharmaceuticals.

As a result, some drugmakers have thwarted investigators seeking treatments for addiction. In one such case, according to a researcher who wished to remain unnamed, a drug was available in Europe. But the European company refused to make animal data available to U.S. researchers, stalling efforts to obtain permission from the Food and Drug Administration to investigate the product as treatment for addiction. Companies "will do everything in their power to stop us from playing with their compounds," comments Thomas R. Kosten, an associate professor of psychiatry and acting co-director of the Substance Abuse Treatment Unit at Yale University.

Stigma is not the only concern. Because addicts are often not paragons of health, companies fear that addicts might develop side effects that would delay approval from the FDA or lead to liability claims. Any "nasty adverse effects in addicts are going to be a problem," concedes Frank J. Vocci, chief of developmental therapeutics in the medications development program at the National Institute on Drug Abuse (NIDA). Says one drug industry executive: "It sounds cruel, but companies are out to make a profit, and society hasn't accepted that addiction is a disease."

Vocci and other government officials hope to change that attitude. In 1988 Congress authorized $10 million to create NIDA's medications development program. To entice the manufacturers, NIDA offered research secrecy agreements and access to the government's medication-screening capabilities and to clinical beds. The FDA has pitched in by promising special attention to medications for drug addiction.

The NIDA approach is based on the successful model of the National Cancer Institute, which many years ago found itself short of cancer treatments and encouraged industry to come in and help. And the effort may be paying off. Last winter NIDA's efforts received a boost from the Pharmaceutical Manufacturers Association (PMA)—representing 100 member companies—which created a commission to encourage members to pursue treatments for addiction. "There is a lot of movement all of a sudden," Vocci notes, adding that NIDA is now working with some 15 companies.

Even so, many industry executives believe Congress will have to become involved before drugmakers devote resources to fighting addiction. Despite NIDA estimates, precise numbers of addicts are difficult to quantify, as is the question of who would seek treatment. "Without legislative incentives, many companies are not going to get involved," admitted an industry executive, who spoke anonymously.

One way to ensure drug companies could cover their development costs would be to give drugs for addiction the same protection granted to orphan drugs, medications developed for rare diseases or small markets. Last year Senator Joseph R. Biden, Jr., of Delaware proposed such legislative incentives, including seven-year marketing exclusivity, but the measures were not enacted into law.

Meanwhile some researchers see European drug manufacturers as a rich source of drugs to test. They say these companies have devoted more money to developing CNS drugs than have those in the U.S. For instance, clozapine, a "new" drug for the treatment of schizophrenia, has been on the market in Europe for at least a decade, according to Donald F. Klein, director of research at the New York State Psychiatric Institute. In a recent survey of 50 European compounds, Klein found 20 of immediate interest for drug abuse and mental illness treatment.

Even if the FDA, NIDA and PMA do their utmost to propel development of CNS medications, drug addiction is clouded with ethical and practical concerns. "If you had the cure today, who would pay for it? How would it be used? It is my understanding that we don't even have enough methadone clinics," comments John W. Kebabian, senior project leader of the pharmaceutical products division at Abbott Laboratories. "It is easier to look at the neurochemical aspects of drug addiction; social issues are more difficult to deal with."

of dopamine receptors, the first of its kind, is proudly displayed. To produce these images, Kuhar and others inject experimental animals with radioactive compounds that bind to the dopamine receptors. When those compounds bind, areas with large numbers of dopamine receptors appear red or yellow. Areas without dopamine receptors appear blue.

Cocaine throws a wrench into the works, according to Kuhar. It hops on board the shuttle, leaving no room for dopamine, which continues to bombard its receptors, causing heightened feelings of pleasure in the drug user. (John D. Elsworth and his colleagues at Yale University reported last year that a new and potentially lethal drug—cocaethylene—formed by cocaine and alcohol together also binds to the transporter.) Kuhar and several other laboratories competing with his are rushing to characterize the transporter.

The Reward Pathway

Understanding the dopamine transporter may provide clues about dopamine itself and, like good counterintelligence, allow researchers to run interference on cocaine's meddling. Such knowledge could also help resolve a controversy over whether dopamine is the critical neurotransmitter responsible for the enjoyable effects of many illicit drugs. Most drugs of abuse are thought to produce good feelings by ultimately acting on the mesolimbic system, which may be one theoretical "reward pathway."

One group of scientists believes that in the end all pleasure comes down to dopamine or the cells with which dopamine communicates. Indeed, the neurotransmitter has been shown to bind to many receptors in the mesolimbic system; neurons producing dopamine make up a significant part of this system. Dopamine may also play a role in mental illnesses such as schizophrenia, which has been hypothesized to involve the overactivity of dopamine-producing neurons, and in Parkinson's disease, which is partly the result of a loss of dopamine-producing neurons.

Proposed by Roy A. Wise, a professor of psychiatry at Concordia University, the dopamine theory holds that strongly habit-forming drugs ultimately cause the release of dopamine in a part of the mesolimbic system called the nucleus accumbens. "Behind those opposite effects [of amphetamines and opiates] were very subtle effects that were common," Wise says.

A leading proponent of this dopamine hypothesis is Gaetano Di Chiara

of the Institute of Experimental Pharmacology and Toxicology at the University of Cagliari in Italy. Three years ago Di Chiara reported that opiates, alcohol, nicotine, amphetamines and cocaine caused an accumulation of dopamine in the nucleus accumbens. At the recent San Juan meeting, Di Chiara found himself face to face with his nemesis, George F. Koob, a critic of the hypothesis. When Di Chiara made his presentation, some researchers anticipated "blood on the floor."

There was no bloodshed, but no agreement either. Koob, an associate member of the Research Institute of Scripps Clinic in La Jolla, Calif., says he remains committed to his own theory. He holds that dopamine is important but not primary—that many other neurotransmitters are involved. Indeed, "it would be a great oversimplification and disservice to the elegance of the brain to postulate one system," agrees Edward A. Sellers, a professor of pharmacology at the University of Toronto who has tested many compounds for the treatment of alcoholism.

Koob does think, however, that the first step in the pleasure route may involve the nucleus accumbens. But given the elusive nature of the brain, even pinning down the functions of different regions can be hard. Hans C. Fibiger, a neurobiologist at the University of British Columbia in Vancouver, pointed out that participants at the Society for Neuroscience meeting in St. Louis last year said they did not know where the nucleus accumbens started or ended. Nor, for that matter, did they know if it existed at all, Fibiger added with a hint of rascality in his voice.

Even without precise knowledge about a pleasure pathway, or pathways, drug developers know enough about neurotransmitters and receptors to create and evaluate compounds. Indeed, most medications for the brain on drugstore shelves today operate by modulating one or the other, or both.

Treatments for addiction often seek to block the effects of a drug or the craving for it. Generally, drug-abuse medications take two approaches: agonism or antagonism. In the first strategy the medication binds with the receptor to produce a feeling of satisfaction but with less potential for abuse. Antagonism, in contrast, causes the compound to bind to a receptor blocking the usual neurotransmitter, preventing feelings of pleasure. Some agonists and antagonists being tested in clinical trials and laboratory animals are already on the market [*see box on next page*].

Methadone, made by Eli Lilly, is the most famous agonist. Addicts can stay on it indefinitely, but if they stop treatment they must weather a withdrawal that lasts twice as long as that from heroin, albeit a milder one. Methadone, unlike heroin, does not disrupt normal hormonal functioning or the body's response to stress, says Mary Jeanne Kreek, an associate professor at the Rockefeller University.

Naltrexone, which is marketed as Trexan by Du Pont, is an antagonist. Because it binds to opioid receptors and can outcompete heroin for these receptors, it is used to counteract heroin overdoses. But as a treatment for overcoming addiction, some researchers think naltrexone is not very effective.

Unmotivated Addicts

"Just blocking the euphoria is not the panacea that some naive individuals think it is," says Frank H. Gawin, an associate professor of clinical psychiatry at the University of California at Los Angeles. Roy W. Pickens, acting director of the ARC, agrees. "People may switch to another drug that is not blocked by these antagonists," he says. Many drug abusers are multiple-drug users, which makes rehabilitation even more complicated.

As a treatment for addiction, naltrexone may be effective only in people who are highly motivated to stay drug free. "It is most successful in those who have a lot to lose because of their addiction," says James W. Cornish, a clinical assistant professor of psychiatry at the University of Pennsylvania. Cornish just completed a study of federal probationers taking naltrexone and found them highly compliant. The reason, he says, is that the results of their weekly urine tests determined the length of their probation.

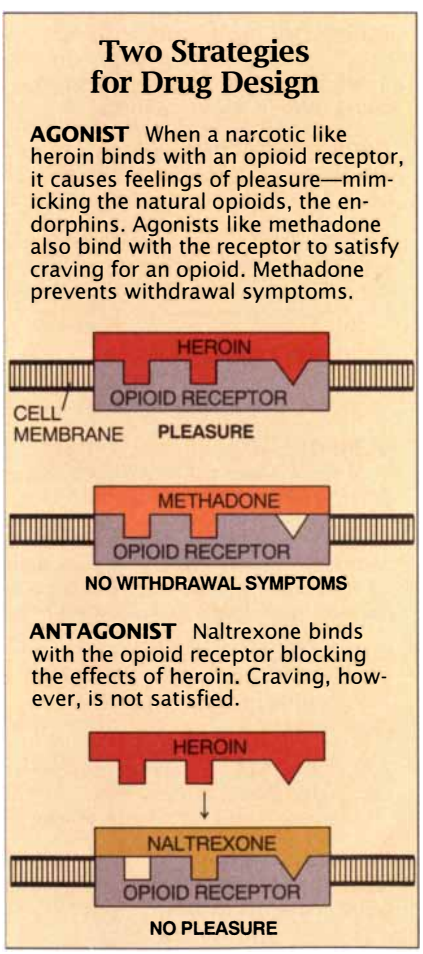
For those with less incentive, another approach could improve compliance. A naltrexone implant is being developed, says Frank J. Vocci, chief of developmental therapeutics at NIDA. Both Cornish's results and the potential use of an implant raise the possibility that some successful drug treatment programs could be coercive, says Donald F. Klein, director of research at the New York State Psychiatric Institute. "We have to face that bluntly," he observes.

Naltrexone recently revealed yet another side. In a finding that illustrates the complex interactions among neurotransmitters and reward pathways in the brain, a clinician reported at the San Juan meeting that naltrexone also blocks the craving for alcohol. Charles P. O'Brien, chief of psychiatry at the Veteran's Administration Medical Center in Philadelphia and a professor of psychiatry at the University of Pennsylvania, presented the initial data from a trial he and his colleagues are conducting at the university. Of 52 alcoholics taking naltrexone, the relapse rate was remarkably low—only 8 percent as compared with 48 percent of those taking a placebo. The findings were replicated at Yale University, O'Brien added.

The naltrexone data compelled E. Leong Way, a professor of pharmacology and toxicology at the University of California at San Francisco, to comment that "if it can be confirmed, this is the most exciting stuff I've heard at the meeting." The source of his incredulity was that the craving for alcohol, for which no specific receptor has been identified, seems to be reduced by an opioid antagonist.

Joseph R. Volpicelli, program director at the University of Pennsylvania's Treatment Research Center, may have an explanation. The common link between alcohol and opiates, he thinks, is that alcohol may cause the release of endogenous opioids like endorphins, and so blocking opioid receptors could block craving.

Stress may also be involved. The body's usual response to stress is fight



or flight—which causes the release of opioids. By the time stress has subsided, the body is accustomed to these excess painkillers and wants more. Alcohol therefore could provide a perfect way to medicate oneself. Volpicelli first tested his hypothesis in rats in 1987. But he explains that the connection was historically recognized: morphine was used in the U.S. at the turn of the century to treat alcoholism.

Among the drugs being tested against addiction is one that combines agonism and antagonism. Called buprenorphine, this pain-killing drug was developed by the British company Reckitt and Coleman Products Ltd. and licensed in the U.S. by Norwich Eaton. At low doses it works as an agonist, satisfying the craving for cocaine and heroin. At very high doses, however, it blocks the effects of opiates. "The bad news is that at higher doses it may enhance self-administration of cocaine," says Jack H. Mendelson, a professor of psychiatry and co-director of the Alcohol and Drug Abuse Research Center at McLean Hospital near Boston, who recently completed a study of 12 heroin and cocaine users taking buprenorphine.

In addition to testing these available medications, researchers hope to develop more specific receptor-based therapies for drug addiction. Armed with a growing knowledge of receptors, scientists from industry, academia and the government are working to design ones that have fewer side effects and greater specificity. In particular, such specificity could help treat women and children—the most visible victims of drug scourges—who are often not included in clinical trials. Compounds are being screened that bind with an opioid receptor called delta, says Richard L. Hawks in NIDA's research technology branch. Because fetuses do not have a well-developed delta-receptor system, any medication that could treat the mother by acting on the delta receptors may not endanger the fetus, Hawks explains.

Because of the stigma attached to drug abuse, few companies will discuss their efforts [*see box on page 98*]. But several, including Abbott Laboratories and Schering-Plough, are developing dopamine-receptor blockers that could be effective in treating cocaine addiction. (A spokeswoman for Schering-Plough says their compound currently is being developed solely for the treatment of schizophrenia.)

These experimental drugs are aimed at a subclass of dopamine receptors—called D1 receptors—that may be critical in the process by which cocaine becomes addicting. Most medications, such as clozapine, an antipsychotic being used to treat schizophrenics, work on a combination of D1 and another group known as D2 receptors simultaneously, or just on D2s. Abbott has developed an experimental D1-receptor antagonist called A69024, and Schering-Plough has developed another designated 23390.

Those compounds could prove important. Last year William L. Woolverton, an associate professor of pharmacological and physiological sciences and of psychiatry at the University of Chicago, reported that D1 antagonists could prevent monkeys from taking cocaine. "To the best of our knowledge, the pharmacology of cocaine is identi-

Some Medications Being Tested to Treat Addiction

ABBOTT 69024 is a dopamine antagonist that selectively binds with the D1 subclass of receptors. D1 antagonists have been reported to be effective in preventing animals from taking doses of cocaine.

AMANTIDINE, a treatment for Parkinson's disease, has been tested on cocaine abusers. In animals, it seems to cause a release of dopamine; in humans, it is unclear how it works. Results have not been striking.

BUPROPION is an antidepressant that appears to inhibit the uptake of dopamine. In tests at Yale University, it is proving to be fairly effective against the depression that follows cocaine use and addiction.

BUPRENORPHINE, an analgesic, binds to one of the subclasses of opioid receptors called mu receptors. At very high doses it blocks the effects of heroin but may increase craving for cocaine. Low doses may be an effective treatment for both heroin and cocaine craving. It is also being tested in combination with naltrexone for heroin addiction.

BROMOCRIPTINE binds with dopamine receptors and may suppress craving for cocaine. Clinical trials using bromocriptine as a treatment for cocaine addicts who are receiving methadone are planned. Earlier trials found no positive results.

BUSPIRONE, an antianxiety medication, apparently binds with serotonin—another neurotransmitter—receptors and may affect dopamine receptors as well. It has been reported to block cocaine self-administration in animals. It is also being used to treat alcoholics.

CARBAMAZEPINE (Tegretol) is an anticonvulsant that has been shown in animals to prevent "kindling"—the development of seizures that can result from repeated cocaine use. Human trials are under way.

FLUOXETINE (Prozac), an antidepressant, apparently blocks the reuptake of serotonin but not of norepinephrine—another neurotransmitter. It is currently being tested for its usefulness in treating cocaine and alcohol addiction. So far results are not impressive.

FLUPENTHIXOL is a tranquilizer that seems to be a dopamine-receptor blocker. It works primarily on the D2 receptors, with some effects on the D1 receptors. Craving in some cocaine addicts becomes manageable but is not eliminated.

GEPIRONE, an antidepressant, acts on serotonin and dopamine levels—and is very similar to buspirone. It is being tested for its potential in changing drug-seeking behavior as well as for depression and anxiety in cocaine addicts.

LAAM (levo-alpha acetylmethadol) is an experimental treatment for heroin addiction that was developed by German scientists around 1948 as an analgesic. Like methadone, it binds with opioid receptors, but it is longer acting. The drug has not been produced by a company, because it is no longer patentable.

MAZINDOL, an appetite suppressant, seems to act on the limbic system in a manner similar to amphetamines. Because it binds to the dopamine transporter more tightly than cocaine, it has shown some encouraging results in a few cocaine addicts.

NALTREXONE is an opioid antagonist used for the treatment of heroin addiction. It appears to be beneficial in addicts motivated to stay drug free. Recently researchers have found that it is also effective in blocking the effects of alcohol.

SCHERING 23390 is a D1-receptor antagonist being developed for the treatment of schizophrenia. Some researchers are testing it as a way of curtailing cocaine abuse in animals.

cal in humans and monkeys," Woolverton notes. Observes Koob: "If you could get a long-acting D1 drug, it would be like methadone for cocaine."

The current focus on neurotransmitters and receptors may turn out to be just a starting point for drug development. "Most people realize that if you just look at the synapse, you are missing a whole world of other signals that act in the brain," says Bruce M. Cohen, a psychiatrist and molecular geneticist at McLean Hospital.

Second Messengers

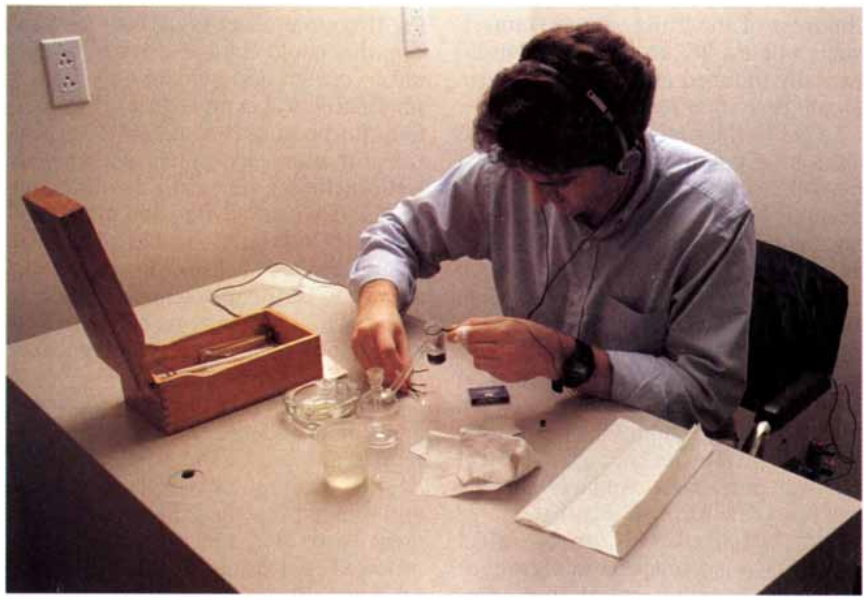
When a neurotransmitter binds with a receptor, it is like the first domino falling in a series. Only recently have scientists started to understand the intricate details of this cellular response. So-called second messengers, like the second runners in a relay race, pick up where the receptor left off.

One group of second messengers is known as G proteins. Discovered in the past decade by Alfred G. Gilman, a professor of pharmacology at the University of Texas at Dallas, G proteins lie embedded in the cell membrane. They issue instructions when a neurotransmitter binds to a cell-surface receptor. Several G proteins have been found; they are named according to their inhibitory, excitatory or other abilities.

When a narcotic such as morphine binds with a receptor, the shape of the receptor is changed. That change allows the receptor to bind to a G protein. In turn, G proteins can alter the polarity of neurons, triggering the electric impulse that travels along a nerve cell by regulating the passage of ions through the cell membranes. They can also play an indirect role in the expression of genes in the cell by causing proteins to bind with DNA.

Although all medications that act on receptors indirectly affect second messengers, they have been studied in a hit-or-miss fashion, says Steven E. Hyman, a molecular neurobiologist at the Massachusetts General Hospital. That is, they have never been designed to intervene after the receptor-based reaction, although some, like lithium, act only on second messengers. "Drugs could be developed that interfere in this area rather than at the receptor site," says Way, whose work on narcotics elucidated some of the second-messenger changes.

David C. U'Prichard, vice president for biomedical research at ICI Pharmaceuticals Group, and others speculate that modulating the second messengers may offer scientists a way to fine-tune the effects they want to induce in a neuron. Medications could be designed specifically to target receptors that interact with different subclasses of G proteins, offering greater control of the drug's effects. Other treatments could work on autoreceptors—receptors, located on the first neuron, that serve as a thermostat to regulate the release of a neurotransmitter.



CRAVING FOR COCAINE can be brought about by the sight of white powder. A researcher at the University of Pennsylvania's Treatment Research Center demonstrates how the physiological response of addicts to drug apparatus is monitored.

Simply intervening in receptor and neurotransmitter systems—even with second messengers—gets at only part of the problem, however. "Something slow happens in the brain. It changes how it responds to a drug," Cohen says, citing the example of antidepressants, which often take several weeks to have an effect.

Using PET to study radioactively labeled dopamine receptors, Nora D. Volcow, associate chief of staff in the medical department at Brookhaven National Laboratory, has documented some of these changes. She found fewer dopamine receptors in cocaine addicts as compared with normal controls. Whether this change is permanent is unclear, but at this point "it is not obvious that the number of receptors goes back to normal," Volcow says.

Volcow's PET findings reflect what clinicians report. When they are not high, cocaine addicts can feel depressed or cannot feel any pleasure (anhedonic). Feeling less pleasure could be the result of there being fewer receptors to receive normal amounts of dopamine. (This idea supports the "self-medication" theory of drug abuse: people take drugs to restore neurochemical abnormalities.) Medications that increase the number of dopamine receptors may therefore be effective in treating anhedonia—and treating anhedonia could keep people from craving cocaine.

Gawin, one of a handful of young researchers working on drug addiction, has tested several antidepressants already on the market to see if they could help cocaine addicts. One compound, flupenthixol, was not available in the U.S., so Gawin set sail for the Bahamas to test a first round of patients several years ago.

The drug, which the addicts nicknamed Fixall, works to make craving manageable but does not eliminate it. "One addict described craving as being two hands grabbing him by the back of the neck and pushing him into the gutter," Gawin relates. After taking flupenthixol, the subject said the craving was "like one hand that is not pushing him so hard." Gawin is now testing flupenthixol in a double-blind trial.

Also hoping to combat craving in addicts, London is ready to study images of glucose metabolism during opiate and cocaine withdrawal. She found that rats going through withdrawal have frenzied glucose activity—as if stopping opiates causes the brain to work overtime. Since some aspect of pleasure seems to be associated with decreased metabolism, the misery of withdrawal may be associated with excess activity. If this proves true in humans, London will test buprenorphine and clonidine, a drug for high blood pressure that binds with opioid receptors, to see if they decrease metabo-

lism. Another researcher, Anna Rose Childress of the University of Pennsylvania, will use PET to examine environmentally induced craving [*see illustration on preceding page*].

To get to the roots of these changes, some investigators believe they must intervene on the genetic level. Recent research by Eric J. Nestler, a molecular psychiatrist at Yale, Hyman at Massachusetts General and Cohen at McLean, among others, has shown that even though genes are not altered, they can be turned on or off by drugs of abuse as well as by medications that work in the brain. Finding out how to turn them on or off could be the key to new treatments. "The technology to look at this has only been available for the past few years," Cohen points out.

Understanding how drugs affect genes may also unlock the secrets of addiction. Scientists still do not know what neurochemical changes lead to tolerance or addiction. Cohen, for one, believes that watching changes in gene expression can yield a better understanding of reward systems. He views those pathways as based on circuits extending through different brain regions rather than confined to one region. By tracing which genes are turned on by, say, cocaine, he and his colleagues hope to use the drug as a probe. If they can see which genes are activated in which nerve cells, it would highlight the brain circuit where cocaine has its effects.

Changes in a pathway that occur over time—caused by repeated drug use—may underlie addiction. Because of this wiring, "there may be some overlap between the craving, the need for drugs and a shared reward system," Cohen explains. With regard to treatment, finding this circuit could lead to a medication that could combat craving for opioids, cocaine and alcohol—something pharmaceutical companies are ever vigilant for because it could have application for more acceptable cravings as well, including those for nicotine and food. "If we could find the aspirin of the abuse system, we would be in great shape," related Michael Williams, acting area head for neuroscience research at Abbott, to a group of researchers at a recent conference on developing drugs to treat drug addiction.

New evidence indicates that the genes that underlie the dopamine system might be a good starting point. At the meeting in San Juan, Cohen and others presented their findings on gene expression and drug use. Cohen reported that drugs that acted on the rat brain—including cocaine and two for the treatment of schizophrenia—caused an increase in the production of certain types of messenger RNA (mRNA), a likely sign that genes had been activated.

Cohen determined that in the case of the antipsychotic drugs, the mRNAs led to the synthesis of dopamine receptors and to the activation of two immediate early genes—genes that respond to a stimulus, such as a drug, right away. As is often true, these genes activate other groups of genes. The changes in gene expression varied in both their extent and their location in the brain depending on which drug was used, Cohen observed.

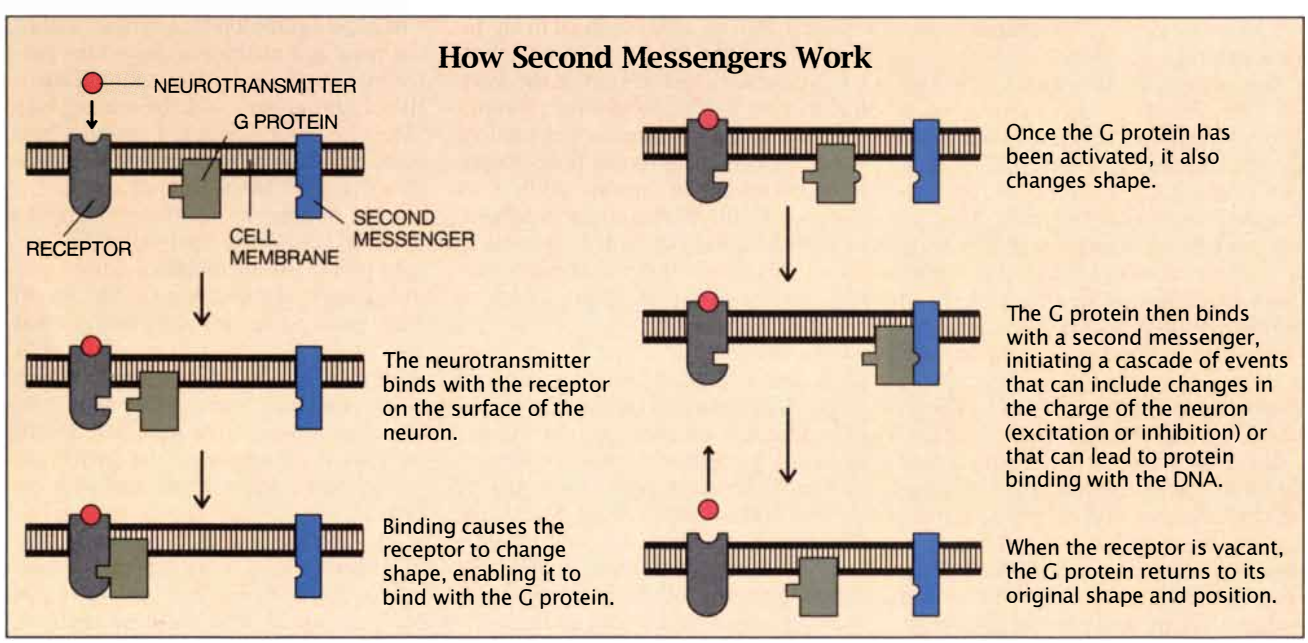
Although scientists have known that drugs could alter the number of dopamine receptors—as Volcow of Brookhaven found in her PET scans—they were not sure how. "But now we know new receptors are being made," Cohen notes, referring to the antipsychotic findings. "We are able to look directly at the gene product, the RNA right off the gene."

Viral Shuttle

The next step, and one that could take years, will be finding ways to alter gene expression or undo the effects of abused drugs on genes. One possibility is to flood cells with RNA that is a mirror image of that produced by the cells. This "antisense" RNA would bind with the cells' mRNA, rendering it unable to transcribe proteins.

Using vectors, or carriers, such as carefully tailored viruses that travel only to neurons, researchers could get the antisense strands to the right cell. For example, workers at the University of Pittsburgh and Harvard Medical School are using herpes simplex as a shuttle to implant genes into neurons. Such vectors might also introduce regulatory sequences: segments of the DNA that control the transcription of certain genes and proteins.

Such gene regulation is very far off, but "the possibilities are mind-boggling," Cohen asserts. "At some point it becomes like going to the moon. The technology is now beginning to look so powerful that it becomes reasonable to talk about these things." Indeed, several pharmaceutical companies have approached Hyman, who works on regulatory sequences. "Companies are looking for drugs that act on transcription factors," Hyman declares. And they



want to "look at changes in gene expression as a biological readout of the neurons that are affected by a compound." That would provide drugmakers with a new way to screen potential drugs for activity in the CNS, he notes.

Still very undecided is the debate over whether genes do in fact contribute to addiction and other mental illnesses. Few question the striking similarities between some mental illnesses and drug abuse—both of which may be characterized by imbalances in neurotransmitters. These alterations can be observed neurochemically as well as behaviorally.

None of these connections, however, has been made genetically, only epidemiologically. A recent study coordinated by Darrel A. Regier, director of the division of clinical research at NIMH, looked at 20,291 people from the general community, from mental hospitals and from nursing homes and prisons and found that 53 percent of those who abused drugs had a mental health disorder such as schizophrenia, anxiety or major depression. (The prison population, when taken alone, had nearly a 90 percent overlap.) The study "suggests that one disorder may cause the other or that an underlying biologic vulnerability to these disorders exists in affected individuals," Regier reported.

The effort to locate genes for specific mental illnesses, such as manic depression and schizophrenia, has not yet born fruit, says Elliot S. Gershon, chief of the clinical neurogenetics branch at NIMH, who has been screening chromosomes to find genes that could underlie these disorders for many years. In studies of twins conducted in the early 1980s, Gershon documented a response to amphetamine that was genetically based. He believes that genetics may predispose individuals to drug addiction.

One effort to determine a genetic component to drug abuse has focused on alcoholics. The research remains highly controversial. A team led by Kenneth Blum of the University of Texas Health Sciences Center at San Antonio reported last year an association between alcoholism and a gene that encoded a dopamine receptor. Later that year David Goldman, chief of genetic studies at the National Institute on Alcohol Abuse and Alcoholism reported finding no such association. But Blum was looking at cadavers while Goldman was studying living alcoholics, so the issue is far from resolved.

Although most researchers agree that alcoholism has some hereditary component, linking it to a specific gene is difficult. In an as yet unpublished study of twins, Pickens of the ARC concluded that heredity was responsible for between 20 and 30 percent of the risk for alcoholism (although the genetic influence was greater in certain subtypes of alcoholism). "The literature is so murky, and this is the first study that uses a standard genetic approach," comments George Uhl, a molecular geneticist at the ARC who is working to clone the dopamine transporter.

MARGARET CATRAMBONE recently participated in a clinical trial for naltrexone at the University of Pennsylvania. She found that the medication blocked her craving for alcohol.

While they wait for the laboratories to produce medications based on receptors, second messengers or even gene expression, clinicians are struggling to treat the myriad problems of addicts. By easing some side effects of addiction—or some associated mental disorders—they can relieve pain. "It is simplistic to think of these drugs as being curative," points out O'Brien of the University of Pennsylvania, whose sentiments are echoed by nearly every researcher in the field. Treatment must work in concert with counseling, changes in daily activities and help with housing and employment. "Our best hope is to find medications that will treat the biological changes produced by abusing drugs," he adds.

But shortages of treatment programs as well as staff impair clinicians' ability to provide good care to everyone who needs and wants it. Compounding the shortage is the fact that no one is clamoring for a methadone clinic or its equivalent to be set up in his or her neighborhood. Few pharmaceutical companies are pushing back the frontiers of science in order to lock up the addict market. "Despite the hype—and that's what it has been, hype—of the war on drugs, the addict on the street is getting less treatment money than he was in 1971," O'Brien notes.

Perhaps the loudest objection is philosophical: drugs to treat addiction just perpetuate dependency, an emotional weakness. "We have the simple notion that we can solve drug addiction by fixing bad chemistry with better chemistry," says Lester Grinspoon, an associate professor of psychiatry at Harvard Medical School.

Some drug abusers also worry about becoming addicted to another substance, even if it is a medication. Margaret Catrambone, a middle-aged administrator who started drinking when she was a teenager, only reluctantly entered the naltrexone clinical trial at the University of Pennsylvania. "I thought, 'This can't work, this pill can't take away the craving,'" Catrambone remembers. But after three months, she says she did not feel the craving. "It enabled me to see how I could be sober and change my life." Catrambone now takes the medication only if a difficult time is approaching—like the holidays. "I do not feel dependent on naltrexone, and I was very much afraid of that."

Clearly, many clinicians agree that medications may be able to help addicts get their lives in order. "I don't fully understand the philosophical objections," says Stephen Magura, deputy director of research at Narcotic and Drug Research, Inc., in New York City. "Drug abuse is an illness. If a medication would help an addict, why would you withhold it? For your own benefit or for the addict's benefit?" But until the drugs are developed—and until all the addicts that wish to be treated can be accommodated—that question is moot.

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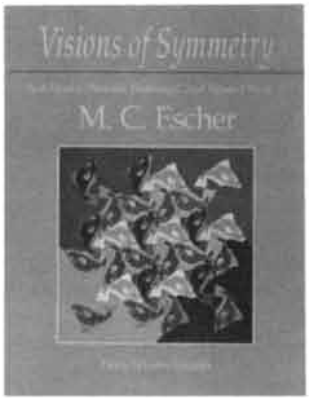

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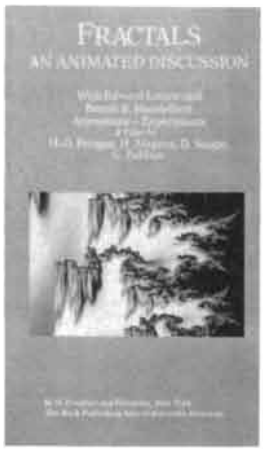

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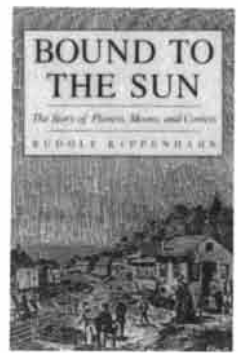

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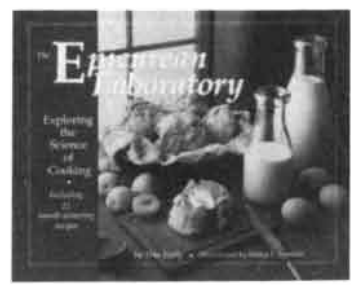

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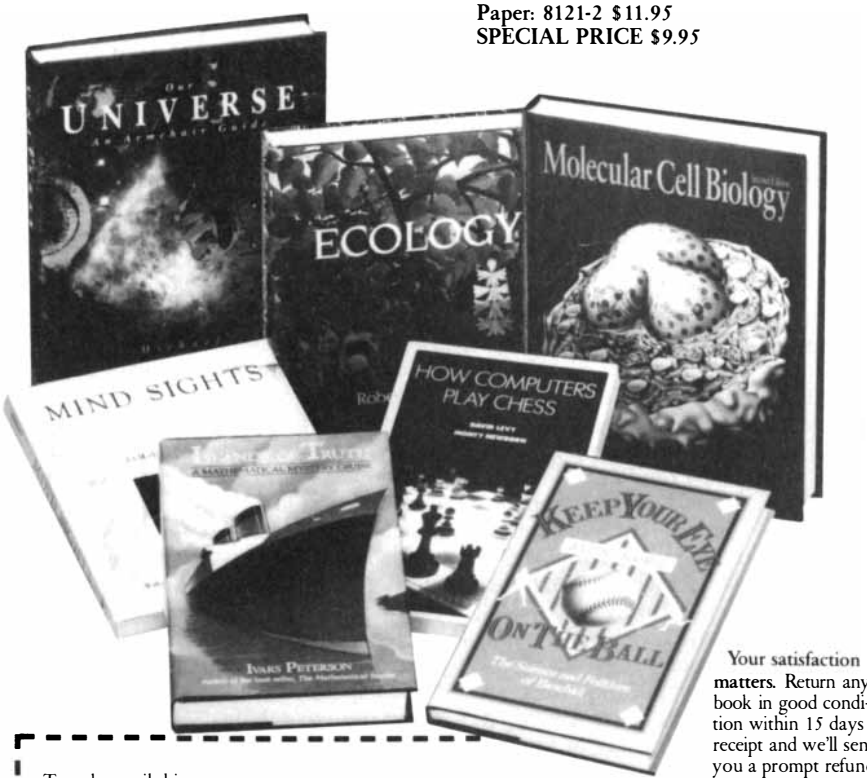

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Light Traffic

Optical amplifiers promise to unclog lightwave communications

Mainframe airplane, fending off phylloxera, superconducting sensors, hydrogen hits the road

On a bookshelf in Emmanuel Desurvire's office at Columbia University sits a spool of optical fiber looking as innocuous as fishing line. Embedded in these glass threads, however, are a smattering of ions of the rare-earth element erbium. By itself, this doped fiber absorbs rather than transmits light. Couple a short segment of it to a tiny diode laser, however, and the system becomes an optical amplifier, boosting the light signals that pass through it.

Within the past two years such optical amplifiers have become one of the hottest topics in telecommunications hardware research. Their promise is tantalizing: inexpensive, long-distance communications and dramatic increases in the amount of information sent across communications networks.

Erbium ions in glass are "a miracle of nature," proclaims Desurvire, who recently left AT&T Bell Laboratories to become a professor at Columbia. He and other researchers are convinced, moreover, that the amplifiers will swiftly find their way into applications. "There are no new fundamental materials or process inventions required," points out David A. Thompson, who manages components technology at Corning. The unanswered issues are largely ones of engineering and of cost.

Ironically, given the current excitement, erbium-doped fibers have been waiting to find an application for more than 20 years. In the early 1960s Elias Snitzer, now a professor at Rutgers University working with the fiber-optic materials research program, found he could generate pulsed light from glass doped with neodynium or erbium ions when it was pumped, or energized, by a flash lamp.

The results were a consequence of the unusual internal structure of multiple energy levels of the rare-earth ions. When pumped with light, more ions are forced to a higher energy level than remain in the lower levels. (This is called a population inversion.) Over time the ions decay to lower levels, spontaneously emitting some light. But if they are stimulated by another light signal before they decay (namely, one equal in energy to the difference between the higher and lower energy states), the ions will emit more light. Therefore, they boost, or amplify, that passing signal.

To make a laser of glass, Snitzer needed only to force the spontaneously emitted light to oscillate between mirrors. Taking away the mirrors and adding another incoming signal turned the system into an amplifier. "Those were 'hero experiments' that just showed we could do those things," Snitzer recalls. "We talked about these becoming amplifiers," he adds. But insufficient funding, Snitzer says, meant that optical amplifiers remained an idea embedded in academic journals.

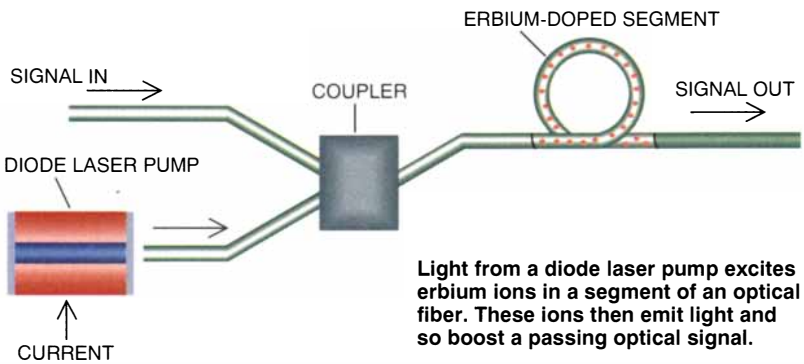
Within 20 years, however, threads of fused silica fibers had become the stuff of telecommunications highways, carrying far more traffic than did their copper-cable predecessors. But there were roadblocks. Because optical signals could not travel much farther than 40 miles over silica lines before growing increasingly distorted and noisy, long-distance networks required expensive electronic repeaters. These repeaters had to convert the light into electronic signals before cleaning up and regenerating the optical signal.

Repeaters have become as endemic—and as constraining—on this telecommunications freeway as tollbooths on a turnpike. Even though optical fibers can, in theory, carry many frequencies of light, repeaters can handle only one at a time. Thus, signals composed of multiple frequencies must be sifted, distributed to separate repeaters and then recombined and retransmitted. Repeaters are also calibrated to treat only signals traveling at specific speeds, or bit rates. Increasing the bit rate (which would increase the amount of data flowing through the network) means replacing the repeaters.

When erbium-doped fiber amplifiers resurfaced around 1985 in work done by researchers at the University of Southampton in Britain (and soon thereafter by Desurvire and his colleagues at Bell Labs), their commercial possibilities seemed more intriguing. That promise loomed even larger in 1989 when workers at NTT in Japan showed that semiconductor diode lasers could provide enough power to excite the erbium ions. NTT workers demonstrated that these rugged, tiny lasers meant that optical amplifiers could conceivably be reduced to packages about the size of a matchbox.

Enthusiasm for optical amplifiers has spread over the past two years, particularly because the devices seem largely indifferent to the quirks of the optical signals passing through them. Because they can boost signals traveling at any bit rate, transmission networks can be upgraded by simply changing the transmitters (and receivers). Virtually any video, data or voice signal can be dumped "like marbles" into one end of these "transparent light pipes" and roll out intact at the other end, says

Amplifying signals in optical fibers with light



Light from a diode laser pump excites erbium ions in a segment of an optical fiber. These ions then emit light and so boost a passing optical signal.

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"Before you had to think about how much loss was in the system and what were the limits of the equipment," Olsson says. "This takes the loss out of the equation." Adds Anthony S. Acampora, who directs the Center for Telecommunications Research at Columbia University: "If three years ago someone asked me what was the single key to make a transparent network a reality, I would have said an optical amplifier."

Devices have yet to be integrated into working systems, but companies around the world are conducting numerous field trials with prototypes. At least four companies are already selling such components, including BT&D Technologies in Wilmington, Del. (a British Telecom–Du Pont joint venture), Pirelli Cavi in Milan, Furukawa Electric in Tokyo and AT&T. Corning was expected to announce its own wares in late February.

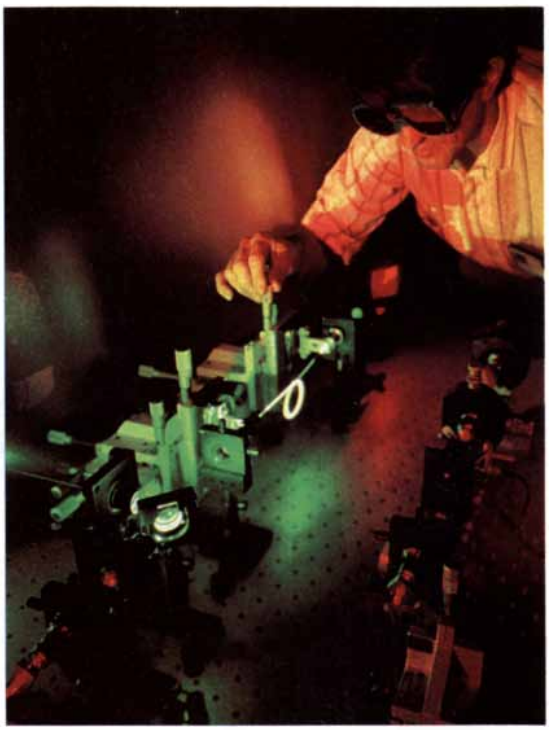
The designs generally follow Snitzer's lead. Erbium ions are mixed into silica as the fiber is made. The precise concentration of ions depends on the intended length of the final doped fiber. A "lumped" amplifier will include a few parts per million of erbium ions throughout several meters of fiber. A "distributed" amplifier, in contrast, may be tens of kilometers long and have only a few fractions of a part per million of erbium.

A second fiber, which carries the light from a semiconductor diode laser, is coupled to the doped segment. Depending on the strength of the laser and design of the network, this laser pump may be located in a distant pumping station or be adjacent to the doped fiber. The optical cable carrying the signal is spliced to the doped segment as well.

Researchers predict that cable television transmission and transoceanic telecommunications networks will be among the first applications for the fiber amplifiers. Fiber amplifiers could enable a video broadcaster to lay one cable from the transmission center to a neighborhood, then split up the signal, amplify it and route the fibers directly into homes.

AT&T and Kokusai Denshin Denwa, Japan's long-distance telecommunications company, have already announced that they are planning to build a 2.4-gigabit, all-optical network under the Pacific Ocean, slated for operation by 1996. Still a subject of debate is the design of that network. Placing a lumped amplifier just after the signal transmitter and another just before the receiver is one possible topology.

Alternatively, workers could gradually correct signal distortions (rather than boosting signals) with distributed amplifiers. This scheme is particularly promising should the researchers choose to transmit signals via solitons, wavelike optical pulses that can travel more than 10,000 kilometers without spreading.



ERBIUM-DOPED OPTICAL AMPLIFIER* (loop) *is tested by Emmanuel Desurvire at AT&T Bell Labs.

Yet like speed traps along the highway, a host of troubling, mundane issues persist on this optical route. For instance, erbium can be excited by numerous wavelengths of light; researchers are experimenting with three different laser diode pumps. Thus far lasers that produce light at the 0.98-micron wavelength are the most efficient; they can generate a 10-decibel gain in a signal per milliwatt of pump power. (Because gain cannot be increased indefinitely, an increase of 40 decibels provoked by a 50-milliwatt laser is considered one of the best results.)

Generating a 0.98-micron light, however, does require a specially crafted indium–gallium arsenide laser. Less costly, although slightly less efficient, may be a 1.48-micron pump laser, made of indium phosphide. Typical gains for these amplifiers remain closer to six decibels per milliwatt. Cheaper still to make would be a 0.82-micron gallium arsenide pump, which is comparable to the diode lasers in compact disc players. These lasers have yet to show significant gain, however.

"Cost is the critical issue," points out Leonard J. Andrews, manager of the optical fiber and components department at GTE, which is investigating fiber amplifiers for local communications loops. Because the cost of an optical amplifier is largely driven by the cost of its laser pump, most researchers hope prices will fall as production volume increases.

Even so, integrating optical amplifiers into existing fiber networks will be a slow business. Most fibers in operation are designed to transmit signals at 1.3 microns rather than at 1.5 microns. This is because conventional silica fibers do not cause dispersion to optical signals transmitted at 1.3 microns. No company is about to rip out its network.

As a result, signal providers may have to choose either to add the new amplifiers to existing systems and ignore the losses or to wait until they lay "dispersion-shifted" fibers optimized to carry 1.5-micron signals. Although most companies are experimenting with a variety of dopants in fluorine-based fibers in hopes of finding a 1.3-micron amplifier, "that's really hard," Andrews says. "It's a completely new material."

"A 1.3-micron optical transmitter would be fantastic," Olsson agrees. But at least for long-distance communications, 1.5-micron transmissions look most promising. From Olsson's vantage, the key issue is the reliability of the laser diode pumps. Particularly for underwater systems, they must be guaranteed to work properly for at least 20 years.

Few doubt that the new technology will eventually eclipse electronic repeaters. "The challenges are all engineering ones now," emphasizes John Mellis, product manager of optical amplifiers at BT&D in Ipswich, England. "Because [optical amplifiers] are being seriously considered in transoceanic submarine systems, they will certainly happen, if not in this decade then the next." Adds Olsson: "There's absolutely no doubt that this is the thing to work on. It's changed how we think about fiber-optic systems." —*Elizabeth Corcoran*

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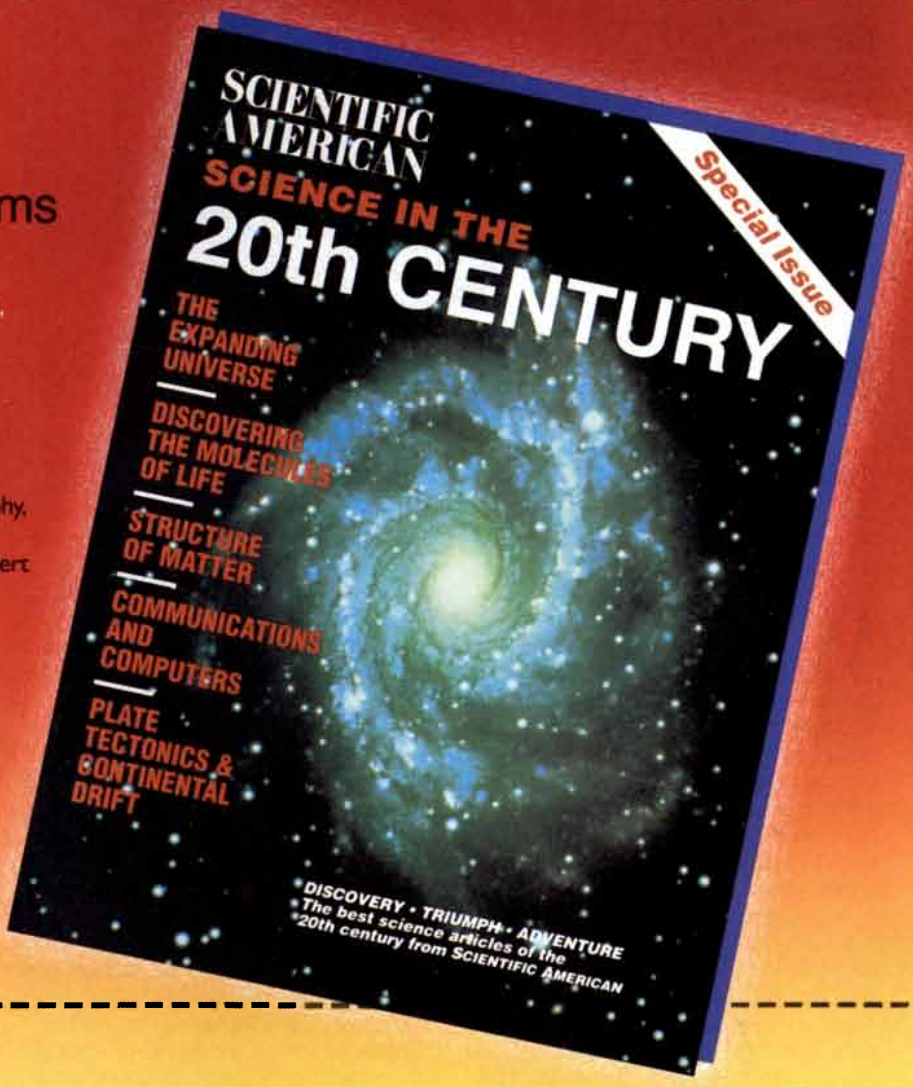

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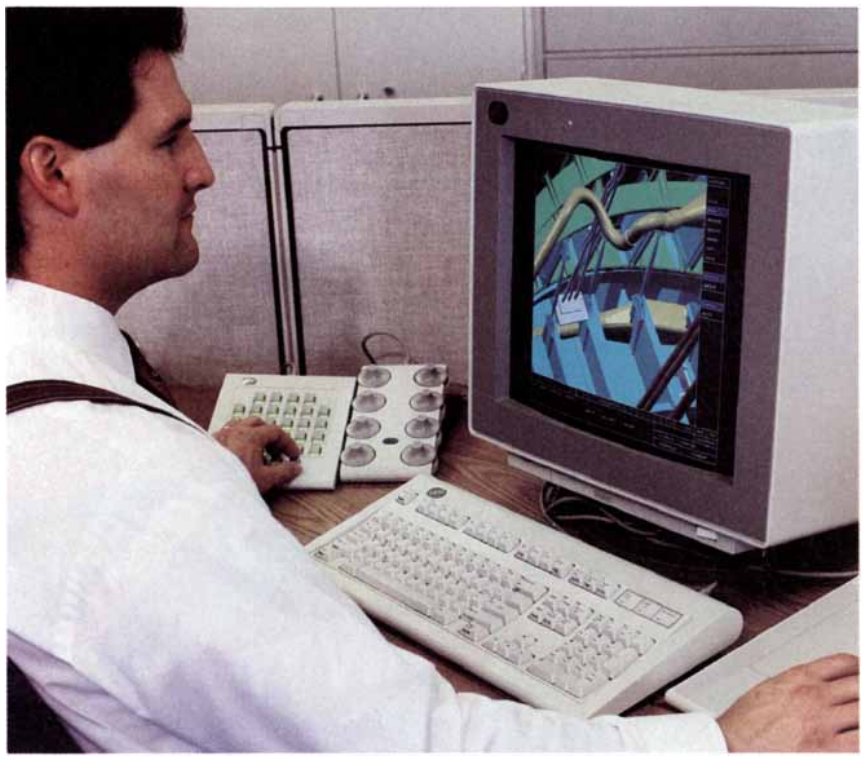


THREE-DIMENSIONAL DESIGN lets the Boeing Company simulate the assembly of the 130,000 unique parts in its new 777 jet. In so doing, designers can tell whether the placement of the cargo compartment, smoke-detection system (narrow tubes) *and a hydraulic line inadvertently overlap* (above). *Source: Boeing Company.*

Plane Geometry

Boeing uses CAD to design 130,000 parts for its new 777

When the Boeing Company threw a party last autumn in honor of its next-generation aircraft, the 777, the University of Washington Marching Band played "Tequila." But the crowd of 5,000 pennant-waving employees did not let forth with a rousing shout of "Tequila" at each pause in the music, as is the custom at university football games. Instead, when the music stopped, they roared the word "CATIA."

CATIA is an acronym for a ponderously named computer program sold by IBM: Computer-graphics Aided Three-dimensional Interactive Application. The software is allowing Boeing to design on a computer each of the 130,000 unique parts of the world's largest twin-engine passenger aircraft, which seats up to 390 people. "I believe this will be the first 100 percent digitally defined commercial airliner anywhere," says M. Richard Johnson, Boeing's chief project engineer for digital product design.

Computer-aided design (CAD) has been used in building Boeing commercial aircraft since 1978, but only for portions of an airplane. It would have been used sooner except for the cancellation of the 7J7, a fuel-efficient jet that was scrapped in 1987. The 777 gives engineers in the Boeing Commercial Airplane Group the first clean slate since the 757 was launched in the early 1980s.

Other manufacturers too have yet to wholly embrace CAD. The MD-11, McDonnell Douglas's new, three-engine jet, has carried over many manual-design elements from the DC-10.

Boeing's computerized design system will replace the huge vaults that store rack after rack of engineering drawings. In their place will sit eight of IBM's largest mainframe computers, which will be accessed by 2,200 terminals at Boeing's main design site in Seattle.

Other mainframes are being installed at other design centers in Kansas and Japan. Boeing is contracting with a consortium of three Japanese companies—Mitsubishi Heavy Industries, Kawasaki Heavy Industries and Fuji Heavy Industries—to produce about 20 percent of the airframe.

The CATIA software—developed by Dassault Systems in Paris and sold by IBM—allows a part to be designed as either a two- or three-dimensional representation. Engineers can avoid building the full-scale models of aircraft, called mock-ups, needed in previous projects before planners could figure where to fit wiring, hydraulic tubes, oxygen lines, air-conditioning ducts and other subsystems. Instead the three-dimensional models of parts can be assembled on the screen into a digital model of the entire aircraft.

That computer mock-up will pinpoint part mismatches, the single biggest cause of last-minute design changes once a plane is in production. "We would put out many designs that later had to be thrown away," says Ben Cosgrove, Boeing's senior vice president of engineering and flight operations. When Boeing tried out digital preassembly in the design of a wing strut on its 767 airliners, the process more than halved the number of changes during production.

Project planners have to contend with the demands that modeling in three dimensions makes on computers. CATIA approximates the shape of a curved solid by aggregating a series of planes at slightly varying angles. Adding enough planar surfaces to represent accurately a part's curves consumes a huge chunk of computing time. For that reason, Boeing says it has put together the largest grouping of interconnected IBM mainframes anywhere. "We're in uncharted waters with this project," says Christoph W. Klomp, Boeing's director of CATIA products.

Besides digital design, the computer is helping to put into practice "concurrent engineering," an attempt by Boeing and other U.S. industrial companies to merge design and production operations. In past projects, Boeing executed each step—from design to testing—in sequence.

Concurrent engineering telescopes some 15 design and engineering steps to build a plane into a single overlapping process. Even as parts are being designed, manufacturing engineers are beginning to write the tooling specifications to make them. When the designs are made final, CAD spills over into CAM, or computer-aided manufacturing. CATIA will generate tooling specifications and the instructions to drive automated machine tools to produce actual parts.

A total of 220 "design-build" teams are coordinating these parallel efforts at Boeing's three main design sites. The company has literally removed department walls by situating in the same office specialists for areas as diverse as design, materials, manufacturing and customer support. Each team member critiques the work of the others. A design engineer, for example, may describe a part that a production engineer knows cannot be manufactured. The basis for these discussions is the CAD data.

Striving to retain its majority share of the commercial airliner market, Boeing has involved customers in the earliest stages of the 777 design. The company hopes that such interaction will enable it to meet the stiff competition provided by its two main rivals in the commercial market: Airbus Industrie and McDonnell Douglas, both of which have already begun to roll out a new generation of planes. A comment from one Boeing customer has already caused the placement of the door and the engine to be moved slightly, so that the airline's mobile loading dock would not bump the engine.

CAD and concurrent engineering may not produce the 777 any faster than previous aircraft. Schooling Boeing's vast technical cadre is taking time. "Retraining 4,000 engineers to think in three dimensions instead of two is a big hurdle," Johnson says. "We're not far enough along to judge how well this will work." The payoff may come in reduced expenses for design changes and fewer service problems for the first aircraft off the line.

If all goes well, the 777, boasting optional folding wing tips to fit the airplane's long wings into existing gates and seats that can be rearranged during a stopover, may set a new standard for aircraft design. And by the 1995 delivery date, the thousands of design and manufacturing engineers working on the 777 may remember the old transparent plastic drafting sheets with the same nostalgia as their colleagues working on earlier projects did the slide rule. —*Gary Stix*

Through the Grapevine

Tissue culture attacks a scourge of wine grapes

It's bad and it's back. The aphidike insect that devastated the world's vineyards during the 19th century is now eating its way through California's finest grapes. In Sonoma and Napa counties alone, more than 50,000 acres of vineyards are expected to succumb over the next 10 years. The menace—a new biotype of the root louse called phylloxera—is browsing up the Pacific coast to other wine-producing regions. There is a lot of replanting to do but little time to raise enough young plants to satisfy demand.

This could be a job for plant tissue culture. "We can do in a year what takes five years by traditional means," declares James A. Stamp, staff scientist at Agritope, a young biotechnology company in Beaverton, Ore. The firm expects that its method of multiplying grapevine buds—which, like the eyes of potatoes, are programmed to become exact replicas of the original plant—will flourish long after phylloxera is vanquished.

In conventional propagation, a fruit-bearing vine is grafted to a rootstock, and the union is then planted. Europeans began using this technique in the 1860s, when they learned that certain wild grape species withstood the onslaught of phylloxera. The rootstock with superior resistance turned out to be a species called *Vitis riparia,* a native of the eastern U.S., where the insect is believed to have originated. Today Europe's vineyards are planted almost entirely on *V. riparia* or related species and are immune to phylloxera.

Not so in California. "We've been planting on rootstock we thought was resistant, even though the rest of the world kept telling us it wasn't," admits James A. Wolpert, extension viticulturist at the University of California at Davis. Since the 1950s the school has recommended a hybrid rootstock, designated AXR1, that is half a variety of *V. vinifera,* the classic European wine grapes, half the resistant species *V. rupestris.* But the mix is proving to be no match for the new strain of bug.

In fact, it is preferred eating. While snacking eight feet below the ground, the vermin inject a toxin that causes pinhead-size galls to form. The root is effectively severed, depriving the plant of nutrients and water.

For Agritope, the impending disaster is a perfect opportunity. "Traditional nurseries can't deliver resistant material quickly. I can't order what I want," complains Chuck Wagner, general manager of Caymus Vineyards, a Napa Valley producer known for its cabernet sauvignon. The predicament is even worse for growers outside of California: there is a moratorium on exporting rootstock to other states until 1994. In Oregon "alternatives to AXR1 are considered fairly esoteric and are not widely available," says Mark Chien, manager of Temperance Hill Vineyards in Salem, Ore. The pinot noir producer adds, "If you were to find a rootstock that works well, the question would

DEVASTATION SPREADS through the vineyards of Napa Valley. These infrared views show phylloxera infestation in 1979* (bottom), *then 1986 and 1987. Photos: William E. Wildman.

be whether you could get enough of it."

"With tissue culture, you could get two or three million cuttings from a single plant if you wanted to," versus 100 a year via conventional propagation, Stamp offers. Agritope has about 30 rootstock clones in its greenhouse laboratories. These are combinations of four resistant species, including *V. riparia* and *V. rupestris* and two new ones from Eastern Europe. By the beginning of this year's growing season, the firm plans to have 30 fruit-bearing clones to choose from, some of which are popular in Europe but in scarce supply here.

Each bud taken from a length of vine is sterilized, then raised for a few weeks in an environmental growth chamber until it produces a shoot with several daughter nodes. The shoots are cut up into sections, each containing a bud that produces another shoot with daughters and so on.

After multiplication, the tissues are transferred to the greenhouse and planted in soil; intensive feeding, light and warmth promote rapid growth. Within four months of leaving the culture environment, fruit-bearing shoots are grafted to the young rootstocks. Because green tissue is joined to green tissue, the grafts heal more rapidly than woody cuttings. The plants grow for a few months and then go dormant, just as they overwinter out in the field. Dormant plants are less fragile to ship.

"It's not just a matter of can they do the multiplication," Wolpert asserts. He questions whether plants grown in tissue culture will be deep-rooted enough to withstand drought in early years of growth and whether buds on those plants will give rise to suckers that steal herbicide meant for weeds. Agritope will send six growers several thousand plants to evaluate later this year and plans to ship 100,000 in 1992 and then a million by 1993.

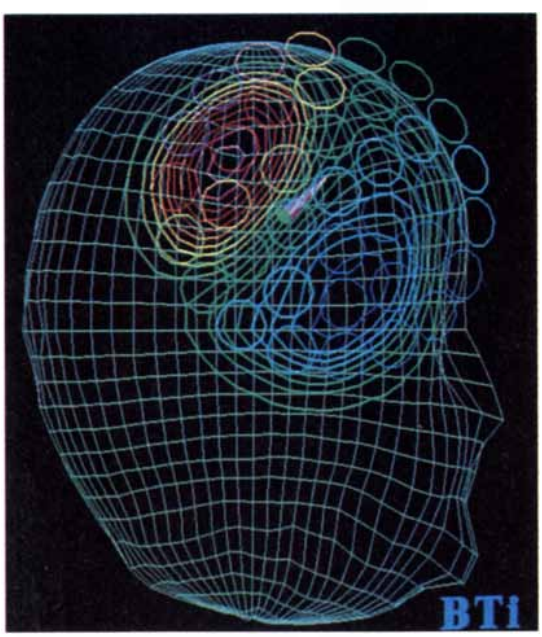
Infestation aside, tissue culture is getting growers excited. Because the process is sterile, plants are bound to be disease free. Clones are by definition true to type, an attribute wine makers would prize for dependability of characteristics. Vineyards are already signing up for Agritope's Eliteclone program, to have their best vines quickly reproduced and grafted to a rootstock of their choice.

The burgeoning market is not going unnoticed by potential competitors. Calgene, an agricultural biotechnology company in Davis, Calif., is also considering getting into the grape propagation business, says Ken Moonie, director of product planning. It is not alone. "If tissue culture works, there will be more than one company doing it," Moonie observes. "The traditional players aren't just going to walk away." —*Deborah Erickson*

Thinking Cap

Superconducting SQUIDs peer into minds—and hearts

In 10 years or so, physicians may be able to assess the relative health of your brain as one item they routinely inspect during a physical examination. That important advance may be made possible by tiny sensors that measure activity in nerve cells. Called superconducting quantum interference devices, or SQUIDs, the devices are so sensitive that they can pick up the minute magnetic fields found in the heart, brain and other areas of the body that generate electricity. Unlike the many imaging techniques that bombard patients with radiation, SQUIDs are purely passive sensors.



BIOMAGNETIC IMAGING depicts a magnetic field generated in the brain. The two sets of concentric rings are where the field enters and exits. The nerve activity lies at the apex of the cone in between the rings. Circles in the vicinity of the field represent the positioning of the sensors. Source: BTI.

Although SQUIDs were first tested 20 years ago, they were not embraced by the medical community as the next clinical imaging technology. The expensive devices were made from niobium, a superconducting element that must be cooled to four kelvins with liquid helium. Only a few companies, including Germany's Siemens Medical Systems and Biomagnetic Technologies Incorporated (BTI) in San Diego, have developed such biomagnetometers for medical research.

Now medical applications may receive a boost from advances in high-temperature superconductivity. During the past 18 months, researchers at the IBM Thomas J. Watson Research Center and at the University of California at Berkeley have separately made SQUID magnetometers using thin films of high-temperature superconducting materials of either yttrium-barium-copper oxide or thallium-barium-calcium-copper oxide.

These materials become superconductive at the temperature of liquid nitrogen—a relatively balmy 77 kelvins. Instead of being immersed in a canister of liquid helium and positioned above the patient's head like an X-ray machine, the high-temperature SQUIDs might permit developers to make a helmet or another flexible array of sensors that conforms to the shape of the head.

Such a thinking cap would allow scientists simultaneously to compare nerve activity from different parts of the brain, enabling them to map higher-order mental functions. In addition, high-temperature SQUIDs may shave a few hundred thousand dollars off the $2-million-plus price tag for instruments based on metallic superconductors.

Assembly lines for high-temperature SQUIDS are still a few years away. Only 10 percent or less of the devices made so far by the two U.S. research teams have proved functional, because it is difficult to fabricate the detectors from the high-temperature materials. "High-temperature SQUIDs aren't yet ready for prime time," says Roger H. Koch, manager of superconducting science and technology at IBM.

Moreover, the higher noise levels at elevated temperatures may be problematic. Siemens, which makes a magnetometer cooled with liquid helium, has decided against pursuing development of high-temperature SQUIDs because they have a poor signal-to-noise ratio.

Siemens believes it can achieve many of the same benefits with arrays of 37 low-temperature sensors.

Before biomagnetic imaging becomes a fixture at major medical centers, developers must make it easier to interpret data from the magnetometers. The magnetic contour lines—which resemble a topographical map of the Rocky Mountains—require specialists to decipher them. Once the coordinates of the field source are deduced, they are often superimposed on a magnetic resonance image in order to visualize where nerves are electrically active.

Current biomagnetometers are used only for clinical and basic research. The Food and Drug Administration has authorized BTI to use its 37-sensor low-temperature magnetometer to detect fields within the brain, but the company has yet to apply to any third-party insurer for reimbursement. The company, which is also developing high-temperature superconductors, is awaiting suitable clinical applications.

Such applications are emerging, however. SQUIDs have proved to be a noninvasive method for pinning down the location of epileptic seizures before surgery to remove the affected part of the brain.

Epilepsy alone will not push biomagnetic sensing into the medical mainstream, since that disease can usually be treated with drugs. But early findings suggest that the technique may be used to detect anomalies in the magnetic fields in the brains of patients with Alzheimer's disease.

It may also help determine the source of arrhythmias and other cardiac disorders without having to insert a catheter into the heart. In addition, biomagnetism may enhance the work of cognitive psychologists. Since 1975 Samuel J. Williamson, a physicist, and Lloyd Kaufman, a psychologist, both at New York University's Center for Neural Science, have used low-temperature magnetometers to map sensory functions of the brain. They were able to locate for the first time in humans a tonal map—specific areas of the cortex that respond to different frequencies of sound.

Although New York University was the first to use biomagnetism to study sensory functioning, approximately 50 laboratories around the world are now doing so. The next major step under way is to study cognitive functions: the possible role of the visual cortex in forming mental images, for example. This early work might eventually lead to a data base of sensory and cognitive functions, a foundation on which clinicians could design the annual mental checkup. —*Gary Stix*

Complete Combustion

Hydrogen and natural gas may be the cleanest fuel yet

Hydrogen has been "the fuel of the future" for 60 years now. Inexhaustible supplies of the combustible element could be obtained by splitting water into its components, and the fuel would be virtually nonpolluting. But proponents are still waiting. Although it works well for rockets, hydrogen has proved troublesome for ground transportation. It is extremely bulky as a gas and becomes liquid only at –423 degrees Fahrenheit. Present supplies of hydrogen, produced primarily from natural gas, cost four to five times as much as gasoline.

Hydrogen may yet win a place as a vehicle fuel. Not by itself, but as an additive in much the same way that alcohol is added to gasoline in the mixture called gasohol. Mixing a bit of hydrogen with compressed natural gas (CNG) could yield the cleanest-burning alternative fuel yet, says Frank E. Lynch, president of Hydrogen Consultants, Inc., in the Denver suburb of Littleton.

Lynch calls his fuel mixture "Hythane" for hydrogen and methane (the principal component of natural gas). Adding hydrogen to virtually any fuel accelerates its combustion, Lynch points out, by reducing ignition delay and increasing flame velocity. "Natural gas burns slowly to a fault," he declares, so even though it is less polluting than gasoline, unburned hydrocarbons and other by-products are still released into the atmosphere. A faster start and more efficient burning should reduce emissions.

A feasibility test of Hythane—5 percent hydrogen by energy content, 15 percent by volume—began in January, in Lynch's own pickup truck, modified to run on either Hythane or gasoline. Compared with a CNG pickup tested previously—which carried an admittedly heavier load than Lynch's truck—Colorado Department of Health tests showed Hythane performing well. Hydrocarbon emissions were less than half of those from CNG, and nitrogen oxide levels were 24 percent of those from CNG. CNG was lower on carbon monoxide, however, at 0.086 versus 1.6 grams per mile. The Auto Oil Consortium in Detroit, a group set up by the big three automakers and 14 oil companies to test alternative fuels, plans to test the fuel sometime this year. So do Colorado State University and the California Air Resources Board.

Denver is particularly eager to test Lynch's idea. The city won a citation from the U.S. Conference of Mayors in 1990 for "most improved air quality," but on bad days a pall of brown smog betrays the city's ongoing violations of federal standards for carbon monoxide and particulate matter. Trying to meet air-quality rules, the city already has an extensive alternative-fuels project that includes trucks and vans powered by CNG. "We are going to test as many vehicles as we can with Hythane," says Steven J. Foute, Denver's director of environmental programs.

Colorado's major utility, Public Service Company of Colorado (PSCo.), is interested in Hythane because "hydrogen is a gaseous fuel, compatible with compressed natural gas," notes Bill Warnock, marketing coordinator for alternative fuels. The utility is the principal shareholder in a distributor of CNG started up last year in Denver, the Natural Fuels Corporation. PSCo. plans a marketing study of Hythane-powered vehicles for 1992, if studies confirm the fuel's promise. "The emphasis will be on vehicles that operate within 50 miles of their base," Warnock says.

The vehicles are suited for urban use because the amount of fuel that can be put on board is limited. Pure hydrogen in gaseous form takes up 12.9 times as much space as gasoline required to travel an equivalent distance and 3.8 times as much space as natural gas. Enough Hythane to make a trip of about 200 miles can be packed into a tank 3.4 times the size of an equivalent gas tank—if it is compressed to about 3,000 pounds per square inch.

Where to fill 'er up? For now, just one place in town. Air Products and Chemicals has volunteered its facilities for the test program. The hydrogen will be fed from a so-called tube trailer, a bundle of high-pressure steel tubes that carries industrial gases of many kinds, and blended with natural gas. "There is nothing special about this," says Venki Raman of AP&C. "We handle gases and mix them all the time."

"The significance of Denver's project lies in the backing by the utility and the city," notes Peter Hoffmann, editor of *The Hydrogen Letter* in Hyattsville, Md. "Those commitments give hydrogen real business potential for wider use via a relatively low-tech compromise technology." The "compromise" part of the deal still sticks in his craw. Like Lynch, Hoffmann wistfully describes Hythane as a "bridging" technology to an all-hydrogen energy supply. He admits that everything has to start somewhere. It might as well be a clean start. —*Deborah Erickson*

THE ANALYTICAL ECONOMIST

Humanizing economics

Macroeconomists have long been leaving a significant factor out of their equations: real world human behavior. This is not entirely unexpected because, after all, macroeconomic questions hang on swings in the economy as a whole: fluctuations in gross national product or in inflation. Sooner or later, though, even these issues boil down to the behavior of individual consumers and producers. Yet during the past 60 years, remarkably few macroeconomists asked people about their economic decisions.

That said, the murmur of a new trend could be heard at the annual gathering of the American Economics Association this past December. Among the iconoclasts is Alan S. Blinder, a professor at Princeton University, who has begun asking company managers in charge of pricing strategies why they raise or lower prices and when do they. There is also W. Brian Arthur, an economist at Stanford University, who is trying to teach computer automata to act like people—then setting them loose on other problems.

"Economists, more so than other social scientists, are deeply skeptical that you can learn much by asking people," Blinder says. There is some basis for skepticism. People may have no incentive to tell the truth. Or, like pool players asked to describe the physics behind a shot, they may fumble in explaining the mechanics of their behavior. Finally, small samples may not be adequately representative.

Yet "theory and econometrics have their limitations, too—limitations that are sometimes more severe than we like to admit," Blinder says. A case in point is the subject of "sticky" prices and wages, a phenomenon identified by John Maynard Keynes in the 1930s. Keynes observed that the prevailing theory—namely, that prices and wages should bob up and down with the tides of supply and demand—simply did not fit. Instead prices and wages move slowly, more like raisins in molasses.

There is no shortage of explanations for price-and-wage stickiness—but also no way of telling which ones are on target. (None predicts precisely how slowly changes should take place.) So back in August 1988 Blinder and a team of graduate students began surveying company decision makers about their pricing strategies.

The preliminary results, based on 72 of the intended 200 interviews, are intriguing. Managers typically change prices only once a year. The respondents also said they do not raise prices more quickly than they lower them.

Of a dozen economic explanations for sticky prices, only four were judged dominant by more than half of those surveyed. Most often the managers said that rather than raising or lowering prices, they would turn to other tactics, including lengthening (or shortening) the time taken to deliver goods or cutting (or adding) extra customer services. They also largely rejected two theories that have gained prominence. For instance, few managers worried that consumers would interpret price cuts as a reduction in quality.

Whether Blinder's survey will convince macroeconomists to talk more with people remains to be seen. Robert J. Shiller of Yale University, one of the few other macroeconomists who has sought such data, has received mixed responses to his work. Last year, for instance, he and two Soviet economists queried people in New York City and Moscow about how fairly they thought firms were in setting prices. Surprisingly, they found few differences in attitudes. Even more unexpected were one reviewer's comments when Shiller submitted the study for publication. "It said, 'This isn't economics' and 'This is of no interest to economics,'" Shiller recalls. "There's some sense that [surveys] aren't deep enough." Blinder's work, Shiller says, "will rectify the damage done by Milton Friedman," whose essay "The Methodology of Positive Economics" has been embraced by economists as a case for highly mathematical analysis.

In contrast, Robert J. Gordon, an economist at Northwestern University, remains doubtful. Surveys are "a big investment of time," he points out. "Blinder is well known and got grant money to do this." Other economists might not be so fortunate.

Blinder is not alone in trying to bring economists back to the real world. Rather than relying on theories of how people act, Arthur proposed to use software "agents," or automata, calibrated to mimic human behavior and even to make the same mistakes.

Using software techniques developed by John H. Holland, a computer scientist at the University of Michigan at Ann Arbor, Arthur's automata can match the choices made by a group of students in a series of experiments conducted at Harvard University in the 1950s. (He would prefer more recent data but has yet to find them.) Arthur then offers the automata problems and watches the choices they make.

So far the software subjects have tackled only simple problems such as choosing among alternatives with different payoffs. Eventually Arthur hopes to use his agents to test whether certain economic assumptions—such as the idea that markets always converge to an equilibrium—hold true.

Arthur's work, even more than Blinder's, is far from provoking a revolution in macroeconomics research. But both are attempts to take better account of the idiosyncracies of flesh and blood. "Even if econometric testing were more successful, we shouldn't throw away information from interviews," argues economics Nobel laureate Robert M. Solow of the Massachusetts Institute of Technology. "Imagine how you'd feel if your doctor didn't ask you where it hurt," he says, "and just said, 'Give me the blood.'"

—Elizabeth Corcoran and Paul Wallich

Why companies delay changing prices	Mean Importance (on scale 1–4)
Change level of service instead	2.86
Wait until other firms change prices	2.85
Wait until costs rise	2.72
Hesitate to break implicit understanding with customers	2.52
Have contracts with customers	2.29
Incur expenses when changing prices	2.28
Believe falling demand makes price cuts ineffective	1.97
Avoid exceeding some price levels: $19.95	1.97
Change inventory levels instead	1.72
Have constant marginal costs	1.56
Feel delayed by corporate bureaucracy	1.54
Worry that consumers will think quality is lower	1.45

SOURCE: Alan S. Blinder

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MATHEMATICAL RECREATIONS

A menu of mathematical morsels, topological tidbits and puzzling plums

by A. K. Dewdney

Ross Honsberger has spent more than two decades collecting mathematical morsels for general consumption. Attending one of his rare public lectures recently, I had the pleasure of sampling one of his mathematical feasts. I found it not just palatable but downright delicious.

Honsberger, who teaches mathematics at the University of Waterloo in Canada, will stop at nothing to demonstrate mathematical principles. To illustrate a topological tidbit one day, he wandered into a colleague's lecture wearing his trousers inside out. He announced that he would turn them right side out without really taking them off.

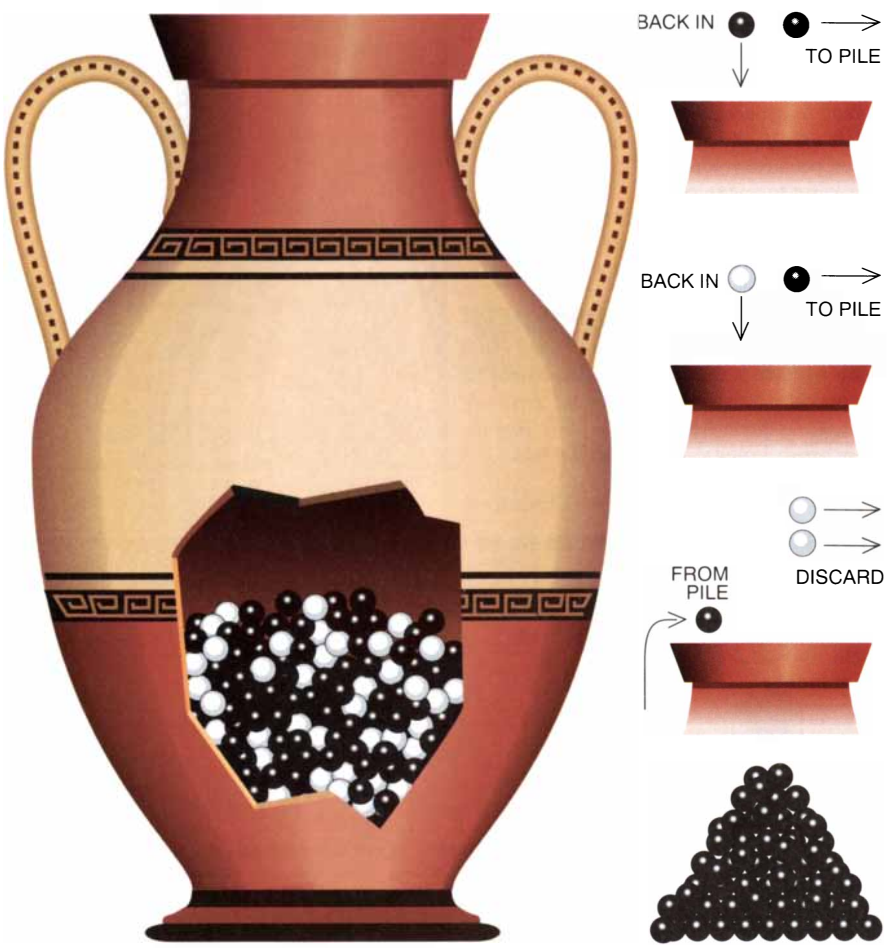
To show that the trousers would not "really" be removed, he tied his own ankles together with an eight-foot length of rope. He proceeded to pull both trouser legs down onto the rope, revealing his favorite heart-spotted undershorts. The students watched closely for any deception as he first twisted the pants through the rope, then turned them right side out and finally wriggled back into them. I can testify that Honsberger's trick requires neither magic nor mirrors.

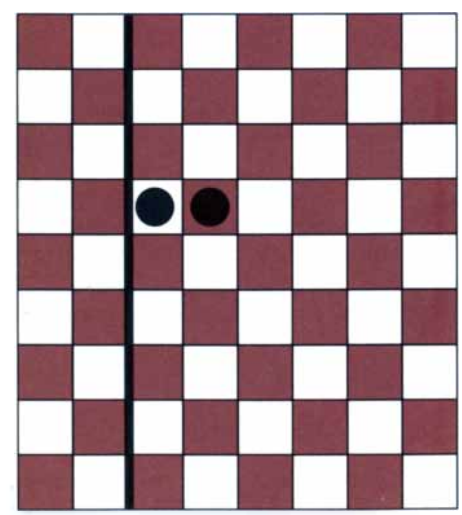
I listened to Honsberger's lecture near my hometown in Ontario. He served to the audience such delights as spheres in a cone, checkers on a board, dots on a dish and beans in a Greek urn.

Honsberger began by describing the marvelous spheres of Germinal Dandelin, a 19th-century Belgian mathematician. Dandelin discovered an amazing connection between the classical and modern concepts of the ellipse. The Greeks conceived of an ellipse as the figure that results when a plane cuts obliquely through a cone. Since the time of Descartes, however, the ellipse has been described analytically in terms of two special points called foci. The sum of the distances from the two foci to any point on the ellipse is constant.

Honsberger introduced Dandelin's spheres by drawing our attention to a projected transparency of a plane cutting a cone. (Readers can follow Dandelin's argument with occasional glances at the top illustration on the opposite page.) I cannot swear that what follows are Honsberger's exact words, but he readily admits to a certain, broad similarity:

"It takes no genius to see that the plane divides the cone into two pieces. But it was Dandelin's idea to insert a sphere into each piece. Like an overinflated balloon, each sphere contacts the wall of the cone and touches the elliptical plane at a certain point. But





What is the color of the last of 75 white beans and 150 black ones in the urn?

where? One can imagine Dandelin's heart leaping at the thought that the two spheres might touch the plane at the two focal points of the ellipse."

Honsberger places his marking pen on the transparency. He labels the two points of contact by the symbols *F* and *G*. Are these the foci of the ellipse?

"Let's take a look at what clever old Dandelin did. First, through any point *P* that we care to select on the ellipse, we may draw a straight line that runs up the side of the cone to its tip. Second, the line will touch the two spheres at two points, say, *A* and *B*. No matter where we pick *P* to lie on the ellipse, the length of *AB* will be the same.

"Ah, but that gives it away! The distance from the point *F* to *P* equals the distance from *F* to *A*. After all, both *PF* and *PA* are tangents to the same sphere from the same point. By the same reasoning, the distance from the second point, *G*, to *P* equals the distance from *G* to *B*. Are we not finished? $PF + PG = PA + PB$, and the latter sum is just the (constant) length of *AB*.

"Now isn't that the darndest thing?" quips Honsberger.

As I look around the lecture hall, students appear stunned. Professors alternately smile and frown. One of them behind me murmurs, "Well, I'll be."

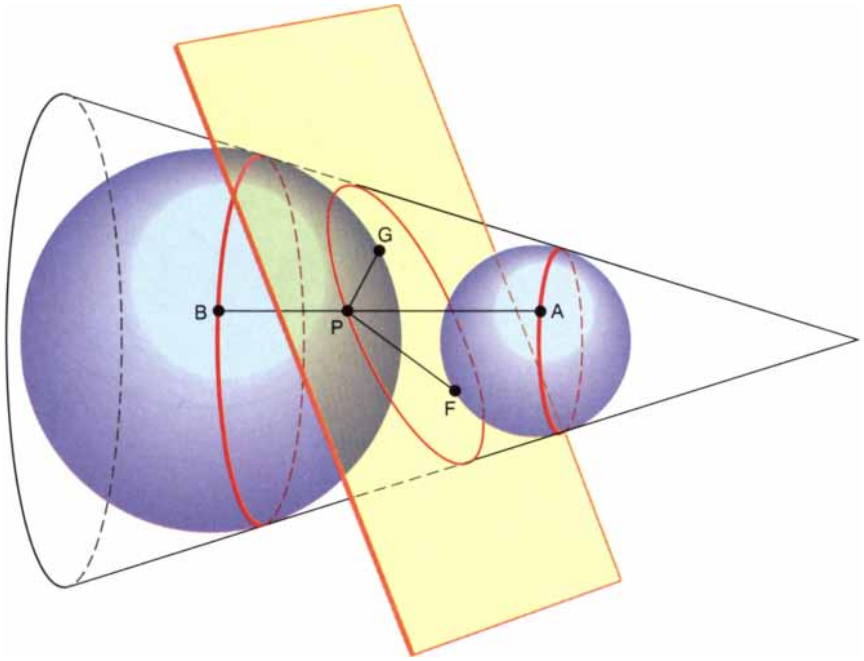
Without pausing for a breath, Honsberger serves up the next morsel. We find ourselves staring at a slide of a peculiar board game.

"Here's a simple little exercise in checker-jumping. I imagine that such a clever audience will have no trouble figuring this one out." A devilish gleam invades his eye, a warning that something unusual is about to happen.

The slide shows a grid of squares with a line drawn through it [*see illustration below*]. Honsberger explains the rules: solvers can arrange a given number of checkers any way they like behind the line. Checkers can be jumped and removed in the vertical or horizontal direction, but the final jump can leave only one checker. The problem is to decide how many checkers it will take, at a minimum, to "propel" the last checker a given distance *d* beyond the line. In deciding this, solvers must also devise an arrangement that allows the frenzy of jumping to take place.

"Does anybody want to take a crack at this problem?" Honsberger looks up at the audience, sees there are no takers and smiles ingenuously.

"Well, then, let's try a few examples."



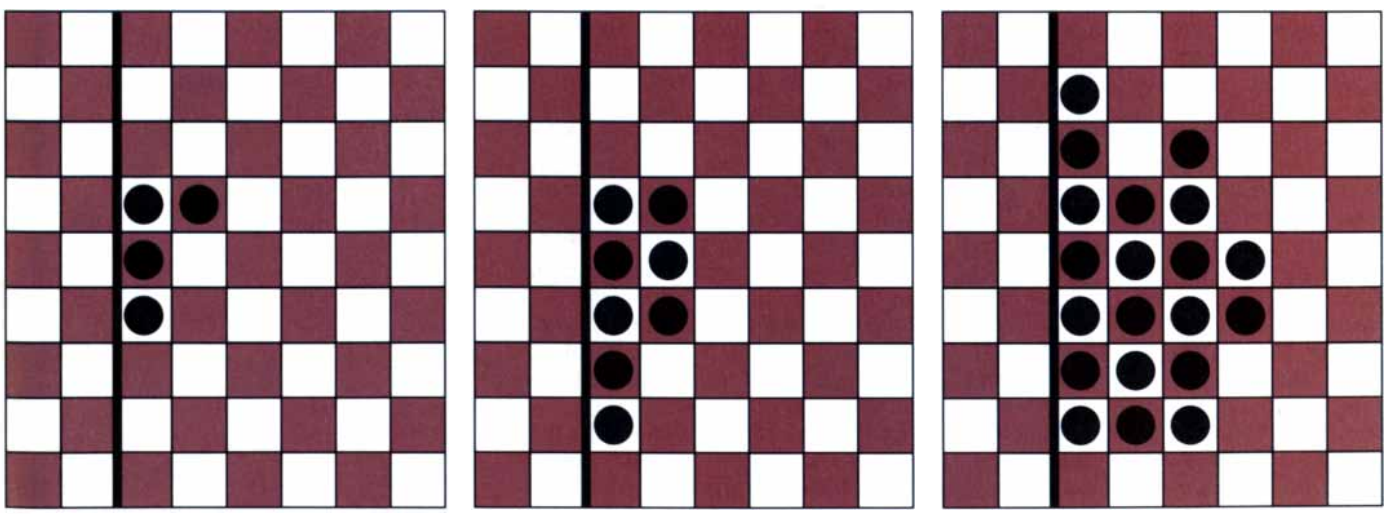
An ellipse in a cone separates Dandelin's spheres

He places two checkers adjacent to each other on the board, jumps the back checker over the front one, then strides triumphantly to the blackboard, where he writes

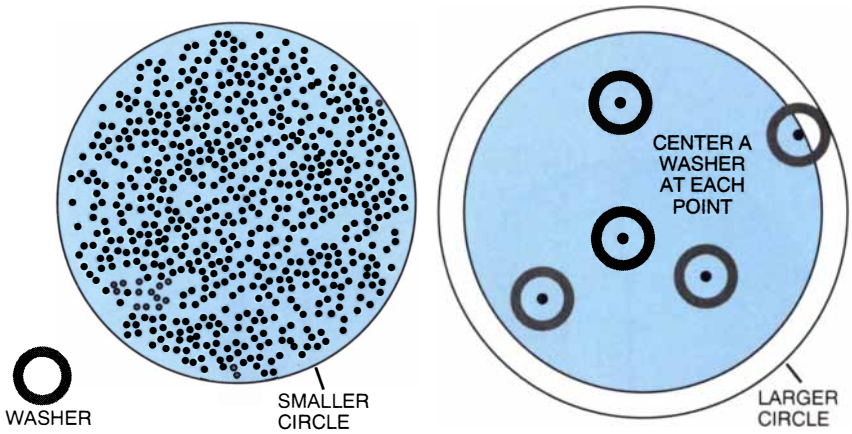
d	number of checkers
1	2

Next he places four checkers on the board. He jumps the checkers until a single checker is left in the second row.

"I'm just saving you people the trouble of figuring it out. Believe me, this is the best that anyone can do." He writes "2" under "*d*" and "4" under "number of checkers." He creates another con-



Four checker-jumping arrangements



The washer problem

figuration of eight checkers and manages to propel one checker to the third row. He scribbles "3" and "8" on the blackboard.

"Anybody want to guess how many checkers it takes to send one checker four units beyond the line?"

Somebody volunteers the figure 16. No. The answer turns out to be 20 checkers, at a minimum.

The audience is now getting somewhat worked up. Could the relation between distance and the number of checkers be described by one of those superexponential functions? Perhaps it will take a million checkers to send one checker five units beyond the line. When Honsberger reveals the answer, members of the audience look at one another, smiling uncomfortably.

"Alas! A million checkers will not be enough, nor a billion. It is simply impossible, no matter how many checkers you assemble behind the line or how you arrange them. It was John Conway, the Cambridge mathematician, who proved the task impossible."

Honsberger does stop the lecture to describe Conway's difficult proof, although he would not dream of discouraging anyone from attempting it. Instead he quickly moves on to a discussion of the pigeonhole principle.

This famed principle simply states that if I build 9,999 pigeonholes for 10,000 pigeons, at least one of the holes would house more than one bird. The pigeonhole principle has been used to prove many theorems in combinatorics, the branch of mathematics that deals with finite collections.

"The next mathematical morsel is one of the strangest applications of the pigeonhole principle ever made. Imagine that someone has placed 650 points inside a circle of radius 16 units. You have been given an annulus, a flat ring in the shape of a washer. The outside radius of the washer is three units, and the inside radius is two. You are then challenged to place the washer so that it covers at least 10 of the 650 points."

"Impossible," whispers an impetuous undergraduate behind me. "What if all the points are in a tiny area?"

"Then he can cover all of them with one washer, you *idiot!*" retorts another student.

Is it really possible to cover 10 points with the washer? Honsberger begins the proof by drawing a diagram [*see illustration above*]. He invites us to imagine that a copy of the washer has been centered at each of the 650 points inside the circle.

Some of the points may be near the edge of the circle, in which case some of the annuli will extend beyond its circumference. But because each point lies inside the circle and because the washer has radius three, all the annuli will lie within the larger circle having the same center and having radius 19, that is, the sum of 16 and three. The area of the washer is the difference between the area of a circle of radius three and one of radius two. This comes to five times π.

"The 650 washers blanket the large circle with a total coverage of 650 times 5π, that is $3{,}250\pi$. Of course, much of the coverage will be overlapping, but suppose for the moment that no point of the inner circle is buried under more than nine washers. In such a case, the total amount of area covered within the larger circle could not come to more than $3{,}249\pi$, nine times the area of the circle. But because $3{,}249\pi$ is less than $3{,}250\pi$, some point, x, must be covered by at least 10 washers. The pigeonhole principle strikes again."

Honsberger pauses to catch his breath. "You see it now, don't you?" Then he feigns surprise. "You don't?"

The application of the pigeonhole principle is clear enough, but some of us are confused. We thought the idea was to cover 10 points by one washer, not to hide some point x under 10 washers. Suddenly, our minds are turned inside out like a pair of trousers.

"Look at the point x. If you take away the 10 washers that cover it and replace these by a single washer centered at x, then that washer alone must cover the centers of the 10 washers that we took away. Each of these centers is one of the 650 original points!" The morsel is digested as we hear a faint gulp from somewhere at the back of the lecture room.

The pièce de résistance of Honsberger's menu arrives in the form of a Grecian urn adorning his next transparency [*see illustration on page 116*]. "How much can a Grecian earn?" quips Honsberger.

When the groans have died away, he explains the problem. An urn is filled with 75 white beans and 150 black ones. Next to the urn is a large pile of black beans. The beans are removed from the urn according to certain rules.

"Here's how it works. Remove two beans from the urn at random. If at least one of the two beans is black, place it on the pile and drop the other bean, whether white or black, back into the urn. But if both of the removed beans are white, discard both of them and take one black bean from the pile and drop it into the urn."

"Each time a Greek or anyone else dips into the urn to remove two beans at random, either operation ensures that there will be one fewer bean in the urn than there was before the move. Slowly and steadily, the original supply of black and white beans dwindles. At last there are three beans left in the urn, then two, then one. What color is the last bean?"

The simple and startling answer is white. By figuring out why, a Greek can earn intangible delights worth much more than a hill of beans.

FURTHER READING

MATHEMATICAL GEMS: FROM ELEMENTARY COMBINATORICS, NUMBER THEORY AND GEOMETRY. Ross Honsberger. Dolciani Mathematical Expositions, No. 1. Mathematical Association of America, 1973.

MATHEMATICAL MORSELS. Ross Honsberger. Dolciani Mathematical Expositions, No. 3. Mathematical Association of America, 1978.

MATHEMATICAL PLUMS. Edited by Ross Honsberger. Dolciani Mathematical Expositions, No. 4. Mathematical Association of America, 1979.

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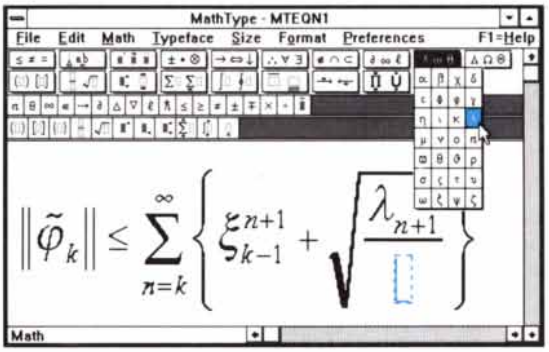

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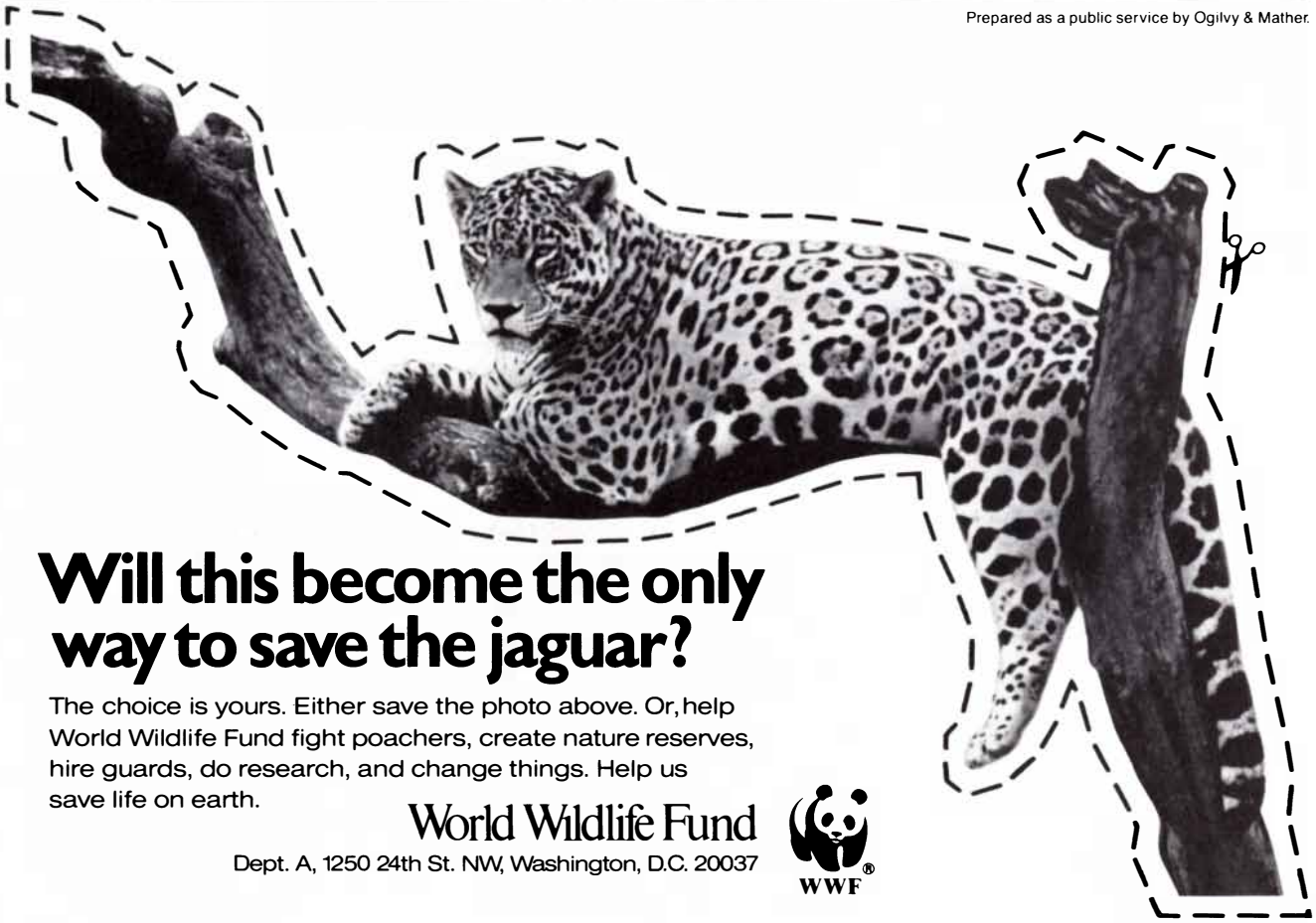

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BOOKS

In search of the universe, a profound mental disorder, a garden of triangles

by Timothy Ferris

LONELY HEARTS OF THE COSMOS: THE SCIENTIFIC QUEST FOR THE SECRET OF THE UNIVERSE, by Dennis Overbye. HarperCollins, 1991 ($25).

ORIGINS: THE LIVES AND WORLDS OF MODERN COSMOLOGISTS, by Alan Lightman and Roberta Brawer. Harvard University Press, 1990 ($29.95).

For decades now, science writers have been expected to "humanize" the scientists they write about. But like finalizing, fictionalizing or Simonizing, humanizing is easier to talk about than to do properly. Ask an editor what it means, and you are likely to hear an injunction that sounds more suitable to a KGB agent than a journalist: the reporter is to drag the scientist down from his ivory tower, strip him of his white coat and expose the details of his private life, "warts and all." In practice, human decency having not yet been extinguished in journalistic circles, the humanizing process usually takes the milder form of simply trying to relate research to the thoughts and feelings of the scientists who conduct it.

Even so, humanizing can be a tricky business, as these two books demonstrate in contrasting ways. Both deal with cosmologists, whose quest to understand the big picture all but guarantees them public attention. ("You may be the best stellar interior theoretician in the world and you will not be heard of, but you're famous if you're a cosmologist," I was once told, by, as I scarcely need add, the best stellar interior theoretician in the world.) But interesting science does not automatically mean interesting scientists. Part of the science writer's job is to know the difference.

TIMOTHY FERRIS, professor of journalism at the University of California, Berkeley, is the author of *Coming of Age in the Milky Way.*

Origins: The Lives and Worlds of Modern Cosmologists consists of the edited transcripts of interviews with 27 cosmologists, conducted by the physicist and science popularizer Alan Lightman with additional interviewing by Roberta Brawer. Much of what these scientists have to say will be of interest to others in the field and, perhaps, to lay readers as well. Some offer surprising opinions: Maarten Schmidt (the astronomer who discovered the redshifts of quasars) volunteers that "the universe is small," while physicist David Schramm remarks that "the number one theoretical problem is: What is the vacuum?" Some can be engagingly modest: astronomer Gérard de Vaucouleurs notes wryly that "cosmological models always have more free parameters than facts." Others offer illuminating personal insights, as when the British astronomer Wallace Sargent confesses that hearing Fred Hoyle on the radio emboldened him to consider, at the age of 15 or 16, that "people without standard English accents—BBC accents—could actually do that kind of work. That was a tremendous liberation."

The interviews in *Origins* are pitched at a semitechnical level that may exclude the uninitiated from its readership, although Lightman has tried to bridge the gap by including both a glossary and a generally reliable introduction outlining the precepts of modern cosmology. The book is flawed, however, by small but irritating factual errors: perhaps it is curmudgeonly to insist that the word "data" be recognized as plural, but surely astronomer Marc Davis, whose name is spelled correctly on page 341, need not have become "Mark" Davis by page 447.

Lightman writes in the preface that the book "explores the ways in which personal, philosophical, and social factors enter the scientific process." Unfortunately, it does so by borrowing the social science technique of asking everybody the same standardized questions and printing their answers even when the responses reveal little except that the question ought not to have been asked in the first place. When Lightman asks the cosmologists, "If you could have designed the universe any way that you wanted to, how would you do it?" he is advised by astrophysicist Sandra Faber that "the question is flawed," while Maarten Schmidt responds, "This is really the worst question I've ever heard." But he keeps on asking it, of everybody.

The interviews humanize the cosmologists with a vengeance, but without much editing for relevance the results too often resemble the famous see-through blouse that one wishes wasn't. Commenting on the smoothness of the cosmic background radiation versus the lumpiness of bright matter, astronomer John Huchra says, "It's not the kind of thing where you've lost your pants and have to go running into the men's room quite yet. But the belt is loose or the fly is open and there may be some problem." Marc Davis says of his profession, "I'm very enthusiastic and excited by it. I'm sure that many other people in different lines of work have similar good feelings about what they do, but being a physicist, I think, is very special." All of which serves but to demonstrate that capable cosmologists when quoted verbatim can sound just as fatuous as the rest of us.

In *Lonely Hearts of the Cosmos,* his first book, science writer Dennis Overbye attempts not only to humanize the cosmologists but also to recount the rich and tangled tale of what they've been doing for the past 50 years or so—from discovering the Hubble law and the cosmic background radiation to theorizing about inflation, string theory and the quantum wave function of the universe. Overbye has thus set his sights high: to write such a book, one must gain command of several vital fields of scientific research, familiarize oneself with an extensive cast of characters, investigate the specific history of their interactions with one another over the years, and then craft all this into a story that is at once artful, involving, lucid and accurate.

Overbye can humanize with the best of them. His book bristles with anecdotes, quotes and enough gossip to fuel a movie magazine. Predictably, he concentrates on the giants of the field: physicists Stephen Hawking and John Wheeler, astronomer Allan Sandage, cosmologist James Peebles and other first-magnitude stars. But he also finds room for many of their lesser-known colleagues, and all come alive here.

There are plenty of late-night stories

An Invitation to Explore

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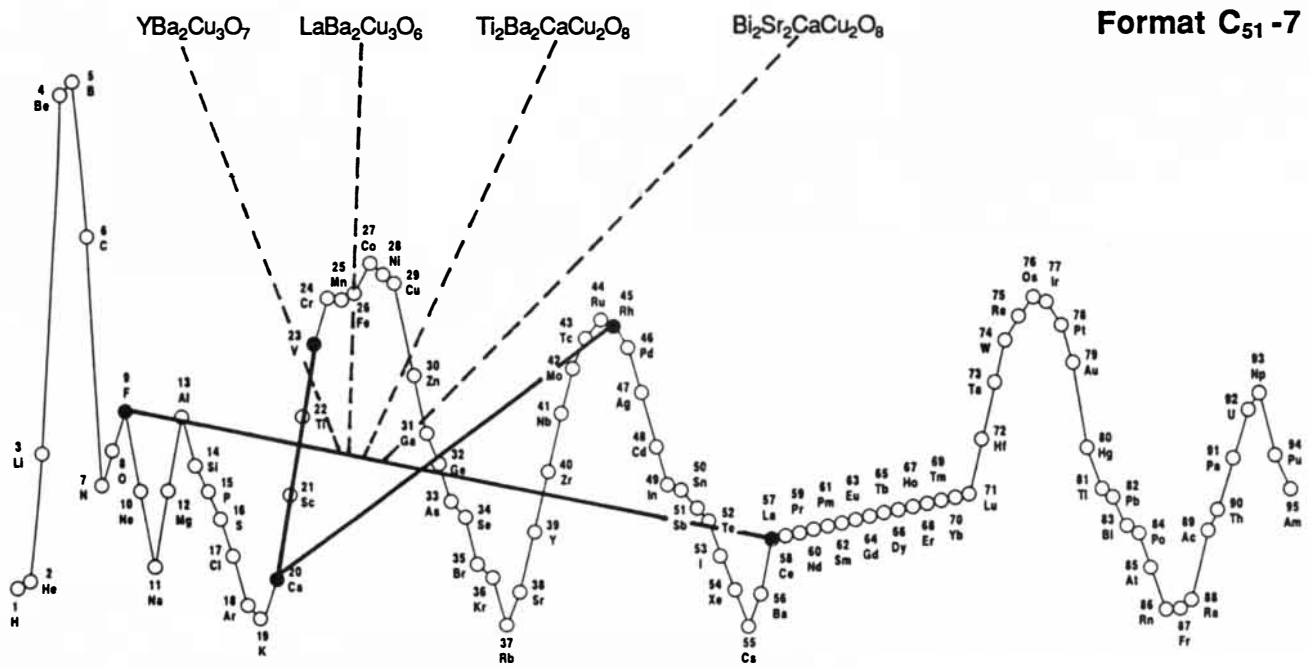

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about personalities. Overbye writes that Soviet astrophysicist Yakov Zeldovich, "a drinker and dancer for whom there were no barriers between life and science…used to put on his medals when he was going out for a bout of drinking so that the Moscow police, notoriously hard on drunks, would not hassle him." The Swiss-American physicist Fritz Zwicky "proposed shooting artillery bursts over Palomar to make the air more transparent." Sandage, entering a room full of hostile scientists after 15 years of shunning conferences, muttered, "Well…we're all in this Gamow box…. The question is whether we can tunnel out…or we just annihilate each other."

There is also more than enough philosophical talk to offend those working scientists who imagine that they can put philosophy behind them like quitting smoking. But most of it comes from men and women who have earned their right to say what they think, and much of it is genuinely thoughtful. Wheeler, musing on the collapse of the quantum wave function, remarks that "a picture without a frame is not a picture. Life without death would lose its value." Peebles, asked about his preference among possible cosmic destinies, replies, "If someone gave me on a tablet of clay, the answer and the numbers, I would be disappointed. I would throw it away, because the great discoveries are not going to be a final number but the method you come to apply to learn that number." Sandage, having spent much of his career extending the research on the expansion of the universe initiated by his mentor, Edwin Hubble, says, "Hubble died too young and left me with a burden, an incredible burden, to carry out his program…. It was all laid out by him…. It would be as if you were appointed to be copy editor to Dante. If you were assistant to Dante and then Dante died, and then you had in your possession the whole of the *Divine Comedy,* what would you do? What actually would you do?"

We have come to require a certain amount of fine writing from our more ambitious science popularizers, and Overbye demonstrates that he can write up a storm when the occasion calls for it. In describing the functioning of a particle accelerator (a benchmark of sorts, in that all who write nontechnical accounts of physics have to do it sooner or later), he turns in a commendable performance: "When two particles—a proton and an antiproton, for example—collided, for an instant too short to be measured there was a fireball of pure possibility, a piece of the big bang circa a trillionth of a second. Whatever laws governed that far time, whatever forms matter and energy had been permitted to take back then, would recrystallize in a spit of fire under the Illinois prairie. Species of energy and matter now vanished more completely than the dinosaurs, but whose brief struts had shaped the universe, would return."

The virtue of any such book, however, ultimately resides in the competence with which it relates hard science and history. In reading the first few chapters of *Lonely Hearts,* one fears that it is going to be a jellyfish, all splendor and no skeleton. Only after 100 pages or so does one begin to realize that its vivid descriptions, memorable anecdotes, lively quotations and portentous philosophical passages serve, like the pastel bulkheads of a commercial airliner, to conceal a strong and flexible frame hammered together from a competent design through sheer hard work. Whether covering such foundation stones of cosmology as Cepheid variable stars and redshifts or recent additions like the Great Attractor and supersymmetry, Overbye displays a discerning taste for the significant issues and an enviable ability to explain them simply and colloquially. His explication of the proper motion of the Milky Way galaxy clearly illuminates a subject too often left fogbound. His discussion of Hawking's role in the development of the new inflationary hypothesis is more accurate and more readable than the one in Hawking's own book, *A Brief History of Time.*

For all the violence and vulgarity loosed on science by lesser popularizations (many of them, sad to say, written by scientists themselves), there will still be hope for the form as long as we have books that try as hard, and do as well, as does *Lonely Hearts:* broad in scope and fraught with literary experiment, it is one of the most ambitious popularizations of science to be attempted in recent memory. Seldom has any science journalist said so much, so well, in so few pages.

SCHIZOPHRENIA GENESIS: THE ORIGINS OF MADNESS, by Irving I. Gottesman, with Dorothea L. Wolfgram. W. H. Freeman and Company, 1991 ($24.95; paperbound, $14.95).

The word "schizophrenia" is now mainly an overworked metaphor for inconsistency in policy or purpose. In this fascinating, meticulous and wise book, it is assuredly no figure of

speech, but the carefully limited diagnosis of a profound mental disorder that currently afflicts or has been endured by two million Americans older than 16, perhaps one in six of all who suffer mental disorders. We don't know its cause, and we hold no cure.

The burden is global; a 1988 study made for the World Health Organization (WHO) using carefully structured interviews with first-contact psychotic patients showed that people are at roughly equal risk in Nagasaki and in rural Punjab, in Honolulu and in Moscow. This is a disease of young adults (once it was even so named, although now we know that a tenth of the sufferers are younger than 20 and a tenth beyond 45). This is a disease of the poor, in good measure because those who have it often drift swiftly downward on the social scale. At least it is not rising in incidence; in 1971 the careful Norwegian record showed an "astonishing stability" over half a century in first-admission rates. Most tantalizing statistic of all, it just may be a modern disease, widespread only for the past two centuries.

Schizophrenia was first sharply described in the year 1809, both by John Haslam of Bethlem Hospital in London and by Philippe Pinel in Paris. By 1832 the major character in one Balzac short story "is clearly schizophrenic," although no such cases can be found in the plays of Shakespeare or in the rich medical literature of classical antiquity, where other psychoses stand out clearly. The inference is not at all secure; we cannot sift the diagnoses of the past in the way WHO can verify the protocols of its doctors. Maybe it was not until the maturing of mental hospitals that keen observers could easily compare the pitiful textures of madness. But the suggestion is there: a hidden virus? some ubiquitous toxic stress of modernity?

The condition is assessed solely by psychopathology inferred from speech and behavior, through probing interview and history-taking. It is variable in symptoms, severity, duration and outcome. By now there are stringent comparisons of diagnoses across national boundaries, and key behavior patterns listed for the doctors. (Notice that the disease is *not* the rare split personality so dear to popular romance, two or more plausibly ordinary identities in one head, whatever its Greek etymology says.) The task of diagnosis is subtle. Put crudely, the first step is to exclude injury, drugs, tumor and other "forgeries." The patient, often seen for months as a changed person by family or friends, may hold delusions or hal-

lucinations, very often of boon or of harm to come from others. Reasoning and awareness are fully present; the patient may shop ably, nurse a baby, balance a checkbook. This is a disorder centered far from everyday mastery, in shadowy domains of inference and anticipation. Although depression or elation may be present for weeks (and no wonder), schizophrenia is not at all the even more common disorder of mood swing.

Here you can read half a dozen accounts by survivors and members of their families, persuasive and affecting stories of the covert signs of hope and despair. One cheery survivor recalled with laughter her hospital "therapeutic breakthrough of typing four-letter words repeatedly for hours." An artist looked back at a year of the disease: "I know...it is craziness when... every laugh is about me...; newspapers suddenly contain cures...sparkles of light are demon eyes." David, then a profoundly paranoid young man, noted that his screen would flicker after any remark on television that had referred to him. A code, perhaps through God, perhaps through the CIA, had somehow notified the station of David's thoughts. Yet he felt he had established critically that "NBC had a transcendental outlook and often designated David as Jesus Christ. CBS... described David as having schizophrenia. ABC expressed mixed feelings...." Such dreams of fitful reason foretell the therapeutic sects and the theories; here, all awry, are images of shaman, scholar, even prophet.

Since 1916 the old observation that the condition was hereditary has been tested statistically. About 90 percent of schizophrenics have neither parent affected, and a majority have "clean pedigrees," with no cases at all in the family tree out to nieces and nephews. But it seems (from 40 European studies over many decades) that identical twins in truth share the biggest risk; if your one-egg twin suffers, your chance of the disorder is about 50/50. For fraternal twins, that chance drops to one sixth. The fast decline of risk with reduced kinship is itself clear evidence that very little schizophrenia can be a matter of a single gene. The author warns as well that "incorruptible watchdog committees" that include citizens and former patients must steadily act to "bolster the...conscience of society" against compulsion in the name of eugenics.

The prize is still unclaimed: all we can say is that the cause of this strange disorder is a genetic predisposition of some complexity, followed by some environmental stressors still unknown. The search for the stressors has been extensive. Consider only two of many candidates. The acute battlefield stress during D-day didn't do it; only a handful of schizophrenic young soldiers appeared among 4,000 invading GIs who were admitted to field hospitals for mental disorders. A whole childhood of schizophrenic mothering doesn't do it either. (Schizophrenics are twice as likely to have schizophrenic mothers as they are to have fathers with the condition. It seems that affected males show symptoms earlier than females and so don't as often have children.) We just don't know what externality can spring the genetic trap.

Molecular genetics has brought help for some of the rare genetic disorders; the more common and more complex examples may be next. With brain imaging and neurochemistry, there is real promise, this engaged optimist says; even within this Decade of the Brain, we may untwist "the twisted molecules and thence...the twisted minds." —*Philip Morrison*

THE ALGORITHMIC BEAUTY OF PLANTS, by Przemyslaw Prusinkiewicz and Aristid Lindenmayer, with James S. Hanan, F. David Fracchia, Deborah R. Fowler, Martin J. M. de Boer and Lynn Mercer. Springer-Verlag, 1990 ($39.95).

Four dozen color photographs of plants light the pages of this slender book of mathematics; the general reader will gain most from browsing among these striking images. You will see ferns, pineapples, lilacs, zinnias, a rose and lily-of-the-valley. These are mostly single flowers or flower heads; a few pictures are showier still, garden beds or whole fields in blossom, even a final scene after Claude Monet: quiet pool, arched wooden bridge, water lilies, texturally a work in the Impressionist style. All of it bloomed only on the computer screen. No real plant image was invoked, no artist's hand with lens or brush; everything is rooted solely in long, long strings of computer commands. The images are less sharp than dewdrops caught on a rose by the stopped-down lens of a celebrated photographer, but they astonish all the same by the abstractness of their origin.

The two senior authors are from the universities of Regina and of Utrecht, respectively; unhappily, Professor Lindenmayer died before the book was completed. The formal system treated is called, after him, the L-system; its original purpose 20 years

ago was to serve as a mathematical theory of plant development. The concept has now been intricately realized in synthetic images. The L-system is a rewriting scheme, elaborating a simple initial object by replacing part after part under tight rules. The structure grows under construction; synthesis gives the process an intuitive quality more powerful than any formal solutions.

Begin with a kindergarten example, long strings built of only two letters, say, *a* and *b*. Apply just two rules: always rewrite *b* as *a;* always rewrite *a* as the pair *ab*. It is easy to begin the sequence: *b, a, ab, aba, abaab, abaababa*... A complex babble arises out of this simplest of grammars. These long linear words even find botanical counterpart in certain algal filaments, where cells of two kinds link in long strings. Three kinds, and you do even better.

Clamber up into two or three dimensions, a few letter codes putting in standard steps with right and left turns. The result is a convoluted series of line segments, an intricate framework. Add branching, perhaps with a few oblique directions. Rewrite a single step as a small branch. By now a very plantlike diagram results. Replace any twig by a patch of area bounded by two or three algebraic curves: leaves appear. Growth? Let some parts be replaced by a string of copies that increase in size proportionately.

Living plants are not so unvaryingly precise as all that. Variations? Merely introduce random choices among some of the alternatives. Still subtler rules can depend on neighboring elements: context. Color patterns can be included and delayed expression of choices. For final lighting, invoke the tracing of ray after ray of imaginary light from its sources out through a couple of stages of successive reflections. (Such programs are already well developed for use by architects and by film animators.)

So rough a summary can only suggest the variety and rigor of the prescriptions. These impressive photographs are all annotated by a list of the procedures used for them. The long list of co-authors names the talented software developers at Regina and Utrecht, some of them graduate students, whose programs painted four fifths of these scenes. Finally, a "virtual laboratory in botany" is outlined, a set of some nine or 10 such programs that can grow magical gardens of blossoms without substance, flowering forth out of interminable strings of symbol. —*Philip Morrison*

ESSAY

AIDS and the next pandemic

by Jonathan Mann

The worldwide AIDS epidemic has grown from approximately 100,000 people infected with the human immunodeficiency virus (HIV) in 1980 to eight to 10 million today. The pandemic remains, 10 years after its discovery, dynamic and volatile, fueled by deep-seated and little understood behavior. Moreover, the decade to come seems inescapably worse. The combination of new HIV infections (estimated at l0 million to 25 million) and the natural history of individuals already infected is expected to result in at least six million new cases of clinical AIDS in adults during the 1990s.

Yet the situation could have been much, much worse. The reaction to AIDS has been truly remarkable at many levels: science has made progress in developing vaccines and therapies; communities and local governments have mobilized quickly; public information efforts have been impressive in scale and, occasionally, in candor; and the world community has gained an increased awareness of the need for solidarity in confronting the pandemic. The global response has been unprecedented (which is not to say that major challenges do not remain). All these developments are of course predicated entirely on the recognition of AIDS in 1981. The world must count itself fortunate to have discovered AIDS then rather than five or even 10 years later. The reasons for the early detection of this disease reveal a lesson of supreme importance for dealing with the next pandemic.

First, by 1981 AIDS was occurring in the U.S., a country with a highly developed disease surveillance system. Had AIDS been limited to developing countries, considerable delay in detecting its presence would have been almost inevitable. Furthermore, a clinically recognizable syndrome developed in a small percentage of some HIV-infected people within just a few years after infection, although we now know the median latency from infection to clinical AIDS to be about 10 years. Had the latency period been longer or had the distribution of the latency differed, discovery of the syndrome would have been further delayed, even in the U.S.

Detection of AIDS was enormously facilitated by the unusual nature of its characteristic infections and malignancies. The immunosuppression caused by HIV could have led to an increase in common diseases rather than rare opportunistic ones. Had HIV caused an increase only in routine pneumonia deaths, for example, its detection would have taken much longer.

Next, AIDS first came to the notice of officials in the U.S. as a health problem among a highly self-aware group of men who had sex with men. Had these men concealed their sexual preferences or had HIV infection in the U.S. been transmitted predominantly by heterosexuals in the early years, the recognition of key epidemiological linkages would have been delayed.

Finally, the technical ability to detect human retroviruses was developed at precisely the same time the HIV pandemic was silently spreading, during the late 1970s. Had this technology and a limited understanding of human retroviruses not already existed, the identification of the pathogen would undoubtedly have taken longer, perhaps much longer. The rapid availability of testing methods not only helped to prevent transmission through blood transfusions but was essential for recognition of the global scope of HIV at a time when the epidemic in most countries was so new that nearly all infections were still asymptomatic.

Thus, extraordinary circumstances, both viral and human, led to detection of a global public health threat within five to 10 years after it became pandemic. But even more to the point, the conditions of the modern world virtually guarantee that HIV will not be the last pandemic. The world is much more of a "global village" today than when the term was coined. During the past 25 years, we have witnessed such a quantitative increase in the movement of people, goods and ideas (including cultural patterns of sexual behavior) that a new qualitative interdependence has been established. More than at any time in history, the food we eat, the air we breathe and the viruses that infect us are globally linked.

The new globalism means that viruses and other pathogens, already known but geographically circumscribed, have an unprecedented potential to spread. HIV has demonstrated how rapidly and thoroughly a pathogenic agent can do so in today's world. HIV existed, somewhere, before it became pandemic; so other viruses, about which we currently know nothing, also exist. The recent discoveries of Ebola virus and Legionnaires' disease are powerful reminders that the battle between human and microbe is an ongoing one.

What can we do to catch the next pandemic in time? I suggest a "global pathogen watch." Simply extending existing mechanisms for surveillance of communicable diseases is not sufficient. In any event, such systems are well developed in only a few countries, and we cannot afford to wait for a pandemic to spread to the industrialized nations before it is detected. Instead we need to change the way we look for outbreaks of disease—a qualitative leap that will develop the capacity to detect changes in health-related patterns. For we must be prepared to look for evidence of a pathogen that is not yet known. Thus, we must think anew about the basic problem and not hide behind a Maginot Line of passive detection based on concepts of surveillance designed for the challenges of the past.

This task will require the involvement of psychologists, sociologists and anthropologists as well as virologists and specialists in communicable diseases to develop creative ways of uncovering patterns in health and disease. For example, we should explore the finding gleaned from investigating many epidemics that the local community (often the mothers and grandmothers) has been "aware" that something unusual was happening. We must consider a broad range of nontraditional informants and indicators.

Finding different ways of looking for patterns of disease will be conceptually difficult and may be fairly expensive to implement. Yet the AIDS pandemic tells us that in the face of some dangers we must develop the capacity to respond globally. Failure to do so will condemn us to the vagaries of chance in our confrontation with the health challenges that appear, today as in the past, to be the inevitable traveling companions of social, economic and political change.

JONATHAN MANN founded the Global Program on AIDS at the World Health Organization and served as its head from 1986 to 1990. He is now a professor at the Harvard School of Public Health and director of the Harvard AIDS Institute's International AIDS Center.

Bord Na Móna - Irish Peat Board is a state owned organisation which was founded by the Irish Government in 1946. It was set up, on a commercial basis, to develop Ireland's vast peat resources.

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New peat-based products
Horticultural peat
Peat sciences, systems and basic research
Peat production
Peat processing
Peat and peatlands
Peat products for treating environmental pollution

THE CLOSING DATE FOR RECEIPT OF ENTRIES FOR THE 1991 AWARDS IS 2nd SEPTEMBER 1991.

BORDNAMÓNA

For further information, contact Director, Bord Na Móna,Peat Research Centre, Newbridge, Co. Kildare, Ireland.
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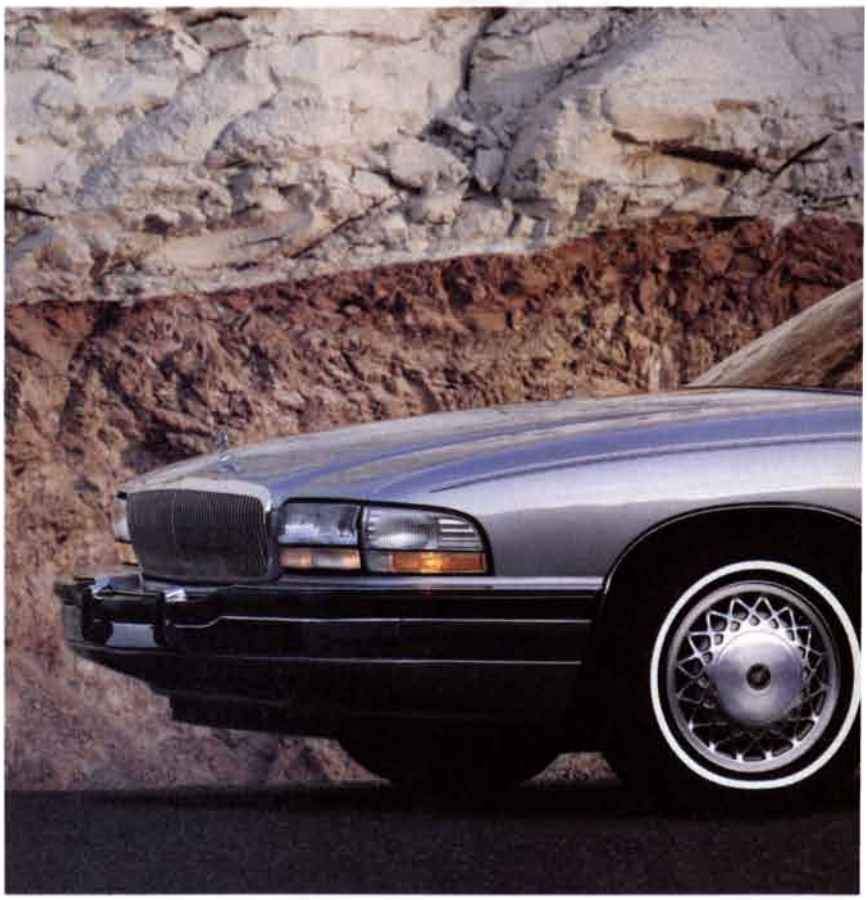

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