SCIENTIFIC AMERICAN

JUNE 1992
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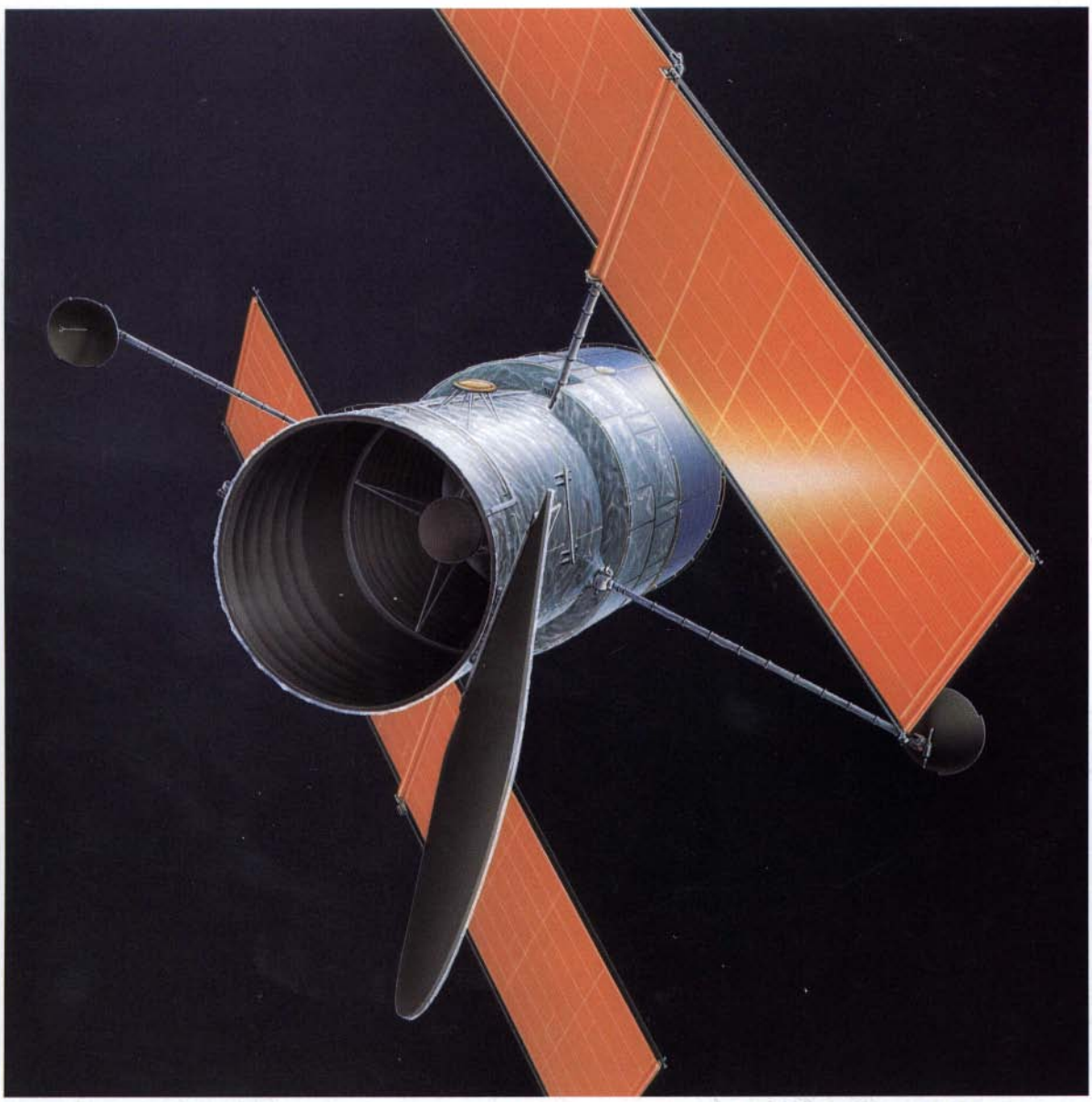
Why the "low at risk" can still have heart attacks.

Toward the single-electron transistor.

Codex Mendoza: the last records of the Aztecs.



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air conditioner, they designed an automatic temperature control system that not only keeps the passengers comfortable, but also keeps the ozone safe because it uses an environmentally friendly refrigerant.

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Imagine you could design your own personal computer. What would it be? It would be fast, of course. Faster than your basic 486 machine. Fast

The Apple Macintosh Quadra.

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It would have immense storage and memory capacity. And it would have features like high-performance networking and accelerated video support built in.

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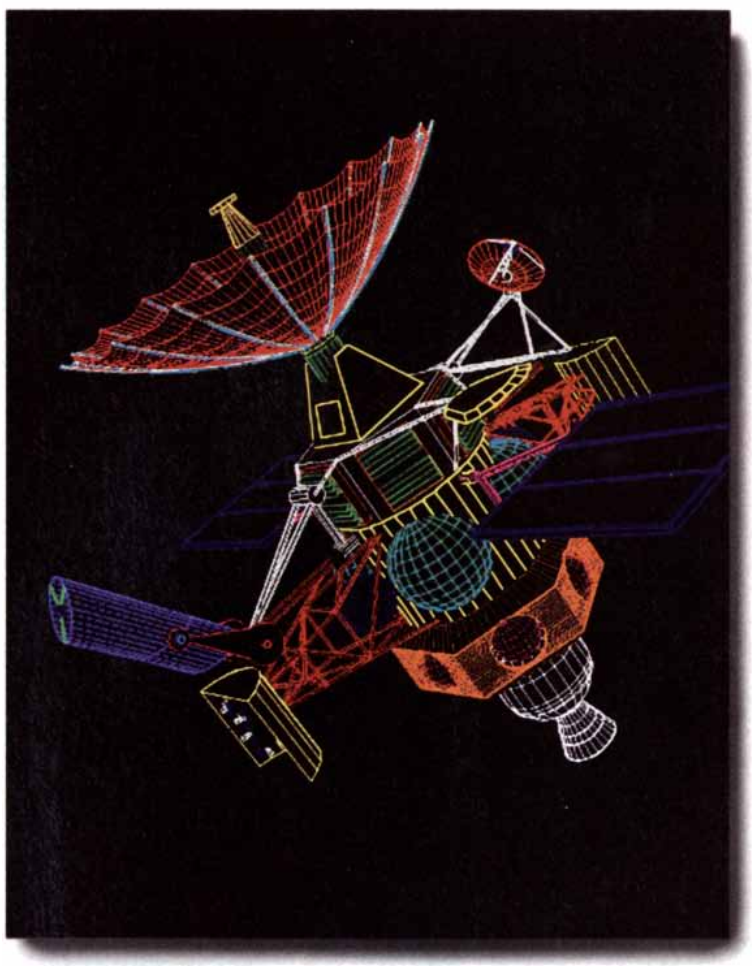


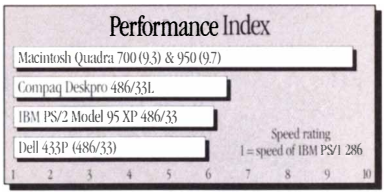
*"Comparisons are based on a 1991 independent research study conducted by Ingram Laboratories that tested a variety of personal computers running applications available for both the Macintosh and Microsoft Windows 3.0 environments. **24-bit video support for up to a 16" mon specifications and descriptions were supplied by the respective vendor or supplier. Orbiter images created by Jerry Flynn. ©1992 Apple Computer, Inc. Apple, the Apple logo, A/UX, Mac, Macintosh and "The power to be your best" are registered trademarks and Macintosh Quadra and SuperDrive trademark of Wolfram Research, Inc. MicroStation is a registered trademark of Bentley Systems Inc. MS-DOS is a registered trademark and Windows is a trademark of Microsoft Corp. Motorola is a registered trademark of Motorola Corp. NuBus is a trademark of Texas Instrum*

with the power revolution.

There are two Macintosh Quadra models. The 950 sits next to your desk; the 700 fits on top of it.

communications architecture lets you easily take advantage of features like distributed processing, allowing programs like RenderPro and BackBurner to utilize excess CPU cycles on other Mac computers or workstations for faster renderings.

And Macintosh Quadra fits in with the PCs you already own. The built-in Apple SuperDrive,™ used with Apple's new Macintosh PC Exchange software, allows you to share files easily with MS-DOS PCs via floppy disk or over a network. And with Apple's fully compliant version of UNIX®—A/UX®—you can even run UNIX, X Window, MS-DOS and Macintosh programs all at the same time.



Macintosh Quadra significantly outperforms 486 PCs from IBM, Compaq and Dell running Windows 3.0.

It all adds up to the kind of power that moved *PC Week* to give the Macintosh Quadra its highest satisfaction rating in the categories of overall performance, price relative to performance, expansion capability and ease of installation and configuration.†

the 700 and the 950 to accommodate the largest CAD files. And the 950 even lets you add a CD-ROM drive or a removable cartridge drive, and a disk array or more than a gigabyte of internal hard disk storage.

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also available for 21" monitors with optional third-party video card. †PC Week, December 23/30, 1991. ©1991 Ziff Communications Company. Mention of third-party products is for informational purposes only and constitutes neither an endorsement nor a recommendation. All product trademarks of Apple Computer, Inc. AutoCAD is a registered trademark of Autodesk, Inc. BackBurner is a trademark of Specular International. MacBRAVO! is a trademark of Schlumberger Technologies, Inc. MacTOPAS is a registered trademark of AT&T Graphics Software Labs. Mathematica is a RenderPro is a trademark of Strata, Inc. Vellum is a registered trademark of Ashlar Incorporated. VersaCAD is a registered trademark of Versacad Corp. X Window System is a trademark of MIT. UNIX is a registered trademark of AT&T. This ad was created using Macintosh computers.

SCIENTIFIC AMERICAN

June 1992 Volume 266 Number 6

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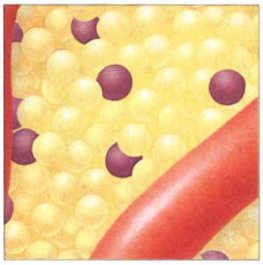
Early Results from the Hubble Space Telescope
Eric J. Chaisson

Even though its primary mirror is flawed and its solar panels have given *Hubble* the jitters, the orbiting observatory can still match the sensitivity and exceed the resolution of the best earthbound telescopes. In its first two years of operation it has returned a stream of spectacular images, from storms on Saturn to possible black holes, that are triggering a revision of modern astronomy.

54 

Lipoprotein(a) in Heart Disease
Richard M. Lawn

The patient has low blood cholesterol levels, is not obese, does not smoke and does not suffer from high blood pressure. Yet a heart attack still occurs. The agent of heart disease in many individuals with low risk profiles may be a blood particle known as lipoprotein(a). Ironically, the ability of this substance to cause heart disease may be a side effect of its role in repairing damaged blood vessels.

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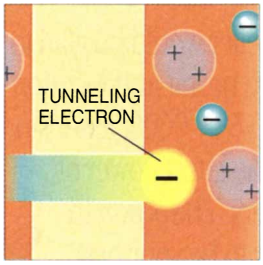
Transgenic Crops
Charles S. Gasser and Robert T. Fraley

In the past decade, genetic engineering has accelerated the age-old process of breeding advantageous traits into crops. Genes that confer resistance to diseases and pests as well as tolerance to herbicides and spoilage or that enhance nutritiousness have been inserted into more than 50 species. Plant biotechnology is now poised to make important contributions to world agriculture.

70 

The Codex Mendoza
Patricia Rieff Anawalt and Frances F. Berdan

To acquaint Charles V with his exotic subjects, the first Spanish viceroy in Mexico commissioned the last pre-Conquest Aztec artists to record their vanishing civilization. Completed in 1541, the magnificent Codex was captured by the French, sold to an Englishman and forgotten until 1831. The first modern edition was destroyed in the London blitz; a new edition has been completed by the authors.

80 

Single Electronics
Konstantin K. Likharev and Tord Claeson

Computers have become more powerful as the devices etched onto silicon chips have become tinier. Experiments have now verified the feasibility of what may be the ultimate miniaturization: devices that require the movement of just a single electron. Whereas today's most advanced chips contain 10 million devices per square centimeter, single electronics could cram 10 billion into the same space.

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Control of Rabies in Wildlife
William G. Winkler and Konrad Bögel

Wild mammals are a major reservoir for the rabies virus, which causes 25,000 human deaths every year. An epidemic in raccoons has spread unchecked up the U.S. East Coast since the 1950s. The solution, these authors say, is vaccine-filled baits, which are controlling the transmittal of rabies by foxes in Europe and Canada.

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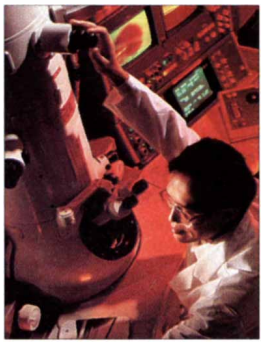
Accounting for Environmental Assets
Robert Repetto

When governments calculating their economic performance fail to account for the depreciation of forests, fisheries, minerals or water caused by development, the balance sheets often show growth and prosperity. In reality, the result is usually impoverishment. The experience of Costa Rica is a case in point.

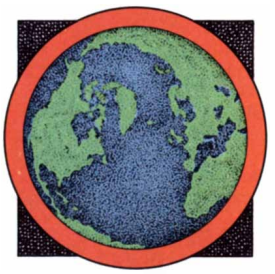
102 

TRENDS IN INDUSTRIAL RESEARCH

Redesigning Research
Elizabeth Corcoran, staff writer

Prominent research laboratories, once the pride of U.S. industrial giants, have been sold, shuttered or simply given away. All too often, their important inventions made little or no contribution to the bottom line. But some companies are not ready to write off research. They are determined to reshape their research operations so that they serve the goals of the business. Can they succeed?

DEPARTMENTS

17 

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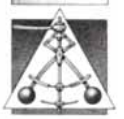
14 

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Essay: *Peter W. Huber*
Who should decide what passes for science in the courtroom?

THE COVER painting shows the *Hubble Space Telescope* as it appears in its orbit 610 kilometers above the earth's surface. The telescope's performance has been compromised by an incorrectly shaped mirror and by several mechanical problems. Scientists have learned to work around these failings, however (see "Early Results from the Hubble Space Telescope," by Eric J. Chaisson, page 44). *Hubble* has yielded some impressive observations, including the sharpest optical images yet made of active galaxies and quasars.

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The name Mitsubishi means three diamonds, and has signified automotive excellence for 75 years.

*Optional equipment. Model shown Diamante LS.

LETTERS TO THE EDITORS

Remembering Timoféeff

After reading the fascinating article on "Nikolai V. Timoféeff-Ressovsky," by Diane B. Paul and Costas B. Krimbas [SCIENTIFIC AMERICAN, February], I sent it to our professor emeritus Clifford Mortimer, Fellow of the Royal Society, who did his doctoral work in genetics in Berlin during the 1930s. His reply adds a valuable historical footnote:

"I knew [Timoféeff] well in Berlin. Many a night we talked over a bubbling samovar of Russian tea; and I feel responsible for having introduced him to a physicist friend, Max Delbrück. That led to the pivotal paper by Timoféeff, Delbrück and [Karl G.] Zimmer.... Timoféeff was no Nazi, only unfortunately foolish in not accepting the Cold Spring Harbor offer in the late 1930s."

PETER WATSON-BOONE
Director, The Golda Meir Library
University of Wisconsin at Milwaukee

Quarks and Clarification

I was flattered that you devoted several columns in the March 1992 issue to a profile of me. The profile was, of course, not flattering, but perhaps it gave some of the flavor of what I am like when in an unusually bad mood after a sleepless night. I had kidded around with reporter John Horgan as I would have with an old drinking buddy; had I been less tired, I would have known better and treated him the way a suspect should treat a homicide detective.

By compressing my remarks concerning technical matters, Horgan lost some important distinctions and qualifications. One serious distortion of meaning involved the work of Joseph H. Greenberg and others on large-scale groupings of human languages. Only part of that work concerns the possibility of a single language ancestral to all the known ones. What I was deploring (no doubt in unsuitably intemperate terms) was the contention of some historical linguists that any such grouping that has a time depth exceeding 6,000 years or so must be unjustifiable.

The reason usually given is that for the larger groupings there is typically no construction of a sound system for the proto-language in the kind of detail that is customary for the recognized families. Yet the lexical similarities that show the kinship of, say, the Indo-European languages are so numerous and striking that it seems unreasonable to suppose one could not legitimately go on to a larger, older grouping even without the detailed sound system.

The technical arguments about particular large groupings, and about the descent of all known languages from a single ancestral tongue, are still at a stage where reasonable people may disagree. I was expressing impatience only with those critics who condemn the whole enterprise out of hand. The same is true, by the way, of my impatience with critics of superstring theory.

There are a few other points I hope to clarify. I am very fond of the U.K., and I would criticize only a very few British scientists as being "more concerned with being clever and paradoxical than with being right." They know who they are.

The word "quark" in *Finnegans Wake* does evoke the cries of gulls, and it is presumably meant to rhyme with "mark." Because I wanted an excuse to pronounce the word as "kwork," however, I invoked a possible further connection with a call for quarts of ale.

In my first publication about quarks, I indicated that by mathematical quarks I meant something akin to the limit of infinite mass and binding energy. In the *Proceedings of the International Conference on High Energy Physics* held in Berkeley in 1966, I defined mathematical as meaning the limit of an infinite confining potential, which is pretty much how permanently confined quarks are regarded today. Many writers still fail to understand that what I meant by mathematical is what turned out to be generally accepted and presumably correct.

During the 1960s, the *scientific* study of unconscious mental processes was not easy to sell to many academic psychologists because they doubted that the subject could be made scientific. It was equally difficult to sell to psychoanalysts because they felt they had already learned much about the subject by their own methods.

In my research with James Hartle, we are building on the pioneering but incomplete work of Hugh Everett III on the interpretation of quantum mechanics. We are disturbed not by Everett's "belief" but by his choice of language. We think he confused many readers by writing about "many worlds" instead of "many histories of the universe" and about the "reality" of all the alternatives rather than that the theory treats them alike except for assigning them various a priori probabilities.

Finally, the programs of the John D. and Catherine T. MacArthur Foundation are determined by the entire board of directors in consultation with the staff and with outside experts; no one director can "establish" any activities or "divert" funds to new ones.

MURRAY GELL-MANN
California Institute of Technology

Gene Screens

The people in favor of genetic screening for employment seem to have forgotten their history ["Fatal Flaw," by Tim Beardsley, "Science and the Citizen"; SCIENTIFIC AMERICAN, December 1991]. The American and Canadian constitutions grant freedom from racial discrimination. Is not race just an old word for genetic code? Let us not forget that we are trying to build a democratic society, not a master race.

NEIL HENDERSON
Toronto, Ontario

ERRATA

"Mirroring the Cosmos" [November 1991] should have said that the Multiple Mirror Telescope is jointly operated by the Smithsonian Institution and the University of Arizona. It is not a part of Steward Observatory.

"Reflecting Differences" ["Science and the Citizen," March] misstated certain statistics: one in nine women will eventually *develop* breast cancer if she does not first die of different causes.

A caption on page 45 of "The Patch Clamp Technique" [March] should have said that the patch pipette is roughly 1/25,000 of an inch in diameter.

Credit for the galaxy map on pages 52–53 of the March issue should have gone to George P. Efstathiou and the department of astrophysics of the University of Oxford.

A caption on page 81 of "Infrared Video Cameras" [March] suggests that William Ewing took the photograph. He designed the camera.

THE BOMBAY SAPPHIRE MARTINI. AS ENVISIONED BY MICHAEL GRAVES.

POUR SOMETHING PRICELESS.

Bombay® Sapphire™ Gin. 47% alc/vol (94 Proof). 100% grain neutral spirits. © 1992 Carillon Importers, Ltd., Teaneck, N.J. © 1992 Michael Graves.

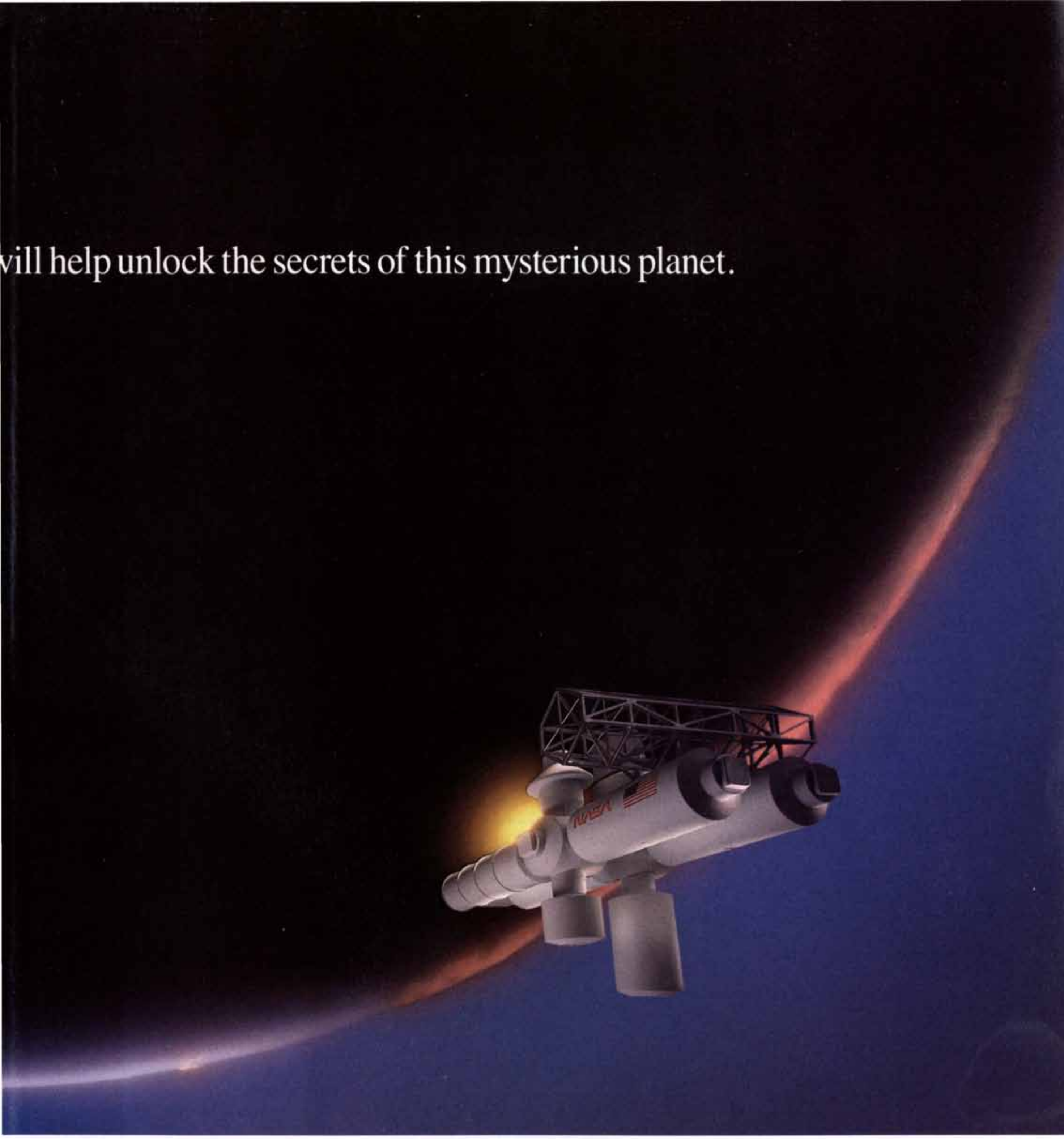
The good health of the home planet is the reason we're building the manned space station today—and why we'll launch the first components for it in less than four years.

Some of the laboratories will be dedicated to the life sciences—studies that touch the lives of virtually everyone on earth. Others are designed to learn more about materials—the basic building blocks of our civilization.

The space station will have unique micro-gravity labs where scientists can do experiments that are impossible on earth.

And it will allow research into the natural processes that created and still change our world. And our lives.

Best of all, research on board the space station will increase our rate of discovery and invention in materials and life sciences.



That's important to every American, and to future generations. To create new jobs, we need new discoveries, new inventions, new ways of looking at the world.

The space station is more than high technology. It also is a practical, down-to-earth idea.

BOEING

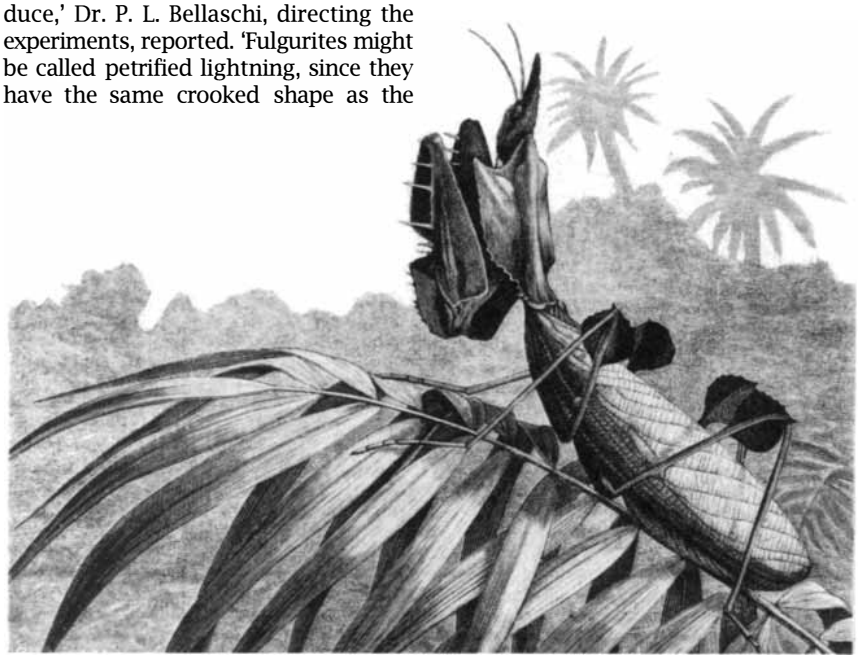
JUNE 1942

"A new airplane with a dual personality—fighter as well as bomber—has enabled the British to develop a technique of bombing entirely new even among the novelties of modern aerial warfare. In a day when new planes are being equipped with superchargers to cruise in the heights of the substratosphere, this latest air weapon hugs the ground and even dips into hollows or ravines to hide from enemy fire. The new technique has produced its own problems in ballistics. When a bomb hits the ground from such a low height, it ricochets along the ground horizontally and hits the target from the side instead of from above. This is all right for a huge target. But one pilot who watched a companion attack a railway station reports that the bombs went clean through both walls and exploded harmlessly some 300 yards away."

"Engineers at the Westinghouse high-voltage laboratory recently caught man-made lightning in a bucket of sand to produce replicas of the glass-like fulgurites formed by natural lightning strokes. 'Since a temperature of about 3000 degrees is required to melt sand into fulgurites, these experiments give us definite knowledge of the tremendous heat which lightning can produce,' Dr. P. L. Bellaschi, directing the experiments, reported. 'Fulgurites might be called petrified lightning, since they have the same crooked shape as the bolts that formed them. Natural specimens occasionally are found buried in the ground, particularly in dry desert sands. They are glass-like tubes of solidified sand, formed when lightning surges through dry earth in search of moist ground in which to neutralize its charge.' "

"In our May issue we presented an article on battleships, the article to be the first of a series. The present number does not contain the second article because of the war-time censorship to which Scientific American has voluntarily submitted."

"Of the many uses to which solar collectors may be put, perhaps the simplest is the heating of a house in a relatively cold but sunny climate. The system would consist of a well insulated tank from which water can be pumped to the collector and back whenever the collector is hotter than the tank, and a set of radiators through which the hot water could be circulated to heat the building. It was for research into this type of heating that a testing cottage was built on the Massachusetts Institute of Technology grounds. For many months the plan has been put to a practical test, and valuable data are being obtained on the optimum number of glass plates, the best tilt, the ratio of roof to tank area, and the advisability of employing special types of glass."



Idolum diabolicum, *a tropical mantis*

SCIENTIFIC AMERICAN

JUNE 1892

"The largest python we found in our stay in the Philippines measured twenty-two feet and eight inches in length, and twenty-two inches in greatest circumference. A snake of this size could bring down a medium sized buffalo, and could crush out the life of a man in a fraction of a minute; and we have no hesitation in expressing the opinion that it could swallow him. We know of the case of a snake of about this size swallowing a full-grown buck with antlers, a male deer of this species being larger around the belly than is a man around the shoulders."

"A dispatch from St. Petersburg says: What is believed to be the largest aerolite ever known to have fallen is lying in the Caspian Sea, a short distance from the peninsula of Apsheron. The aerolite made a terrific noise as it rushed through the air, and the white-hot mass made a light that illuminated the country and sea round about for a great distance. When it struck the water immense clouds of steam arose. Huge masses of water were thrown upward, and the sight to those who were not frightened was an exceedingly beautiful one."

"It is stated on good authority that the tropical species of Mantis (one of which is shown in our illustration) will overpower and eat lizards three times as long as themselves, and even small birds are surprised while sleeping and devoured. The little *Mantis religiosa* of Southern Europe, although less than three inches long, will defend itself against man, and the gigantic species of hot countries cause bloody wounds in the human skin with their saber-like legs. But the worst characteristic of the mantis is the amazon-like trait which it shares only with some spiders. The female mantis is larger and stronger than the male, and she murders her mate in cold blood, when she can get him, and eats the father of her future children without the least compunction."

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—James Cost, Chief of Police, Campbell, CA

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Still Negotiating

As many issues as delegates at the U.N.'s Earth Summit

REPRESENTATIVES from more than 1,000 nongovernmental organizations participated in preparatory meetings for the Earth Summit. Photo: Steve Berman.

The multinational negotiations leading up to the Earth Summit that will take place in Rio de Janeiro in June have been variously described by participants as a zoo and a circus. To those more removed from the whispered doings, compromises, Machiavellian wranglings and trump-card showdowns often taking place behind closed doors, they appear to be, quite simply, chaos. There is "too much to do and not enough time," one observer notes. "There are just too many issues."

But for every expert or delegate who feels pessimistic, there is one who enthusiastically differs. And that is why the United Nations Conference on Environment and Development (UNCED) is expected simultaneously to fail and succeed. The only complete document to emerge from the fourth and final Preparatory Committee, or PrepCom IV, meeting held at United Nations headquarters in New York reflects this paradox.

Hammered out in the early-morning hours of April 4, the Rio Declaration lists 27 principles that provide an ethical framework for humanity's relationship to the earth. These ideals include the right to development and the right of countries to exploit their own resources so long as doing so does not hurt the environment of other nations.

"It is the only unbracketed text going down to Rio," notes Scott A. Hajost, international counsel for the Environmental Defense Fund. During the negotiation process, terms or phrases that are the subject of debate are enclosed in brackets. And bracketing can easily become a fever: "The U.S. even had a comma bracketed in the technology transfer article," says one UNCED participant. (For reasons of diplomacy, many delegates and people close to the process speak only on the condition of anonymity.)

Unbracketed, yes, but also undecided. Many countries reserved the right to renegotiate the document. In all likelihood, for example, the U.S. will object to Principle 7, which confers blame for environmental degradation on developed nations. Israel is expected to oppose Principle 23, which calls for the protection of the environment of people under domination or occupation.

For all the haggling, though, those involved in UNCED expect many parts of the draft to survive. Some say its terms could revolutionize aspects of international environmental governance—such as the right to information about the hazards of pollutants and the obligation to carry out environmental impact assessments. Ideally the Earth Summit will also yield another document: Agenda 21. This text is a plan for implementing the principles in the Rio Declaration in the next century.

Although some delegates say as much as 95 percent of Agenda 21 is worked out, there, too, agreement has not been reached on crucial issues. The U.S. delegation, for example, says addressing overpopulation is an important topic. But "if you read the document, you'd never know that," one observer notes. "They can't even bring themselves to use the words 'family planning.'" Instead phrases such as "demographic dynamics" appear.

And some of the developing countries represented—as well as the Vatican—believe family planning should not be addressed in Agenda 21. As a delegate from an African nation explains, poverty contributes to overpopulation, which in turn degrades the environment. Therefore, developed nations should focus on eradicating poverty; population control will follow as standards of living rise. (At one point, according to a witness, a compromise was discussed: the "north" would stop badgering the "south" about overpopulation; in exchange, the south would stop hounding the north about its consumption of natural resources.)

Negotiators have also reached an impasse on forest protection, another point of contention between northern and southern nations. The Earth Summit was supposed to produce a set

of guidelines to protect forests; these terms were later to form the basis of an international forestry treaty. But some countries, including Malaysia and Brazil, have not agreed to certain forest management provisions. One expert anticipates that delegations from these countries may "hold forests hostage until they get some money from the U.S."

Which raises yet another stumbling block: finances. "We from the south do not view this as an environment conference," says a representative from a developing nation. "We view this as an economic conference." Using a parable, he illustrates the fundamental relation between development and the environment: a poor man cuts trees for fuel so he can boil water to purify it. If the water were clean, he would not have to cut trees. The delegate says that some of the most heated moments of PrepCom IV arose when U.S. delegates were pressed to acknowledge this connection: "They are afraid that if they recognize this, they are going to have to pay."

For its part, the U.S. seems to believe its financial commitments are adequate—that existing resources can cover the world's development needs. In 1990 a fund called the Global Environment Facility (GEF) was established by the World Bank, the United Nations Environment Program and the United Nations Development Program to support environmentally sound development projects. So far the GEF has received pledges for about $1.2 billion.

In one view at least, because GEF was founded a year and a half before UNCED, it has not been considered a solution. If it had been set up during PrepCom IV, "it would have been the centerpiece of UNCED," one expert notes. But many countries say much more funding is needed. And some developing nations are concerned that the World Bank finances large, not necessarily productive, projects rather than more grassroots undertakings.

At the same time as delegates have been feuding over the details of the forest principles, Agenda 21 and the Rio Declaration (none of which are legally binding), countries have been devising two treaties: a convention on climate change and a convention on biological diversity. The first addresses global warming and carbon dioxide emissions; the second seeks to protect biodiversity and attempts to distribute equitably the rights to and benefits from biodiversity and biotechnology.

Negotiations for the biodiversity agreement have been going a little more smoothly and there may be a finished document to sign at the summit, but the climate convention has faltered. As of this writing, the U.S. has objected to deadlines for limiting releases of carbon dioxide. Some experts say the U.S. wants to set up a framework for monitoring agreements and data collection before it commits to a timetable. Others—including representatives from some of the easily flooded tropical islands—say Washington is blind to the writing on the wall.

Each of these topics and others remain open for discussion in Rio. Agenda 21 lists such issues as reducing energy consumption, combating poverty, stemming desertification, protecting oceans and fresh water, limiting the export and transport of hazardous materials as well as regulating disposal of radioactive and military waste (for now, the U.S. objects to any reference to war as harmful to the environment). "Most governments are doing more in their national programs than the language of Agenda 21 will do," one observer laments.

We from the south do not view this as an environment conference, but as an economic one.

Even so, most participants agree that some form of Agenda 21 will be produced at the Earth Summit, when heads of state finally show their hands. "There will be compromise unless the meeting crashes," says a negotiator for a northern country. Of course, "even if it crashes, they will probably agree that it is just the beginning."

The procedures that UNCED ultimately agrees to for follow-up will do much to determine whether the documents are effective. Although many criticize the assiduous attention being paid to texts that are not binding, the soft law of Agenda 21 and the Rio Declaration could harden into binding law. "It will depend entirely on how governments act after UNCED," one expert says. On the other hand, "it could shrivel up and have no lasting effect."

Indeed, that seems to be the fate of some environmental treaties. The General Accounting Office and the United Nations each recently examined the monitoring of international environmental agreements. "What they discovered was not very encouraging," notes Hilary French, a policy analyst at the Worldwatch Institute. Both groups found that reporting is often late and incomplete. Secretariats overseeing agreements do not have the power or the resources to monitor compliance or to verify data, nor do developing countries often have the funds to implement the agreements. Moreover, channels for the resolution of disputes are not exploited.

The need for some overarching body to implement such agreements—even the results of the Earth Summit—has led UNCED negotiators to consider establishing a Commission on Sustainable Development within the United Nations. There is disagreement about whether this commission should report to the General Assembly or whether it should report to the Economic and Social Council, whose membership is limited to 54 countries. Only some of these details may be resolved in Rio; others may wait until 1995, when an anticipated World Summit on Global Governance will discuss reorganizing the United Nations. In addition, some countries are concerned that monitoring could impinge on national sovereignty.

Ironically, it is in the realm of monitoring that one of the unqualified success stories at UNCED may emerge: nongovernmental organizations (NGOs). These groups of citizen activists represent almost every country and issue, from population control and the preservation of indigenous botanic and other knowledge of the Amazon Basin to the rights of chemical manufacturers—and they are exerting an increasing influence on diplomacy. "It is the democratization of the international legal process," says Philippe Sands, legal counsel for St. Lucia and other small Caribbean islands.

More than 1,000 NGOs were accredited by UNCED, and they have worked to lobby and prepare reports for the delegates. They have not, however, reached the inner sanctum. "At some point, all negotiations go behind closed doors, and no one sees what is going on," says Mark Valentine of the U.S. Citizens Network. The NGOs plan to hold a parallel summit in Rio and to prepare as many as 28 alternative documents, their version of Agenda 21, which they hope will be implemented on a grass-roots level. NGOs have been described as ideally suited to monitor agreements and to complain and lobby about environmental transgressions on the part of corporations or governments.

For all the caveats, observers of the preparations for the Earth Summit say an important step has been taken. The world's governments have begun to recognize the links between the environment and development, the need for sustainable development and the importance of citizens' groups. It may not be "everything we dreamed, but it is the beginning of a process," says Angela Harkavy of the National Wildlife Federation. —*Marguerite Holloway*

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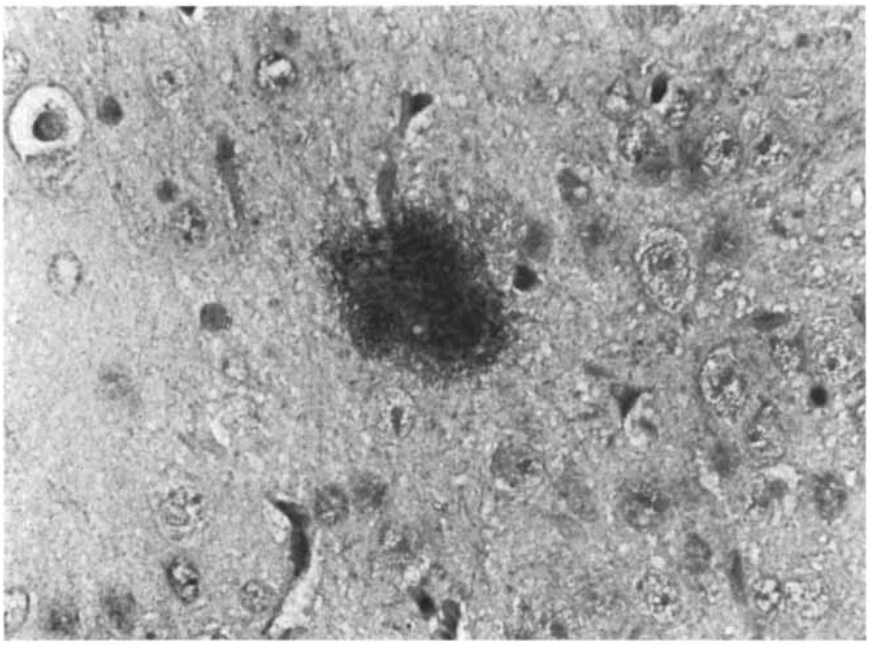


PREAMYLOID PLAQUE* (dark area) *in the brain of a transgenic mouse is the closest that anyone has yet come to simulating the effects of Alzheimer's disease. Photo: Scios.

The Mice That Missed

Two models for Alzheimer's disease are retracted

The march of science is rarely steady, certainly not for Alzheimer's disease researchers who have recently had to execute a particularly awkward shuffle: three steps forward, two steps back.

Last year three types of genetically engineered mice with lesions like those of Alzheimer's disease were presented to neuroscientists, who hoped the animals would advance the research and development of treatments. Two of the three models have since been withdrawn by their creators, and one of the two is further tarnished by questions about the validity of the published data. The surviving model is less than ideal. "It's a real disappointment that no one has yet been able to produce a mouse with Alzheimer's-like pathology," mourns Dennis J. Selkoe, a neurologist at Harvard Medical School.

The guiding idea behind all three models is that a protein fragment called beta-amyloid plays a causative role in the development of Alzheimer's disease. The loss of the mouse models has not shaken the theory itself but has cost it some corroborating evidence.

Two of the mouse models were announced in July 1991. *Nature* carried a report by Barbara Cordell of California Biotechnology (now Scios) and her colleagues; the work of Miles Research Center investigators led by Dana O. Wirak was published in *Science*. Both types of mice, into which all or part of a human amyloid protein gene had been inserted, developed neurological abnormalities that to some extent resembled early signs of Alzheimer's disease.

A more spectacular success—or apparent success—came in December, when Shigeki Kawabata of Yamanouchi Pharmaceutical, Gerald A. Higgins of the National Institute on Aging (NIA) and Jon W. Gordon of the Mount Sinai School of Medicine claimed in *Nature* that the brains of their transgenic mice seemed to show many hallmarks of Alzheimer's disease pathology: beta-amyloid plaques and tangles of proteins around degenerating neurons.

The celebrity of the Kawabata-Higgins-Gordon mouse was short-lived. In March the researchers formally retracted their model in a letter to *Nature,* explaining that they had been unable to reproduce the pathologies Higgins had reported. The retraction did not mention more serious questions raised by the Alzheimer's research community about the validity and even the authenticity of the original pathology data.

Several neuropathologists who have looked at slides provided by Higgins say they have found them far less persuasive than the images published in the December paper. Selkoe, for example, recalls that he met with Higgins this past January and was distressed by the condition of the slide he was shown. All the lesions appeared to be concentrated within one fragmented area of the brain tissue. Selkoe thought the lesioned area could be interpreted as a piece of a diseased brain, possibly from a human patient, that was merely adjacent to normal mouse tissue.

According to Selkoe, Higgins denied that any such confusion of tissues could have occurred but was unable to offer a better slide at that time. Selkoe says he had been assured previously that many examples of transgenic mice exhibiting the pathology were available. Selkoe claims he made other unsuccessful attempts to see the original published slides or others. He also expressed his misgivings about the published data to the NIA.

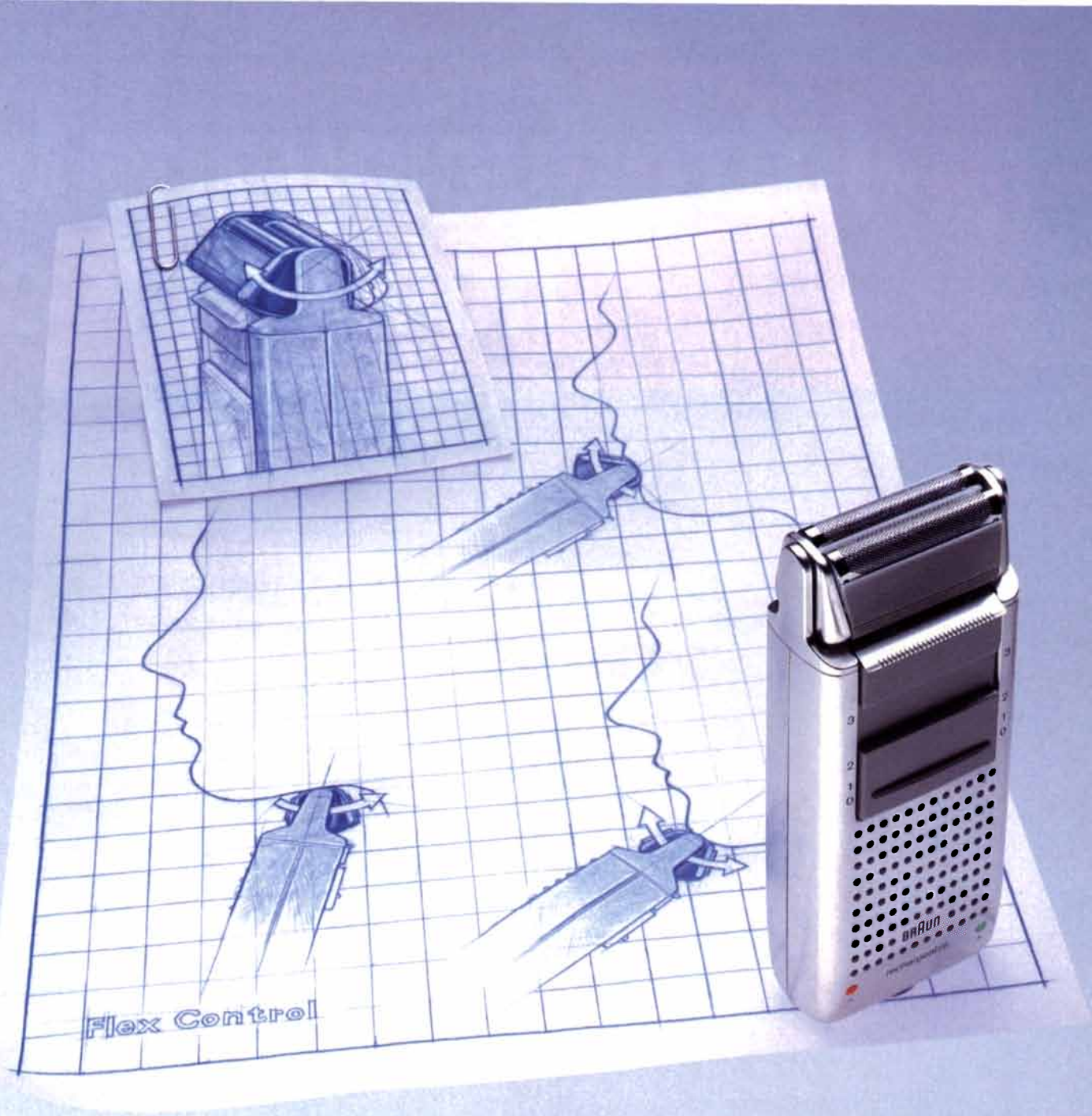
Other researchers, including Donald L. Price and Lary C. Walker of the Johns Hopkins University School of Medicine, have also examined Higgins's slides and the transgenic mouse brains for signs of amyloid plaques or other lesions. "There aren't any, at least in the mice I've looked at," Walker says. Neither he nor Selkoe could name an independent observer who had definitely examined the original published slides.

Responding to the concerns of several researchers that scientific misconduct might be involved, the NIA issued a request for an inquiry into the matter, according to a spokesperson for the agency. The National Institutes of Health refuses to comment on the existence of an inquiry, but sources close to the case confirm that one is in progress. Neither Higgins nor Gordon responded to requests for interviews.

In defense of Higgins, George R. Martin, the head of intramural research at the NIA, points out, "It seems crazy that there would be any kind of deliberate fraud. All these people are very productive, very well known scientists." Transgenic mice are variable and difficult to study because their numbers are so few, Martin explains. "I would always look for an error of some sort before I would think in terms of misconduct."

Unfortunate errors were certainly the undoing of the Wirak model. Mathias Jucker (now at the Swiss Federal Institute of Technology) and Walker heard a warning bell when they read the results of the Wirak report. Months earlier they had observed that normal mice belonging to the C57 strain sometimes had clusters of unidentified material in their brains. Wirak and the Miles Research group had used C57 mice in their experiments—and the structures tagged as amyloid deposits in the transgenic animals appeared identical to the clusters.

Jucker, Walker and their colleagues contacted the Miles group, compared data and carried out further experiments that confirmed the similarities.



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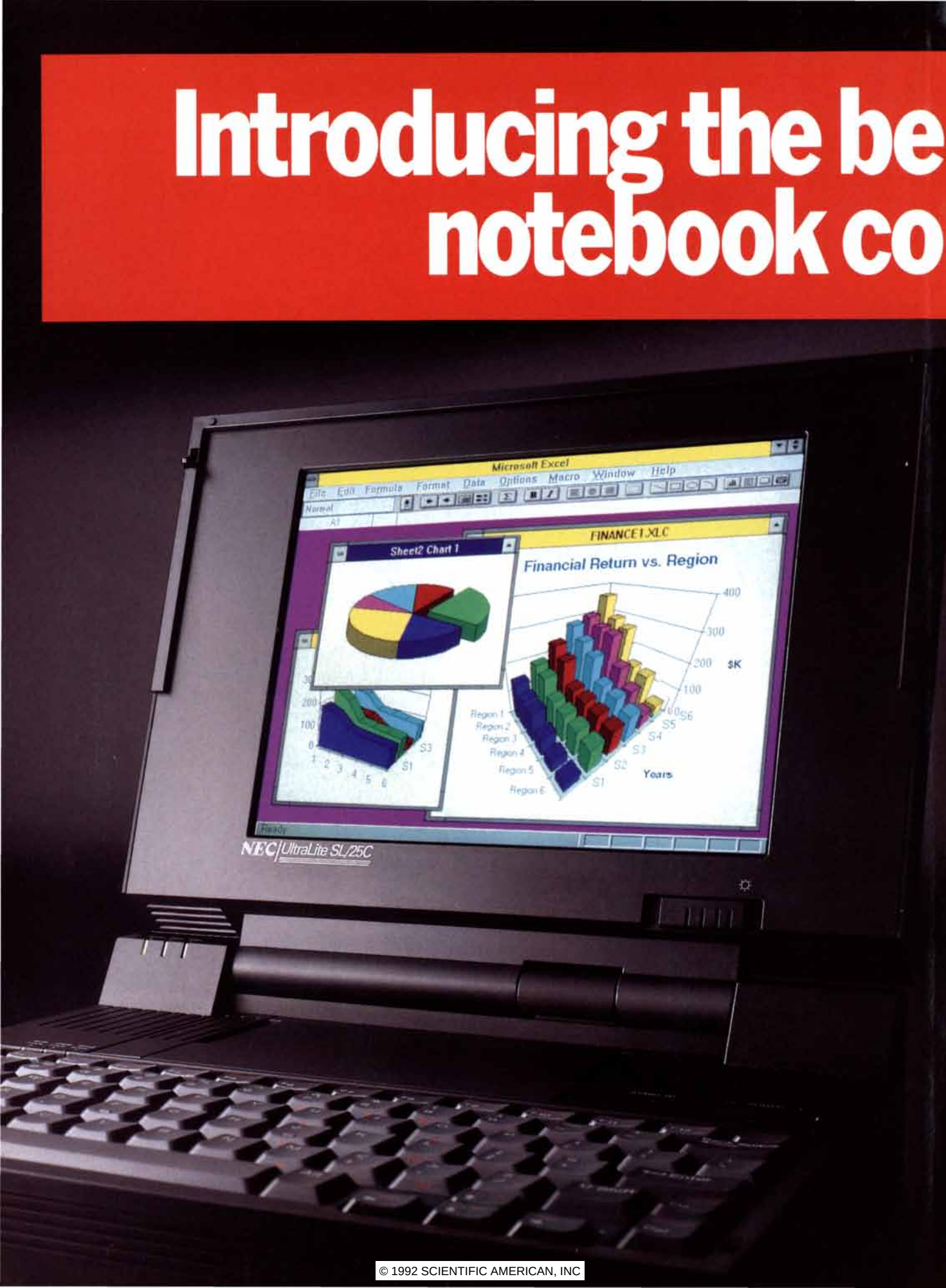

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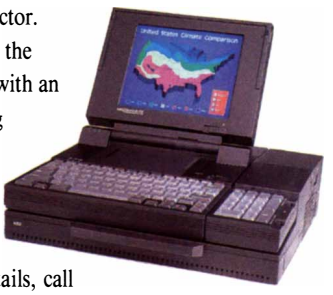

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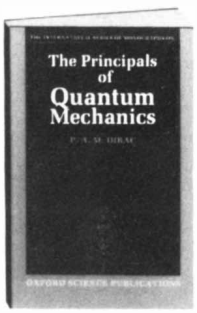

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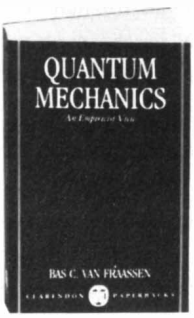

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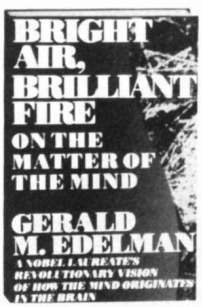

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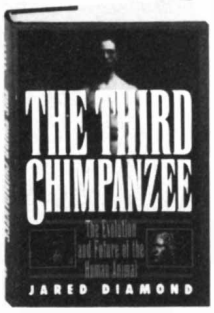

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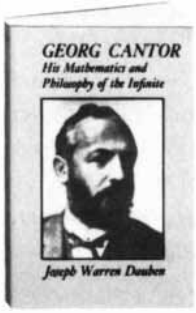

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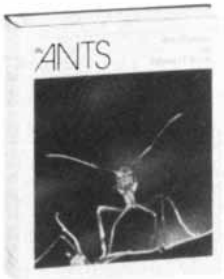

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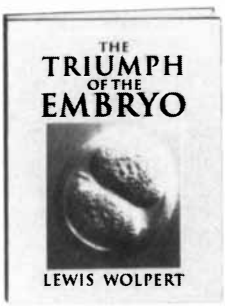

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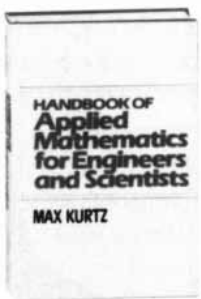

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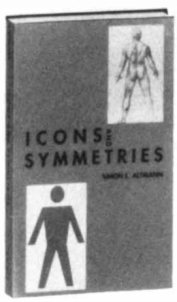

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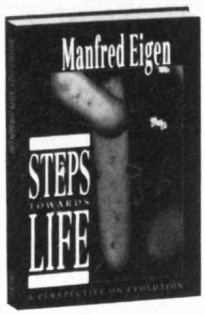

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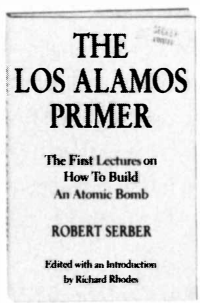

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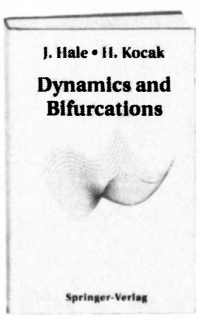

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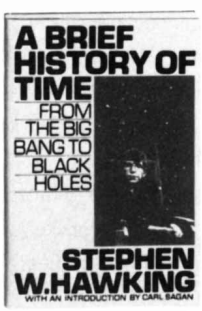

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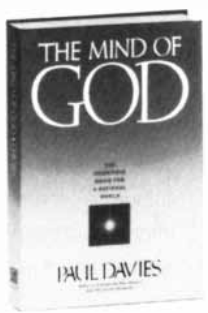

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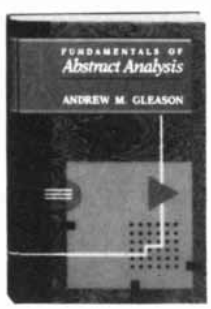

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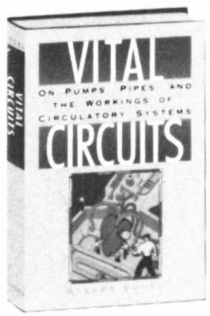

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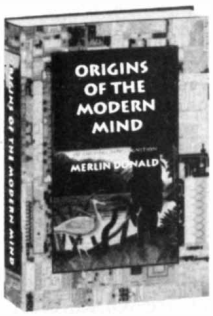

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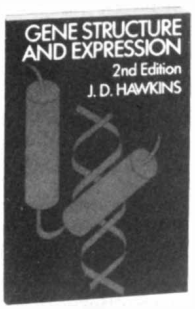

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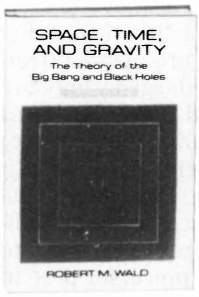

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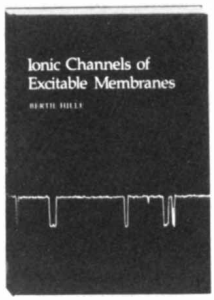

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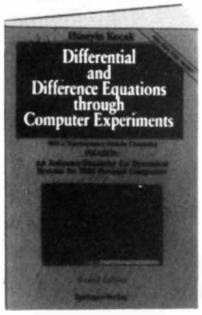

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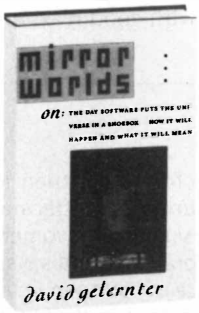

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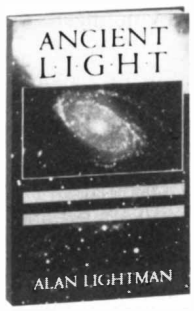

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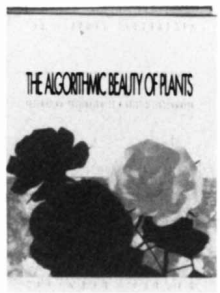

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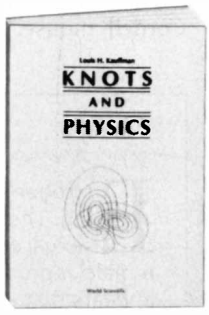

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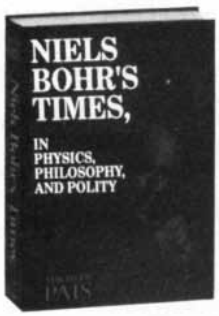

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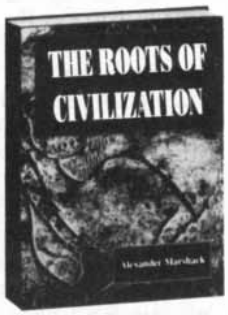

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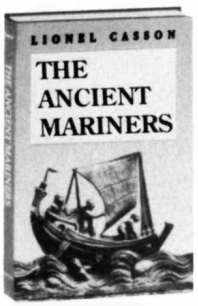

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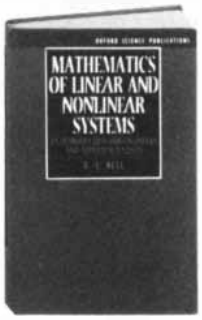

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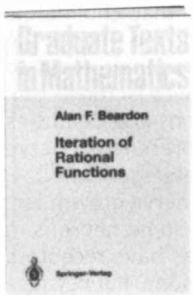

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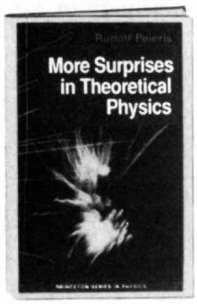

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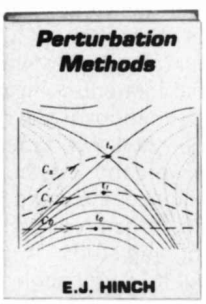

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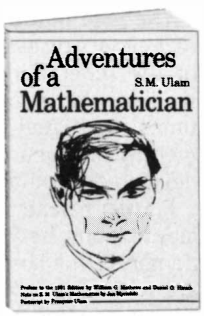

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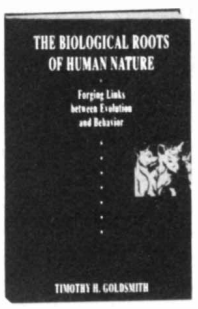

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Scientific American 6/92

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The Miles researchers retracted their paper in March in *Science,* only a week after Kawabata, Higgins and Gordon retracted theirs. As Wirak and his coauthors noted, they had not examined enough normal C57 mice to become aware of the occurrence of the clusters. Because the clusters have a "nonspecific stickiness" for many antibodies, Walker explains, they bound antibodies against beta-amyloid and misled Wirak's group into identifying them as plaques of beta-amyloid.

The two retractions leave only the Cordell mouse. Its validity is not in doubt, but as Cordell acknowledges, it is too incomplete as a disease model to use in realistic tests of potential treatments. Many other transgenic mice are now being developed, Selkoe says, but none of them are known to produce much amyloid protein or to form it readily into plaques. "The whole experience with transgenic mice so far indicates that it's very hard to get them to express the amyloid precursor protein and to slice it up in a way that makes plaques," he concludes.

The quest for an animal model of Alzheimer's disease is by no means exhausted. Moreover, Walker believes all the transgenic mice, even those of the retracted models, still hold promise. "Even if the mice don't develop frank Alzheimer's-like pathology in the normal course of events, it might still be possible to perturb the system in some way to induce those changes," he explains, adding, "It's a hot field, and I hope this setback won't throw too much cold water on it." Martin notes that researchers at the NIA are working on new transgenic models. "We're encouraging them to be cautious," he says, with good reason. —*John Rennie*

The Estrogen Factor

Estrogen's sphere of influence seems to keep growing. The queen of hormones orchestrates aspects of sexual differentiation in the developing brain, directs female reproduction and can slow osteoporosis. Now it appears that estrogen may have a part to play in the treatment of Alzheimer's disease as well.

Researchers at Columbia University have found that receptors for estrogen and nerve growth factor coexist in certain neurons in an area of the brain called the basal forebrain. This finding suggests that estrogen and nerve growth factor may act synergistically or reciprocally to influence the survival and health of these neurons. "It is a very important finding," comments Patricia Goldman-Rakic, professor of neuroscience at Yale University. The discovery of "their interaction is really novel."

The implications for Alzheimer's disease are straightforward, Goldman-Rakic says. Although the study, which was led by C. Dominique Toran-Allerand, was conducted in rats and mice, the basal forebrain of all mammals contains cholinergic neurons. These nerve cells produce the neurotransmitter acetylcholine, which is vital for memory. One characteristic of Alzheimer's disease is that cholinergic neurons can no longer produce acetylcholine—hence the loss of memory. Many scientists are examining ways to treat cholinergic neurons with nerve growth factor, a compound that stimulates the growth of axons and dendrites and that keeps nerve cells alive. In the presence of nerve growth factor, cholinergic neurons do not degenerate.

Toran-Allerand's findings suggest that nerve growth factor alone may not always be sufficient. Some neurons in the basal forebrain as well as other areas have receptors for nerve growth factor or for estrogen alone. But because receptors for estrogen and nerve growth factor are present in some of the same neurons, both compounds may influence the same cell, she explains. In addition, Toran-Allerand says she has found other potential evidence of such interaction. The gene sequence of nerve growth factor contains what is called an estrogen response element. "Everywhere there is nerve growth factor, it appears there is estrogen," Toran-Allerand notes. "It may be a universal principle."

This discovery may hold particular relevance for women. More than half of the estimated four million Americans who have Alzheimer's disease are women. But whereas the prevalence rates for women are greater than those for men—perhaps because women live longer—it has also been suggested that women acquire the disease more frequently. If estrogen is necessary for the development and survival of neurons in the basal forebrain, then losing their major source of estrogen during and after menopause or after ovariectomy may put vulnerable women at greater risk of Alzheimer's disease, Toran-Allerand says. (Men, in contrast, have an intrinsic source of estrogen in testosterone, which can be converted to estrogen in the brain.)

Although they have been few and far between, several studies support this hypothesis. During the early 1980s, Victoria N. Luine, now at Hunter College, found that estrogen could cause the production of the enzyme that synthesizes acetylcholine in parts of the brain of ovariectomized female rats. Luine's findings prompted Howard Fillit, now at the Mount Sinai Medical Center—and, later, a team of Japanese scientists—to give estrogen to a small group of women with Alzheimer's disease.

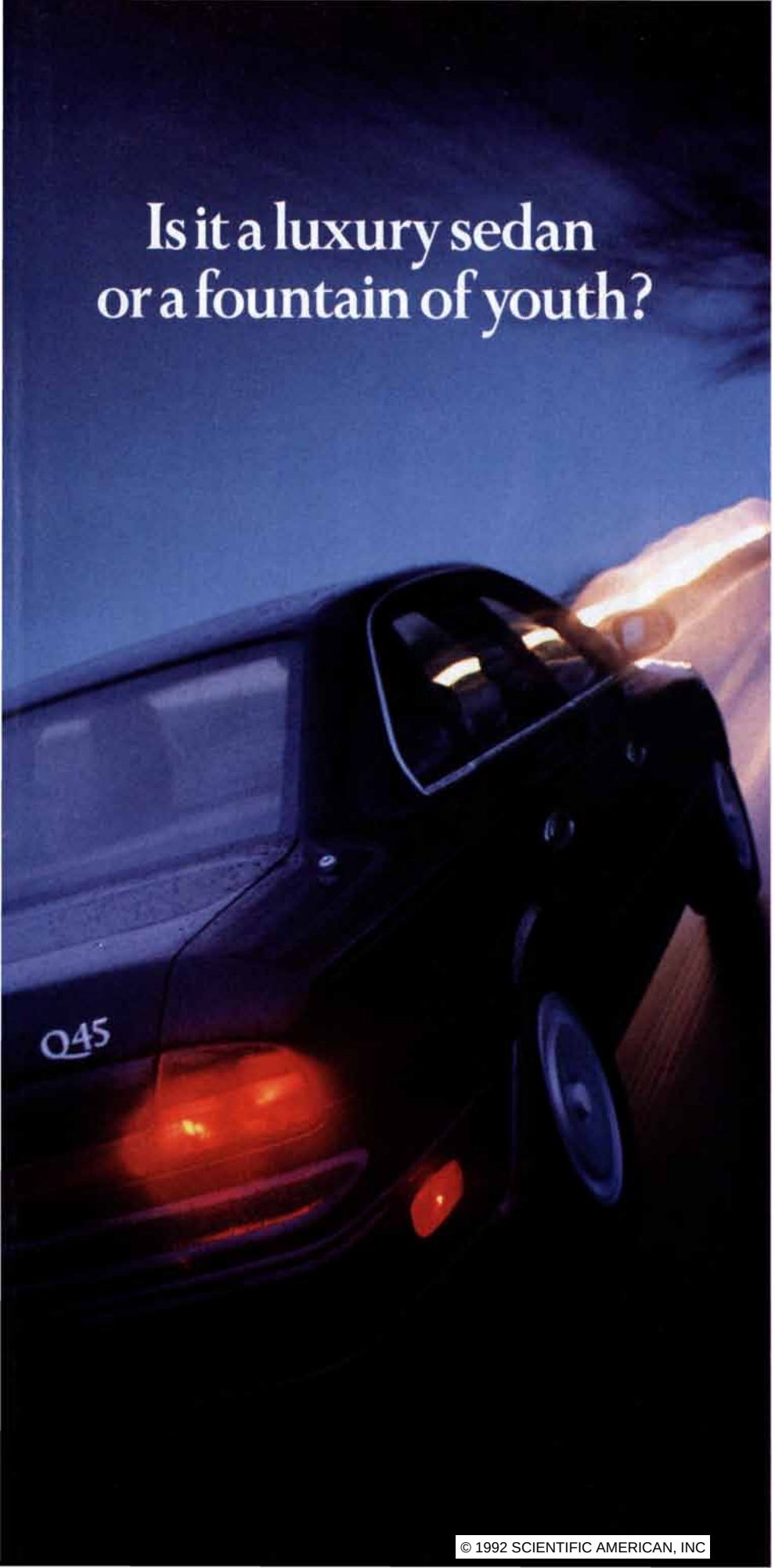
Both groups found that aspects of dementia diminished in certain patients after treatment. But some researchers were critical of the studies. They questioned the small sample size and argued that estrogen had already been shown to improve mood in postmenopausal women. Therefore, they contended, mood enhancement accounted for the apparent reversal of aspects of dementia.

Nevertheless, many researchers remain intrigued. Barbara B. Sherwin and Susana Phillips of McGill University, who study estrogen replacement therapy in women, have found that it enhances short-term memory. But Sherwin observes that "mood in and of itself cannot account for the changes in cognitive function that we see."

"A number of very smart, well-trained people have said anecdotally that in clinics where elderly women are treated with estrogen replacement therapy, they don't see Alzheimer's disease," observes Teresa Radebaugh, chief of the dementia and aging branch at the National Institute on Aging. "It could be a total mirage, but it is certainly worth looking at, particularly given Toran-Allerand's findings."

The idea that estrogen deficiency could contribute to Alzheimer's disease has other support. Miriam K. Aronson of the Albert Einstein College of Medicine found that women with myocardial infarction—heart attacks sometimes associated in postmenopausal women with plummeting estrogen levels—were five times more prone to develop dementia than were those without such a history.

Further research is planned, including looking at the relation, if any, between estrogen replacement therapy and dementia in a large, ongoing study. "A number of people are starting to talk about it," Radebaugh says. "It is a fascinating question." —*Marguerite Holloway*



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Weird Wonders

Was the Cambrian explosion a big bang or a whimper?

The turbulent sediments of paleontological thought are being roiled by a new and passionate debate. At issue is why so many curious animals seem to have evolved at more or less the same time, at the start of the Cambrian era, about 560 million years ago.

At the center of the dispute is the iconoclastic Harvard paleontologist Stephen Jay Gould. He rejects the usual explanation for the "Cambrian explosion." According to this view, many new ecological niches—such as becoming a predator—opened up when animals first evolved extensive hard tissues. Gould does not see how such an event can account for the astonishing range of bizarre creatures exquisitely preserved in the mid-Cambrian Burgess Shale in British Columbia.

In his 1989 book, *Wonderful Life,* Gould argued that special evolutionary processes must have occurred to create such "weird wonders." He scandalized paleontologists even further by arguing that chance rather than genetic fitness was the principal agent that selected which of the curious animals then living would populate the earth with their descendants.

More traditionally inclined paleontologists are not letting such radical notions harden into accepted theory. "We are concerned that Gould's claims are rather larger than the evidence can actually bear," says Richard A. Fortey of the British Natural History Museum. And Derek E. G. Briggs of the University of Bristol, who reconstructed many of the Burgess fossils and was one of the heroes of Gould's tale, is now arguing against its conclusion. Briggs says he is trying to "dampen the Cambrian explosion."

The fossils in the Burgess Shale are indeed puzzling. Most of them, just a few centimeters long, have been reconstructed over the past decade by paleontologists working in England. Among them are Briggs and his colleagues Harry B. Whittington and Simon Conway Morris of the University of Cambridge. Many of the fossils are thought to be arthropods, but some resemble crustaceans, whereas others have characteristics of spiders and scorpions, horseshoe crabs or trilobites. Yet most of the fossils are not strictly any of these things. They have too many head segments or too few antennae or some other feature that prevents them from fitting into known groups.

Gould recounted in *Wonderful Life* that at least eight Burgess Shale forms did not conform to any of the high-ranking groups called phyla. Among these evolutionary quirks were *Hallucigenia,* a wormlike creature that Conway Morris named for its "dreamlike appearance," and *Wiwaxia,* also reconstructed by Conway Morris. *Hallucigenia* apparently walked on a double row of spines and bore a single row of tentacles along its back. *Wiwaxia* was a flattened oval creature that crawled through bottom sediments, its back covered with plates from which protruded two rows of spines.

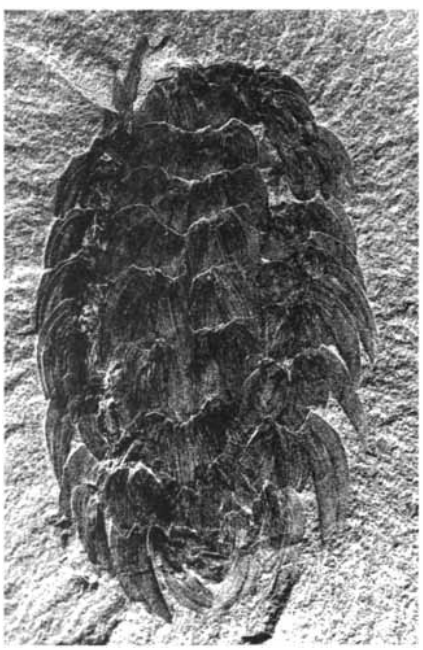
Inspired by such strangeness, Gould suggested that "today's oceans contain many more species based on many fewer anatomical plans." After the early Cambrian flowering, Gould argued, "the history of life is a story of massive removal followed by differentiation within a few surviving stocks."

It did not take long for other biologists to start picking holes in Gould's claim that the diversity of Cambrian animals could not have been produced by conventional evolution. Several reviewers pointed out that Gould's arguments rely on the taxonomist's habit of putting unfamiliar fossils into new classes. That practice "has the effect of exaggerating the apparent degree of disparity resulting from the Cambrian radiation," Briggs asserts. "The sample of [Cambrian] organisms available to us is both morphologically and ecologically less rather than more diverse than the living arthropod fauna."

Other paleontologists have come to similar conclusions about the dangers of using taxonomic oddity as a means of assessing diversity. Andrew B. Smith of the British Natural History Museum believes that several studies of echinoderms—starfish and the like—have fallen into the same error, falsely concluding that evolution was in overdrive during the Cambrian.

Moreover, some of Gould's prime examples of Cambrian uniqueness have started to disappear. Although at the time Gould wrote *Wonderful Life* paleontologists classified both *Wiwaxia* and *Hallucigenia* as creatures with no known relatives, opinions are changing. In 1990 Nicholas J. Butterfield of Harvard University published in *Paleobiology* a high-magnification study of the spines and plates of the enigmatic *Wiwaxia.* According to Butterfield, the results indicate that the creature can be classified as a polychaete worm, a well-known group with more than 5,000 living species.

Then, last year, L. Ramsköld and Hou Xianguang argued in *Nature* that *Hallucigenia* had seemed so strange to Conway Morris mainly because he had got it upside down. Minute comparisons with other fossils indicated that *Hallucigenia*'s two rows of spines were actually armor, not legs. And the single row of preserved tentacles was almost certainly half of a pair of rows of tentacular legs. The inverted *Hallucigenia*



BIZARRE FOSSILS from the Burgess Shale in British Columbia are being recognized as members of known groups. **Wiwaxia corrugata (left)** ***may be related to the living*** **Bhawania heteroseta (right),** ***a polychaete worm.***

STONEHENGE AND THE SPACE TELESCOPE

Over 4,100 years ago a Neolithic people built a remarkable monument on a windswept plain near what would one day be Salisbury, England. But though the builders of Stonehenge worked only with Stone Age technology, they were in fact building an astronomical computer.

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A leap of forty-one centuries and we are still faced with the same cosmological questions that drove the prehistoric Britons to build Stonehenge. The Hubble Space Telescope will help us solve these primeval mysteries. It will be able to detect objects as far as fourteen billion light-years away, and witness events shortly after the beginning of time.

The Space Telescope represents a momentous leap in the history of mankind. The builders of Stonehenge must have felt themselves on the verge of the same kind of moment as they discovered that creation actually had order. Within our own grasp is a view of the creation itself.

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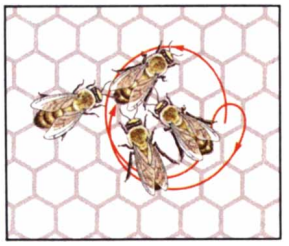

From The Honey Bee, *foragers dance to indicate a food source; drawing by John Hatzakis, adapted from K. von Frisch,* Tanzsprache und Orientierung der Bienen.

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From Eye, Brain, and Vision, *the neurobiology group at Harvard Medical School, 1963, including Nobel Prize winners David Hubel, standing right, and Torsten Wiesel, seated right. Photograph by Joseph Gagliardi.*

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◄ *From* From Quarks to the Cosmos, *a schematic of a particle collider detector; drawing by George Kelvin.*

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AN EXCITING NEW GENRE IN THE LITERATURE OF SCIENCE

thus became recognizable as a member of the phylum of soft-legged worms known as Onychophora (although some researchers, including Butterfield, are not convinced).

Other anomalous Burgess Shale fossils might follow *Wiwaxia* and *Hallucigenia* into respectability. *Amiskwia,* a rare Burgess Shale swimming organism that Gould believed was an orphan, might actually belong to the obscure phylum known as Chaetognatha, Butterfield contends. And according to Conway Morris, even Gould's prize superweirdo, a startling, large predator called *Anomalocaris,* may be related to a newly discovered fossil group.

Gould is not giving up the fight. He says the recent recognition that *Hallucigenia* and *Wiwaxia* may belong to known phyla cuts both ways. Their new status may decrease the number of Cambrian phyla, he points out, but it increases the diversity within the remaining phyla. And in any event, there are plenty of other strange cases. "Much as I hate to lose an example," Gould says, "if I had to lose one it would be *Hallucigenia.* The fact remains that the Cambrian was a melting pot."

But Gould has made one tactical retreat. In *Wonderful Life* he derives strong support for his argument from Burgess Shale creatures that cannot be assigned to known groups. But he now concedes that taxonomic strangeness is itself irrelevant for assessing diversity. Gould acknowledges that his claim of extraordinary variety "cannot be confidently established until we develop quantitative techniques for the characterization of morphospace."

Unfortunately, it is far from clear how evolutionary variety can be measured without bias, because the entire Linnaean classification system for animals is based on living organisms. "Our modern prejudices influence our perceptions of morphological disparity," says Mark Ridley, an evolutionist at Emory University. But Fortey and Briggs are trying to assess diversity in an unbiased way, and according to Fortey, "so far the evidence is either ambiguous or does not support Gould."

Despite the disputes, everyone agrees that the Cambrian was a period of rapid change. The question is whether it was so rapid that unconventional evolution is needed to explain it. Until paleontologists achieve a better understanding of the Cambrian explosion, Ridley says, such unconventional hypotheses are "a solution awaiting a problem." And Lady Luck remains tantalizingly in the shadows, pulling some of evolution's strings—but nobody knows how many. —*Tim Beardsley*

Astronomical Austerity

Lean times loom for space science

In front of an Academy Awards audience numbering in the millions, smiling astronauts on board the space shuttle *Atlantis* huddled around a floating, weightless Oscar to salute George Lucas, the director of the science fiction movie *Star Wars.* The moment was a public relations coup for the National Aeronautics and Space Administration, but it will take more than show biz to cheer up space scientists. A clash between ambitious plans and tight budgets at NASA means that several major research projects are being trimmed or terminated in the agency's 1993 budget.

The *Comet Rendezvous/Asteroid Flyby* probe, designed to study two of the least understood kinds of objects in the solar system, is canceled. A sophisticated orbiting x-ray telescope known as the *Advanced X-ray Astrophysical Facility* will be delayed and may be scaled back. Another space-based observatory, the *Space Infrared Telescope Facility,* vanished from the 1992 budget and does not reappear in 1993. These two telescopes were intended to work alongside the *Hubble Space Telescope* and the *Compton Gamma Ray Observatory* to explore the universe at a wide range of wavelengths.

The insult most aggravating to space scientists is that NASA's 1993 budget contains no funds for the continued operation of *Magellan,* the still functioning probe now mapping the surface of Venus. "I can't believe they are going to turn off a live spacecraft," laments William L. Sjogren of the Jet Propulsion Laboratory. *Magellan*'s annual operating cost is only about $30 million, and some scientists suggest they could make do with as little as $10 million next year. But as John M. Logsdon of George Washington University comments, "In the present budget situation, even a dollar is not a minuscule amount."

Plans originally called for changing *Magellan*'s orbit so that the probe could produce high-resolution measurements of Venus's gravity, information crucial for understanding the planet's internal dynamics. A coalition of scientists is working on a compromise that will spread out money from the 1992 budget to allow *Magellan* to collect some data on gravity during early 1993.

These cutbacks reflect a piecemeal response to a broader conflict between NASA's past plans and its future funds. During his confirmation hearing before the Senate, Daniel S. Goldin, the agency's brand-new administrator, admitted, "I don't think we can do everything that sits on the plate."

The Earth Observing System, a fleet of satellites designed to monitor the global environment, will consume more than $1 billion a year by 1995. Expenditures for Space Station *Freedom*—already more than $2 billion in 1992—are scheduled to increase sharply in the next few years. Simply continuing NASA's existing projects will require roughly $20 billion a year by the mid-1990s, according to the Government

STELLAR PERFORMANCE: shuttle astronauts give a cheery plug for the nation's manned space program. Meanwhile space science is suffering. Photo: NASA.

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Accounting Office. But the Bush administration's present five-year plan calls for NASA's annual budget to remain unchanged at $14.99 billion through 1997.

Few space scientists want to provoke a budgetary showdown between space science and the space station. "If there were no space station, there would be more money for space science," says Larry W. Esposito of the University of Colorado, "but that would also be true if there were no S&L bailout." The sheer cost of *Freedom* may nonetheless force NASA to reassess its plans. "I see an opportunity for the space station to self-destruct," Logsdon says hopefully.

Regardless of the station's fate, everyone agrees the era of billion-dollar space science missions is over. Goldin is known to favor a "smaller-faster-cheaper" philosophy, and the buzzword at NASA these days is "descoping." To achieve off-earth *Fahrvergnügen,* the large space-based infrared telescope is being reconfigured to be "more in line with the current budget constraints," says Larry J. Caroff, chief of the Infrared-Radio Astrophysics Branch at NASA. The *Advanced X-ray Astrophysical Facility,* which received $151 million in 1992, is likewise being redesigned to be more cost-effective. It may end up flying as two or more smaller missions, according to Alan N. Bunner, the project's program scientist.

Ambitious, costly planetary missions are also on the way out. "Small craft are the wave of the future," says Carl B. Pilcher, who heads the advanced studies branch of NASA's solar system exploration division. The *Comet Rendezvous/Asteroid Flyby* appears to be dead, and scientists working on *Cassini,* a similar companion probe destined for Saturn, fear their project is next. Engineers at the Jet Propulsion Laboratory are struggling to save *Cassini* by lowering its cost from $1.6 billion to $1.4 billion or less—still a hefty amount by present standards.

Upcoming projects at NASA should reflect a leaner approach. The 1993 budget contains funds for two new lunar mapping missions to be built around low-cost existing technology components; the two together will cost only about $300 million. "I find this very refreshing," says Paul D. Spudis of the Lunar and Planetary Institute. "This is the way we did things back in the 1960s." The two probes are the first step in the new Space Exploration Initiative, which also embraces the far more expensive goal of human exploration of space.

NASA plans a series of bargain-basement solar system expeditions, known as Discovery missions. The first two, a prototype Mars lander and a mission to rendezvous with an asteroid, will start up in the mid-1990s, if funding materializes. Each Discovery mission should cost no more than $150 million and require only three years to complete. Later in the decade the agency hopes to begin work on a probe to sample the nucleus of a comet or to fly past Pluto. Even these more ambitious missions should cost well under $1 billion.

Whether even NASA's reduced space science plans come to fruition largely depends on the political support in the White House and Congress. Scientists and NASA planners hold out hope that Goldin is the right person to cut through the bureaucracy and give shape to a streamlined, more efficient agency. Meanwhile the transition period is proving to be painful. "Anybody can manage when budgets are increasing," Pilcher reflects. "The real challenge is when you don't have that kind of access to resources." —*Corey S. Powell*

A Switch with the Right Spin

In recent years, researchers have exploited the behavior of single atoms and even single electrons to make transistors, devices that turn on and off the flow of electric current. Now a physicist has built a transistor out of a single spin, what might simply be called an atomic-scale magnet. The "spin transistor" is far from becoming a viable technology, but it has provided investigators with an unprecedented opportunity to study the interactions between electrons and spins.

Stephen Gregory of Bellcore built the spin transistor by placing a thin layer of helium between two tungsten wires. He demonstrated that under certain conditions, a single magnetic particle—a spin—could become trapped at the interface between the helium and one of the wires. In the absence of such an impurity, the helium layer would behave like an insulator, allowing electrons only a small chance to tunnel through the layer. Yet when a spin does get trapped, something quite remarkable happens. The spin organizes the flow of electrons through the helium. Indeed, as Gregory reports in the March 30 issue of *Physical Review Letters,* electrons could pass through the helium layer at a rate of 10 trillion per second.

Surprisingly, Gregory could shut off this torrent of electric current by moving the wires together by a minute amount. He suspects that the movement pushes the spin farther into the helium layer. In this position, the spin does not interact strongly with the tunneling electrons, and the flow of electrons decreases substantially. "The most impressive thing is that we are actually looking at the interaction of electrons with just one spin," Gregory explains.

Gregory believes the spin is most likely the magnetic moment of an electron trapped at the edge of the helium layer. It is also possible the spin is associated with an oxygen atom that has found its way into the helium or maybe a tungsten atom that is loosely attached to the surface of the wire. Despite this uncertainty, Gregory says "there is no question that the effect is due to a single spin."

During the 1960s, physicists first realized that magnetic particles in an insulating material could influence the tunneling of electrons. The magnetic particles interact with the tunneling electrons and facilitate their motion through the insulator. This phenomenon, known as the Kondo effect, increases the flow of electrons through the insulator. The effect the Bellcore physicist measured is "at least 100 times bigger than anything that has ever been seen before," he comments.

To make a spin transistor, Gregory hangs two tungsten wires in a small evacuated cell so that one wire rests slightly above and perpendicular to the other. By passing a strong current through the wires, Gregory heats them white-hot, removing all dirt and debris from their surfaces. He then cools the wires to temperatures near absolute zero. Gregory can then move the wires together by applying a magnetic field and changing the electric current that flows through one of them. He can thereby shift one of the wires until it just touches the other. Next he fills the cell with helium gas, which adheres to the wires and forms a coating that is a few atoms thick.

The spin transistor should allow physicists to study the interactions of tunneling electrons with a single spin. The results could yield a better understanding of magnetic interactions in materials and may even provide insights into superconductivity, a phenomenon that depends, in part, on the interaction among spins. Gregory's work should also guide technologists as they strive to build ever smaller electronic devices. —*Russell Ruthen*

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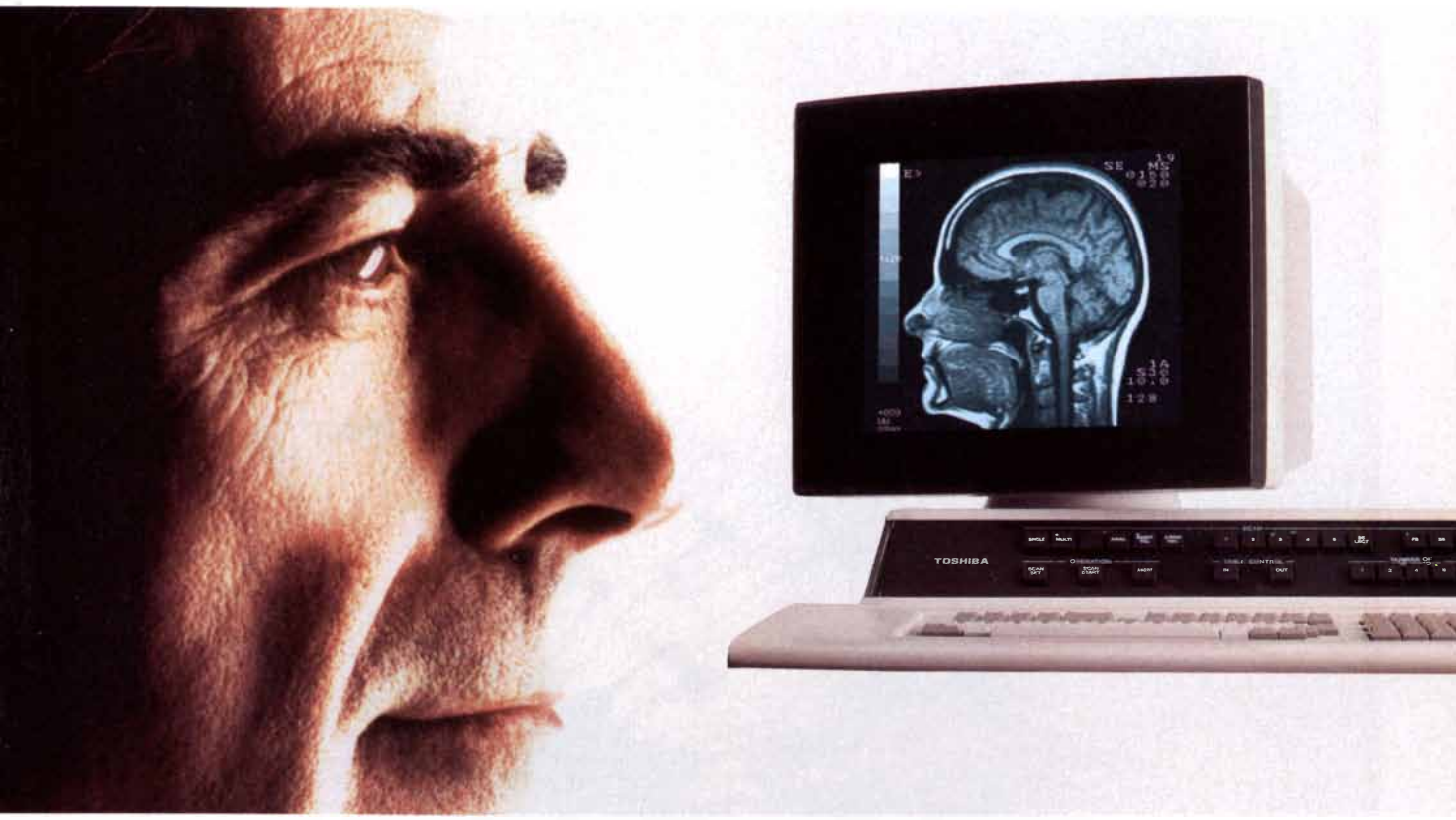

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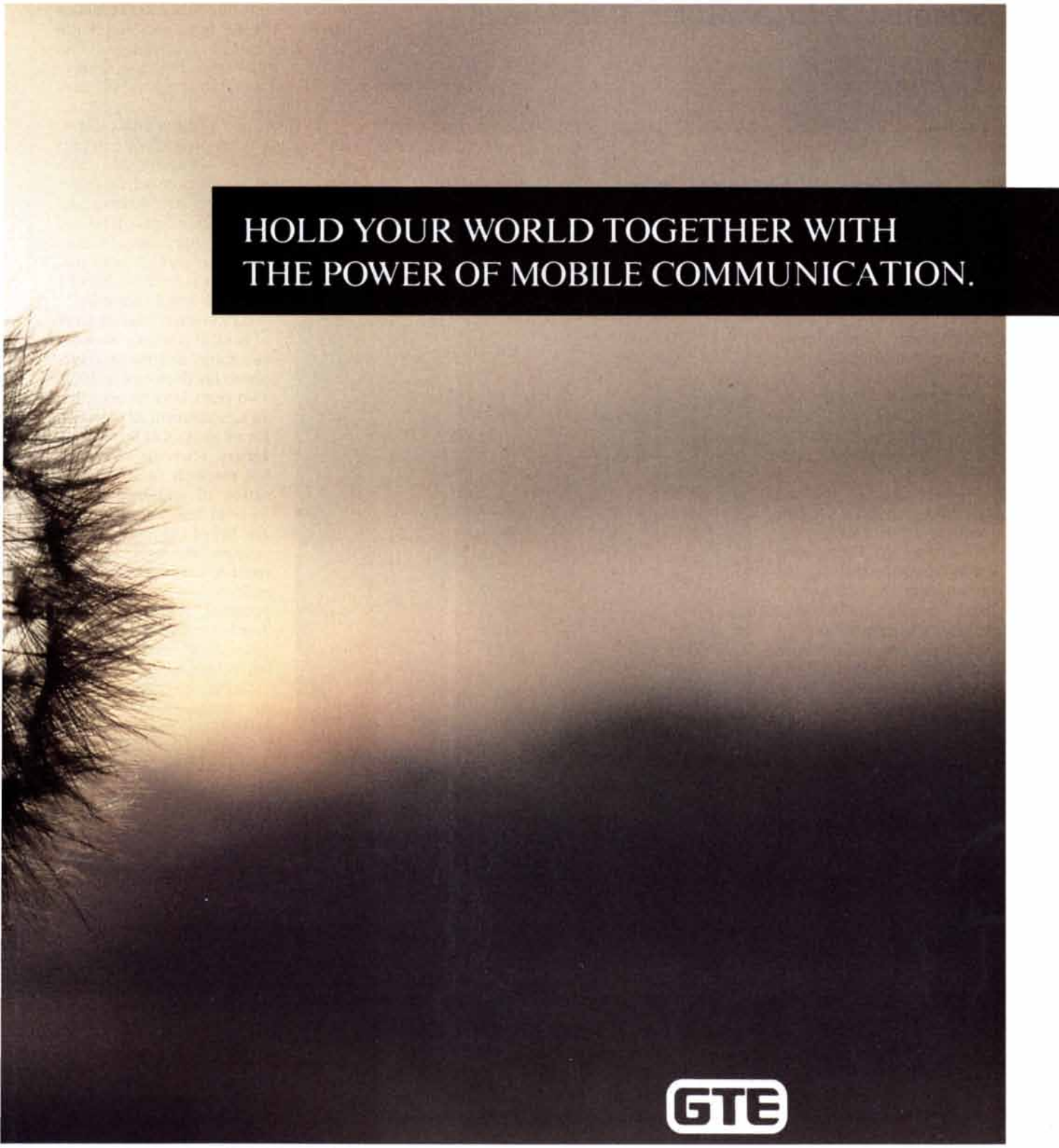


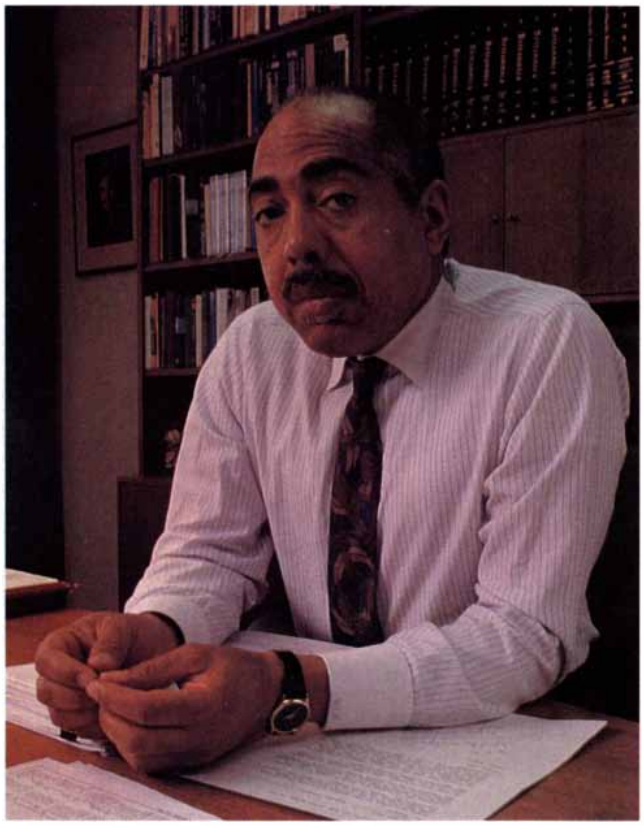
THE POWER IS ON

Scientist, Administrator, Role Model

Walter E. Massey's start in life did not put him on the direct road to leadership of a major government science foundation. Massey, now 54, grew up in Hattiesburg, Miss., long before the famous freedom bus ride. And he left high school at the end of 10th grade, thus managing to avoid even the rudimentary science courses that Royal Street High School had to offer.

But as a child, Massey had an unusual passion: arithmetic. "There was just something about sitting down and working through problems," he recalls with evident pleasure. His flair won him a scholarship to Morehouse College in Atlanta, Ga., and a chance to enter a different world.

Massey has just finished the first year of a six-year term as director of the National Science Foundation (NSF), the principal federal grant agency for nonmedical basic research. In addition to having been a full professor of physics at two major universities, Massey has been thoroughly groomed to be a science policy official. Before becoming director of the NSF, he was on the National Science Board, which oversees the NSF, and was a member of the President's Council of Advisers on Science and Technology. He has also served as director of Argonne National Laboratory and was president of the American Association for the Advancement of Science.



WALTER E. MASSEY wants to encourage women and members of minorities to go into science and engineering.

In his bureaucratic command post, Massey maintains the casual air of a bench scientist. He wears slacks and an immaculate sweater rather than the suit or blazer usually favored by Washington types. A man who manages to be both dignified and open, he affects none of the hauteur sometimes noticeable in senior officials. Massey likes to keep fit. He plays tennis enthusiastically, bicycles and makes frequent use of an exercise machine in a room adjoining his office. He moves quickly and quietly, with an air of attentive calm, but soon relaxes when reminiscing about his past.

Massey attributes his success largely to the influence of exceptional teachers. At Morehouse, still "very uneducated" in science, he adopted Sabinus H. Christensen as a mentor. Christensen, a white man teaching at a traditionally black college, was, Massey says, responsible for inspiring a good proportion of all black U.S. physicists to earn their Ph.D.'s. To this day he has few imitators. The only time Massey raised his voice in anger during two interviews was when he expressed his "great concern" at the dearth of Ph.D.'s awarded to blacks (according to the NSF, 340 Ph.D.'s in science and engineering were awarded to blacks in 1990, out of a total of 14,776).

Massey was the only physics major in his class, so his lessons with Christensen became tutorials. After earning a bachelor's degree in physics and mathematics, he enrolled at Washington University, where Eugene Feenberg, a theoretical physicist, took him on as a graduate student.

Like many doctoral candidates, Massey was often tempted to quit, in part because of a lack of role models. "You just didn't go to graduate school in science," he remembers. But Feenberg provided strong encouragement. "If he had not taken extraordinary care, I would have quit," Massey says. "I was just lucky. That kind of effort he put forth is not common."

Lucky or not, Massey went to work at Argonne National Laboratory in 1966 and completed his doctorate in 1968. Two years later he accepted an appointment as a professor of physics at Brown University. There he continued his research on the application of quantum theory to solid and liquid helium. The life of the mind did not weaken Massey's commitment to social issues. While at Brown, he also founded a program, called Inner City Teachers of Science, to educate science teachers for urban schools.

Massey discerns a powerful factor that discourages women and members of racial minorities from entering science or staying in it after winning a degree. That factor is the lack of mentors and social networks. He is only half joking when he says he used to give speeches in which he would urge universities to double the number of black Ph.D.'s they graduate. But that number was so often zero that he had to change the recommendation to "double plus one."

Later, as a dean at Brown, Massey's talents as an administrator began to attract notice. In 1979 the University of Chicago lured him away to become professor of physics and to lead Argonne National Laboratory, which the university administers.

Massey knew the Argonne post would not be a comfortable one. At the time,

Argonne, as a civilian nuclear laboratory, was in serious trouble. The whole notion of national laboratories (other than weapons laboratories) was being called into question, and Argonne—like the others—was taking no special effort to make its discoveries available to industry. Massey responded by creating an organization, called ARCH, to transfer research results to the private sector. "I really credit Walter with the beginnings of a turnaround when there was a real possibility there would not be an Argonne," says Charles E. Till, head of engineering research at the laboratory. "He's fun to work with because he's a quick study, and he delegates well."

Massey says his experience at Argonne taught him the importance of finding the right people to make the bridge between the laboratory and the world of commerce. He has seen organizations fail "because they haven't taken care to ensure they have the right people." The trick, he observes, is to find people "who are comfortable in an academic culture but who have knowledge and an appreciation of the private sector." The other ingredient is time.

The lessons of technology transfer that Massey learned at Argonne are, he agrees, now helping him at the NSF. "That same end result is a very high priority for the foundation right now," he declares. Massey wants to expand incentives to encourage cooperation between industry and academia, such as fellowships for students to work in industry and grants for industry personnel to work in universities.

On the surface, things are going well for the NSF. President Bush has committed himself to the pledge originally made by Ronald Reagan to double the foundation's budget. The timetable, however, has slipped: the proposed budget for next year allots the foundation $3.02 billion. And unless the budget agreement struck last year between Congress and the White House is abandoned or revised, the Congress's financial largesse to the NSF is unlikely to continue, at least for the present.

Because of the way congressional committees divide their responsibilities, the foundation is competing against the Department of Housing and Urban Development and other domestic agencies for support from a fund whose size is now fixed. So at a time of lingering economic malaise, the level of basic science support may depend on how well Massey defends the administration's proposals before Congress.

Circumstances complicate the challenge. Although it is a traditional congressional favorite, the NSF has for the first time found its integrity challenged. In April, Massey went up to Capitol Hill to answer questions at a hearing held by Congressman Howard Wolpe of Michigan to look into a controversial NSF study known as the "shortfall study." The report was produced a few years ago by an NSF employee, Peter W. House, and it suggested that in the absence of corrective measures, there would be by 2006 a cumulative U.S. shortfall of some 675,000 scientists and engineers. The NSF document has been roundly condemned as erroneous and misleading by experts outside the foundation, and the shortfall—which Erich Bloch, Massey's predecessor, often translated as a "shortage"—has failed to materialize. Congress is also examining alleged contracting and other irregularities at the NSF.

Massey's disarming earnestness quickly lowered the chairman's hackles.

Congressional scrutiny required the experienced scientific administrator to be a polished politician. Fortunately for the foundation, Massey has that talent as well. After a tense morning, which included an exhausting interrogation of House, Massey assured the committee that no spurious data would ever be represented as scholarship under the NSF's imprimatur.

It was a consummate performance. With an easy smile for his interlocutor, Massey gave just enough to keep the attackers at bay but never impugned either his predecessor or House. Massey deftly deflected questions aimed at making him admit the failings of the shortfall study and avoided speculating about motives. Wolpe's temper had been rising throughout a morning of questions about the quality of analysis at the NSF, but Massey's disarming earnestness lowered the chairman's hackles. "Walter is one of the most articulate human beings I know," says Harvey Drucker, an associate laboratory director at Argonne. "He is a man of very high integrity and is very skillful with people," echoes Alan Schriesheim, the current Argonne director.

Massey's smooth style contrasts to that of Bloch. During his term as director, Bloch, a technologist who previously worked for IBM, began several programs to establish collaborative research centers with a distinctly applied focus. About 6 percent of the NSF's budget expended in the form of "Bloch" grants now supports such centers, some designated engineering research centers and others science and technology centers. But, observers say, Bloch's sometimes confrontational style and his pro-industry leanings earned him the enmity of many academics. Massey's instincts lead him to seek compromises, and he seems so far to have retained the goodwill of the research community. "We're fans of his," says Robert L. Park, a physics professor at the University of Maryland and public affairs director of the American Physical Society.

Massey says his principal goal at the NSF is to "contribute to the health of research institutions," primarily universities, which are going through turmoil. Next in importance he lists improving precollege science education, especially for women and minority groups. "Individuals can make a lot of difference," he says.

Grants to single investigators are now once again taking up an increasing share of the foundation's budget, and Massey says he is working on ways to reduce the paperwork burden weighing on investigators—and on hard-pressed foundation staff. Grant periods are already getting longer, and Massey wants to make the awards larger. He notes that the corollary—fewer grants—is unpopular. Massey denies any intention to roll back support for collaborative research centers, and indeed he says new centers are provisionally planned. But no new ones have been established in the year since he took office.

Massey and his team have introduced a string of management reforms at the NSF during the past year. The initiatives include the establishment of a new social sciences directorate. He has also revamped the foundation's long-range planning efforts and separated the planning function from budget preparation and monitoring. "I wanted to stress the question of how we know what we've accomplished when we've accomplished it," he explains. He has also begun meetings to increase the advice contributed by the private sector. Somehow he has managed to bring about these major changes with a minimal amount of fuss.

"Massey has the political instincts you need to negotiate around Washington," says Benjamin S. Shen, an astronomer at the University of Pennsylvania who is a member of the National Science Board. And that means he should be a survivor. Says Roland W. Schmitt, another board member, "He has got a lot of good will to burn up in cases where he has to." But so far there is little indication that Massey will have to draw on that resource. —*Tim Beardsley*

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Early Results from the Hubble Space Telescope

Although hampered by optical and mechanical flaws, Hubble has relayed a plentitude of eye-opening images and revealing spectral portraits of cosmic objects

by Eric J. Chaisson

On April 25, 1990, the *Hubble Space Telescope* was deployed from the bay of the space shuttle *Discovery,* marking the beginning of a new era in optical astronomy. Earthbound optical telescopes, ranging from Galileo's primitive spyglasses to the brand-new Keck Telescope, have always been hindered by the earth's restless, distorting atmosphere. From its vantage 610 kilometers above the surface, *Hubble* was designed to observe the cosmos in unprecedented clarity.

As nearly everyone knows, the telescope has not functioned as intended. A number of mechanical and design failings—most notably a misshapen main mirror—have degraded the telescope's capabilities. These difficulties dismayed many astronomers and attracted critical commentary from the media. But thanks to several improvised procedural changes and innovative computer image correction techniques, *Hubble* can match the sensitivity, and exceed the resolving power, of the finest ground-based telescopes. It can also detect ultraviolet rays (radiation having wavelengths slightly shorter than those of visible light), which do not penetrate the earth's atmosphere.

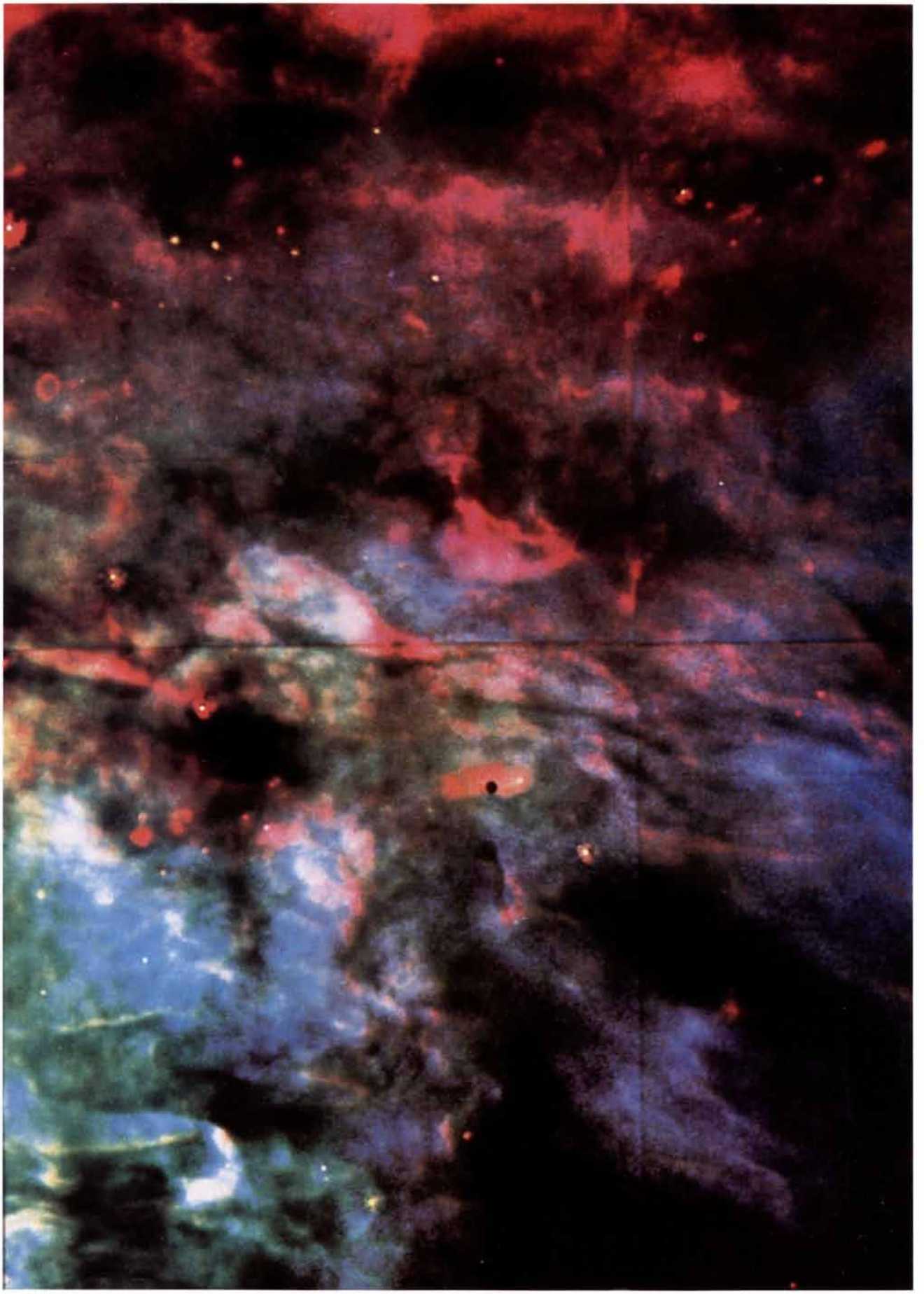
During its first two years of operation, the space telescope has served up dramatic views of storms on Saturn, of the birth and death of stars, and of enigmatic objects lurking in the hearts of galaxies—perhaps giant black holes. Individually, none of *Hubble's* discoveries yet qualifies as revolutionary. But taken together, they are sending astronomers scrambling to rewrite their textbooks.

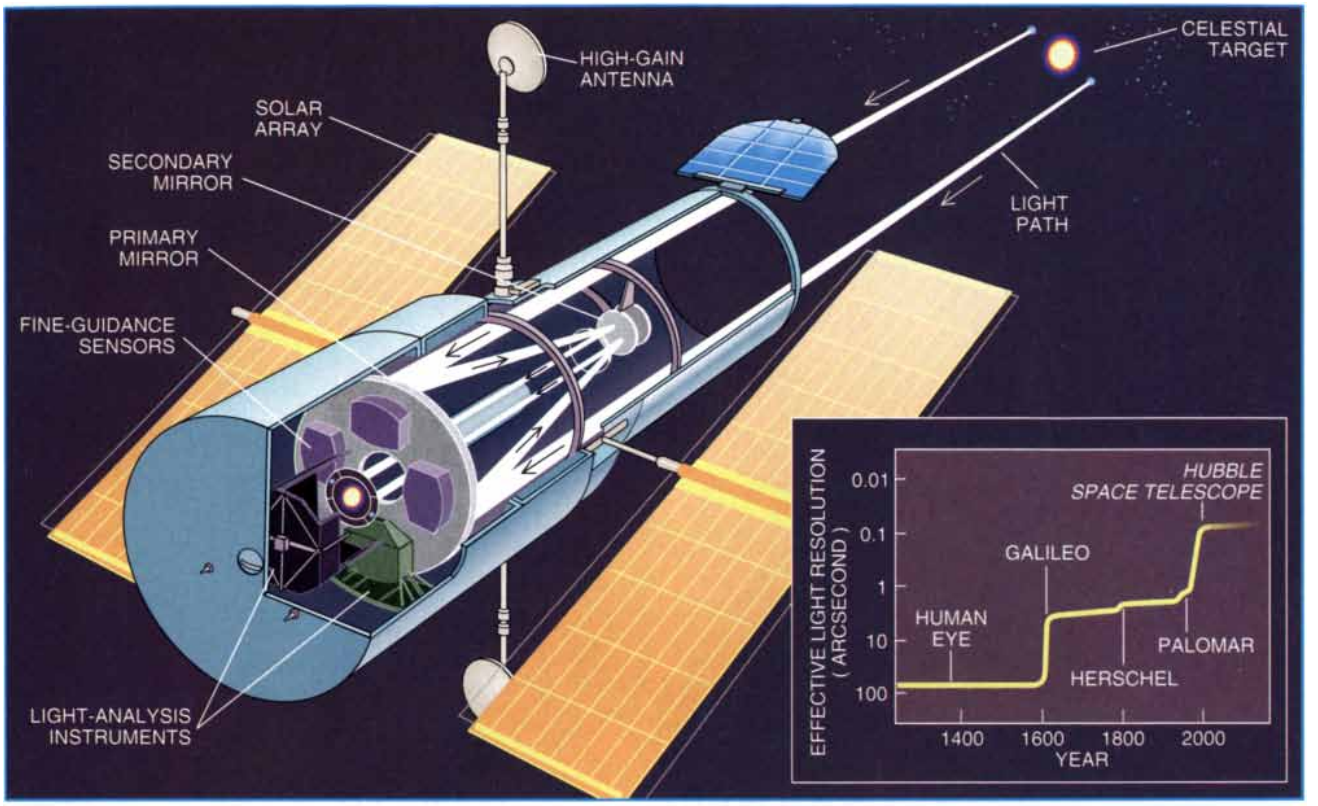
The 11,500-kilogram *Hubble Space Telescope* (six times the weight of a full-size automobile) is the most complex and sensitive civilian observatory ever launched into space [see "The Space Telescope," by John N. Bahcall and Lyman Spitzer, Jr.; SCIENTIFIC AMERICAN, July 1982]. Its 2.4-meter-diameter primary mirror is the smoothest and cleanest one in existence. An advanced guidance system keeps the telescope locked on its targets even as it whips around the earth once every 96 minutes. Five instruments analyze the light that it collects.

The Faint Object Camera offers exceptional sensitivity and resolution, whereas the Wide Field and Planetary Camera provides a broader view. Two spec-

ORION NEBULA, a 10-light-year-wide cloud of hydrogen gas, illustrates the capabilities of the *Hubble Space Telescope.* The nebula has been photographed extensively using terrestrial telescopes (*above*). *Hubble's* view of the boxed region (*right*) shows a snorkel-shaped feature (*at bottom*) and many previously unseen wisps and filaments. The jetlike formation (*at left*) appears to be matter flowing from a newborn star. The image is a composite, consisting of blue light emitted by ionized oxygen, red light from ionized sulfur, and green light from neutral hydrogen.

ERIC J. CHAISSON is deeply involved with both the research and public information aspects of the Hubble project. He is a senior staff scientist and director of educational programs at the Space Telescope Science Institute, located on the Johns Hopkins University campus. He is an adjunct professor of physics at Hopkins and an associate at the Harvard College Observatory. Chaisson earned a Ph.D. in astrophysics at Harvard in 1972. He joined the Space Telescope Science Institute in 1987. Chaisson has written extensively on relativity and cosmology. His interests include the thermodynamic evolution of material systems and public understanding of science and mathematics.





HUBBLE SPACE TELESCOPE **follows essentially the same design as do modern reflecting telescopes on the earth. The 2.4-meter-diameter primary mirror collects light, which is distributed among five analytic instruments. The telescope's focusing problem results from the primary mirror's incorrect curvature. *Hubble* improves on the resolution of ground-based telescopes by nearly the same extent that Galileo's telescope improved on the resolution of the human eye (*inset*).**

trographs (the Faint Object Spectrograph and the Goddard High-Resolution Spectrograph) similarly share the duty of splitting light into its component wavelengths to reveal the dynamics and physical makeup of the object observed. A photometer determines the exact brightness of sources. In addition, *Hubble*'s guidance sensors perform astrometry, the precise measurement of the angular positions of stars.

Immediately after *Hubble*'s launch, operators at the National Aeronautics and Space Administration Goddard Space Flight Center and at the Space Telescope Science Institute began an extensive series of systems checks and calibrations. The first test images revealed an inherent focusing problem, technically known as spherical aberration. A close examination of the images revealed that the telescope's main mirror had been ground to the wrong shape: it is two microns flatter at the edges than stipulated by design (a micron is one millionth of a meter). Small though the error may seem, it is a gross mistake by the standards of modern precision optics.

The shape of the mirror makes it impossible to focus all the light collected by *Hubble* to a single point. *Hubble*'s designers intended that the telescope should be able to concentrate 70 percent of the light of a point source—a distant star, for example—into a spot 0.1 arcsecond across (an arcsecond is a tiny angle, equal to 1/1,800 the apparent diameter of the moon). Actually, only 15 percent of the light falls into this central image; the other 85 percent spills over into an unwanted halo several arcseconds in diameter.

Various other difficulties have surfaced. Twice each orbit, when *Hubble* passes in and out of the earth's shadow, the sudden temperature change causes the telescope's large solar cell panels to flap up and down about 30 centimeters every 10 seconds. The resulting jitter can disrupt the telescope's pointing system and cause additional blurring of astronomical images. Two of *Hubble*'s six gyroscopes have failed, and a third works only intermittently; the telescope needs at least three gyroscopes to perform its normal science operations. Faulty electrical contacts threaten to shut down the High-Resolution Spectrograph.

NASA hopes to address some of these problems in 1994, when astronauts are scheduled to visit *Hubble*. They will attempt to replace the telescope's solar panels and two of the gyroscopes. The astronauts may also try to install a package of corrective optics and an upgraded Wide Field and Planetary Camera if the new devices are completed by then.

In the meantime, scientists have quickly learned how to wring as much performance from the space telescope as possible. Because *Hubble*'s mirror was ground to fine precision and because its error is well understood, computer enhancement can restore many images to their intended sharpness. The resulting astronomical views have eloquently refuted some early pessimism about the telescope's scientific capabilities. Regrettably, attaining such resolution often involves discarding the smeared halos that appear around celestial targets, literally throwing away most of the light captured by *Hubble*.

The greatest blow to *Hubble*'s scientific mission therefore has been not a loss of resolution but a loss of sensitivity. *Hubble* was designed to be able to detect objects a billion times fainter than those visible to the human eye. At present, the telescope is limited to observing objects roughly 20 times brighter than intended. *Hubble* cannot detect some particularly elusive

targets, such as extremely distant galaxies and quasars or possible planets around nearby stars. Astronomers have had to postpone many of their potentially most significant observations until the telescope is fixed.

Although designed to home in on some of the most remote cosmic objects, *Hubble* has proved well suited to studying objects within the solar system. For example, it has captured stunning views of the giant planets, Jupiter and Saturn. NASA's two *Voyager* space probes closely scrutinized Jupiter in 1979 and Saturn in 1980 and 1981. The space telescope can routinely produce images of Jupiter and Saturn comparable in detail to those obtained by the *Voyagers* only a few days before their closest approaches to the two planets.

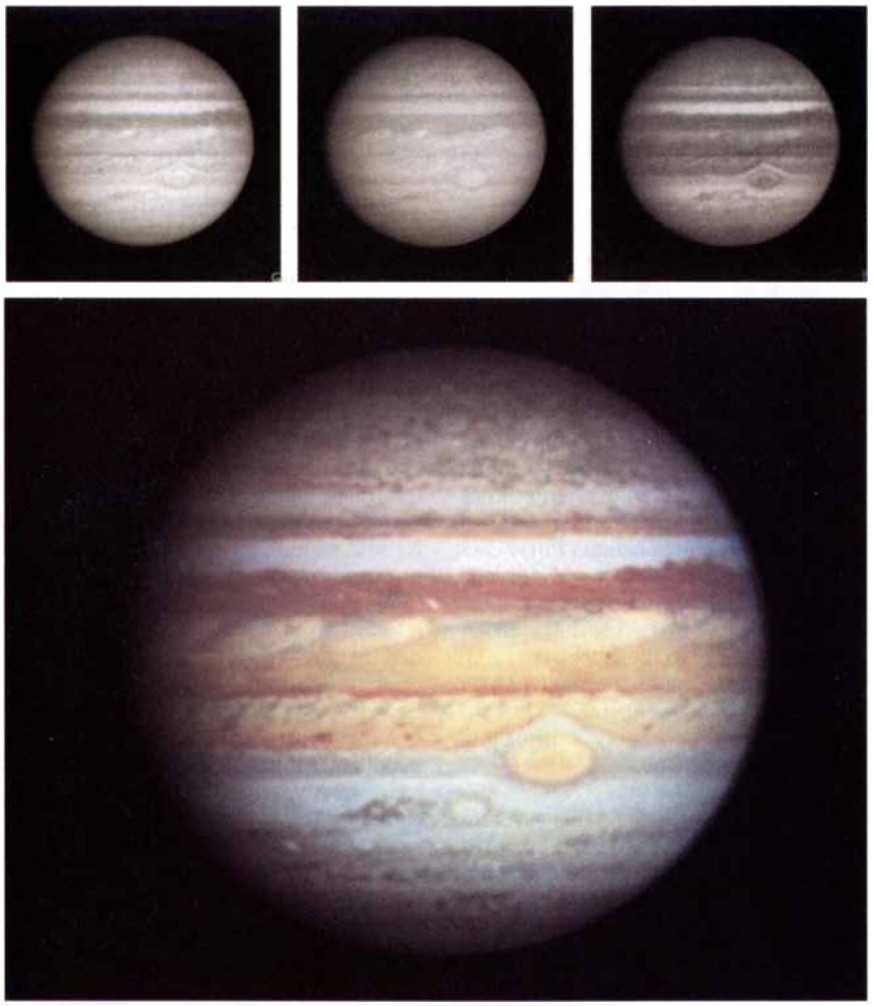
When *Hubble* examined Jupiter, it found a world remarkably changed from the one visited by *Voyagers 1* and *2*. New cloud bands have come and gone, many spots (cyclonelike storms, some of them thousands of kilometers across) have appeared, and turbulent structure has emerged on the edge of the planet's huge South Equatorial Belt. The famed Great Red Spot, a seemingly perpetual hurricane twice the diameter of the earth, has turned a dull, brownish orange.

Hubble's early images of Saturn dramatically illustrate the telescope's resolving power. William A. Baum of the Lowell Observatory and Shawn P. Ewald of the Space Telescope Science Institute assembled a color image of Saturn by instructing *Hubble* to capture three one-second exposures of the planet, one in red light, one in green light and one in blue light. Imaging experts in the institute's Astronomy Visualization Laboratory prepared a computer-enhanced color image that captures the detailed structure in Saturn's cloud bands and rings. The image contains the first high-resolution views of the planet's north polar region.

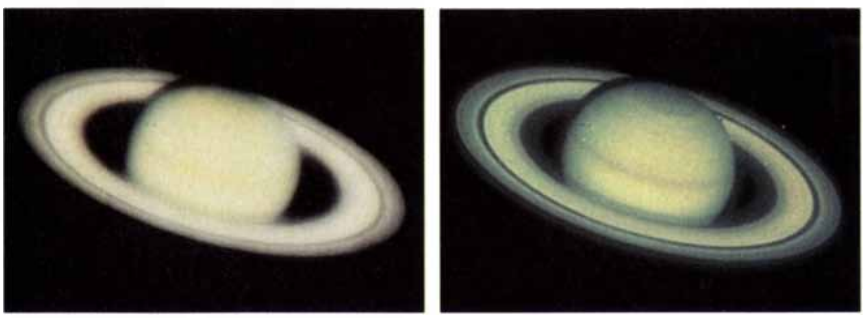
In the fall of 1990 *Hubble* took more than 100 additional images of Saturn in order to track a 50,000-kilometer-wide storm of ammonia ice crystals, termed the Great White Spot. These observations are especially valuable because the spot appears only once every 60 years or so.

The distinct advantage of *Hubble* for planetary astronomers is that it can provide image clarity comparable to that from a space probe whenever an observer calls for it. Philip B. James of the University of Toledo and several colleagues will monitor the atmosphere of Mars for several years to study that planet's weather patterns and to try to understand the events that trigger periodic, planet-wide dust storms. Such research is an important prerequisite for any manned expedition to the red planet. James A. Westphal of the California Institute of Technology plans a similar systematic study of Jupiter's potent weather systems.

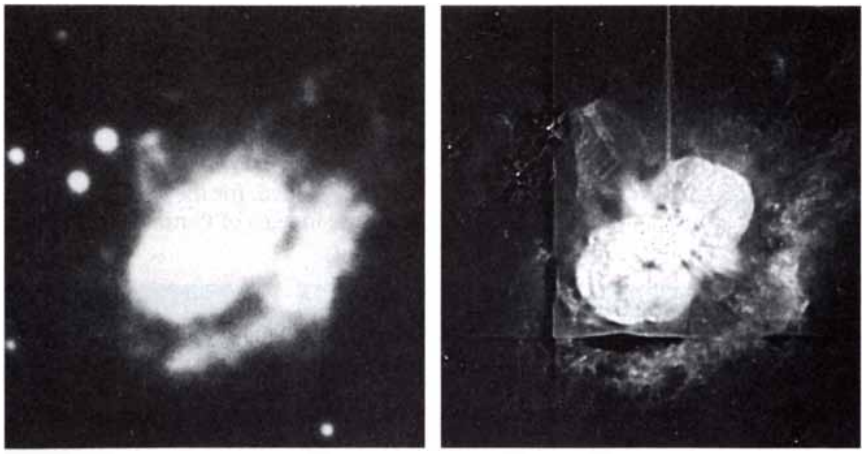
Hubble has also turned its gaze on tiny Pluto, orbiting at the dim outer reaches of the solar system nearly five billion kilometers from the sun. Pluto and its relatively large moon Charon orbit a mere 19,000 kilometers from one another, so the pair appear as hardly more than a lopsided blob when viewed from the earth. *Hubble's* Faint Object Camera yielded, for the first time, clear, separate images of Pluto and Charon.



COLORFUL SHOT OF JUPITER begins as three black-and-white images, each taken through a filter that highlights certain details. The three views are color coded and combined, in much the way that a picture is generated on a color television.



COMPUTER IMAGE CORRECTION enables *Hubble* nearly to attain its intended resolution. A raw image of Saturn (*left*) resembles the view through a hobbyist's telescope. A corrected version (*right*) shows a level of detail bested only by space probes.



ETA CARINAE consists of a dusty cloud ejected from an unstable, extremely massive star. A ground-based photograph (*left*) shows only the general outline of the cloud. A computer-processed *Hubble* image (*right*) reveals complex jets and waves of matter. The vertical spike and segmented divisions are imaging artifacts.

Detailed analysis of the brightness variations of the two bodies will provide data about the changing structures of their thin, methane atmospheres. Rudolf Albrecht of the Space Telescope European Coordinating Facility, who directed the *Hubble* observations of Pluto, hopes computer enhancement may even reveal some surface markings. Precise measurements of the orbits of Pluto and Charon about each other will enable researchers to measure accurately their individual masses and densities. That information will provide clues regarding the compositions and origins of these enigmatic objects.

Looking beyond the solar system, *Hubble* turned to the beautiful Orion Nebula, a patch of glowing ionized gas (atoms stripped of some of their electrons) visible to the naked eye as the middle "star" in the sword of Orion. Huge clouds of this kind are the places where stars are born. The Orion Nebula lies 1,500 light-years distant, making it the closest bright star–forming region. Astronomers have examined it extensively over the years and felt they knew its structure rather well—at least until the *Hubble* images came in.

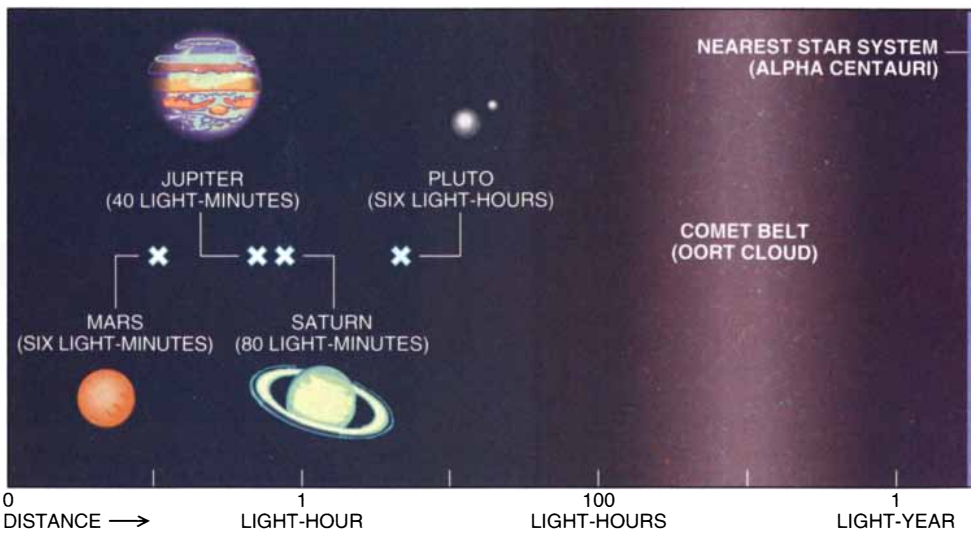
The Wide Field and Planetary Camera took three 10-minute exposures of the nebula, which were later assembled into a color image of the object. The result reveals structures as small as 0.1 arcsecond (or about six billion kilometers, roughly the radius of the solar system, at the distance of the Orion Nebula). Previously unseen wispy arcs, filaments and sheets of ionized gas streak across the image. C. Robert O'Dell of Rice University, who was in charge of the Orion Nebula study, also noticed numerous luminous knots in the nebula. These knots consist of gas ionized by ultraviolet rays from hot, young stars embedded in the nebula. Some researchers tempered enthusiasm about the image, however, worrying that computer image enhancement procedures could have produced spurious features. The Orion Nebula images epitomize the mixture of thrill and frustration astronomers experience when they work with *Hubble*.

One highly intriguing discovery by the telescope concerns a later stage in the birth of stars, when surrounding planets may begin to form. In 1983 the *Infrared Astronomical Satellite* revealed that the nearby star Beta Pictoris (54 light-years away) is encircled by a thin disk of gas and dust at least 80 billion kilometers across, or nearly 10 times the size of Pluto's orbit. Such disks are thought to be the raw material from which planetary systems coalesce. To learn more about the disk, Albert Boggess of the Goddard Space Flight Center and his colleagues used the High-Resolution Spectrograph to examine ultraviolet radiation from Beta Pictoris.

Boggess finds that some of the circumstellar gas is falling in toward the star. Moreover, the star's spectrum varies in appearance, probably because as the disk revolves different patches of radiation-absorbing matter pass between Beta Pictoris and the earth. The rapidity of the variation—some spectral changes occur in less than a month—suggests that the disk is rather clumpy. These findings hint that new material is being released into the disk, possibly gas evaporating from cometlike objects orbiting the star.

The *Hubble* data do not tell whether fully formed planets are present around Beta Pictoris. Most astronomers will not be convinced of the discovery of extrasolar planets until a camera takes a picture of one. In this area, *Hubble*'s optical defect has dealt a crushing blow. The foggy halo of scattered starlight from the misshapen mirror would obliterate the faint light reflected from planets orbiting even the nearest stars. A dedicated search for extrasolar planets, one of the key projects intended for *Hubble,* will have to wait until the telescope's optical system is corrected.

Beta Pictoris is a fairly sedate, sunlike star. In contrast, the highest-priority target in *Hubble*'s first round of observations was the unstable, rapidly evolving star Eta Carinae, located 9,000 light-years away in the southern sky.



ASTRONOMICAL VISTAS available to *Hubble* span a tremendous range of distances. Pluto lies an average of six light-hours from the earth (one light-hour equals roughly one billion kilometers). In comparison, the quasar UM 675 sits some 12 billion light-years away. Distances are shown on a logarithmic scale.

Eta Carinae may be the most massive and energetic star in the Milky Way, about 100 times as massive and four million times as luminous as the sun. It flared up in 1843, briefly becoming the second brightest star in the sky. Subsequent observations showed that a small nebula, called the Homunculus, had started forming around the star.

The best ground-based observations show the Homunculus as a small, fuzzy oblong nebula. *Hubble* unveiled a much more complicated picture of the object. The Homunculus has a peculiar, peanut-shaped form; two opposing, tightly focused jets gush from its middle. The cloud appears clumpy and has a sharp outer edge, suggesting that it is actually a thin, dusty shell of matter rather than a filled volume. Presumably it consists of material either ejected from or swept up by Eta Carinae as a result of its outburst.

One of the jets terminates in a U-shaped feature. This structure is probably a bow shock, analogous to the wake around the bow of a moving ship, that formed when the jet penetrated the slow-moving interstellar matter around the star. A baffling series of parallel lines of luminous gas, resembling the rungs of a ladder, protrudes to one side of Eta Carinae. Perhaps the rungs are light-year-long standing waves, like the sound waves inside an organ pipe. Or they may be ripples that develop as matter rapidly flows along the jet's bow shock. Once again, the possible existence of artifacts from the computer enhancement process complicates interpretation of the image.

While *Hubble* has deepened the mystery of Eta Carinae, it has answered a long-standing question about a more distant denizen of the galaxy, the globular cluster M 15. Globular clusters are dense spherical swarms of up to one million stars. Such a tremendous concentration of stars, many astronomers reason, should be conducive to the formation of a black hole, a collapsed object whose gravity is so strong that even light cannot escape. Other researchers disagree, suggesting that the rapid motions of stars, especially binary stars, near the center could help buoy the core and prevent a catastrophic collapse.

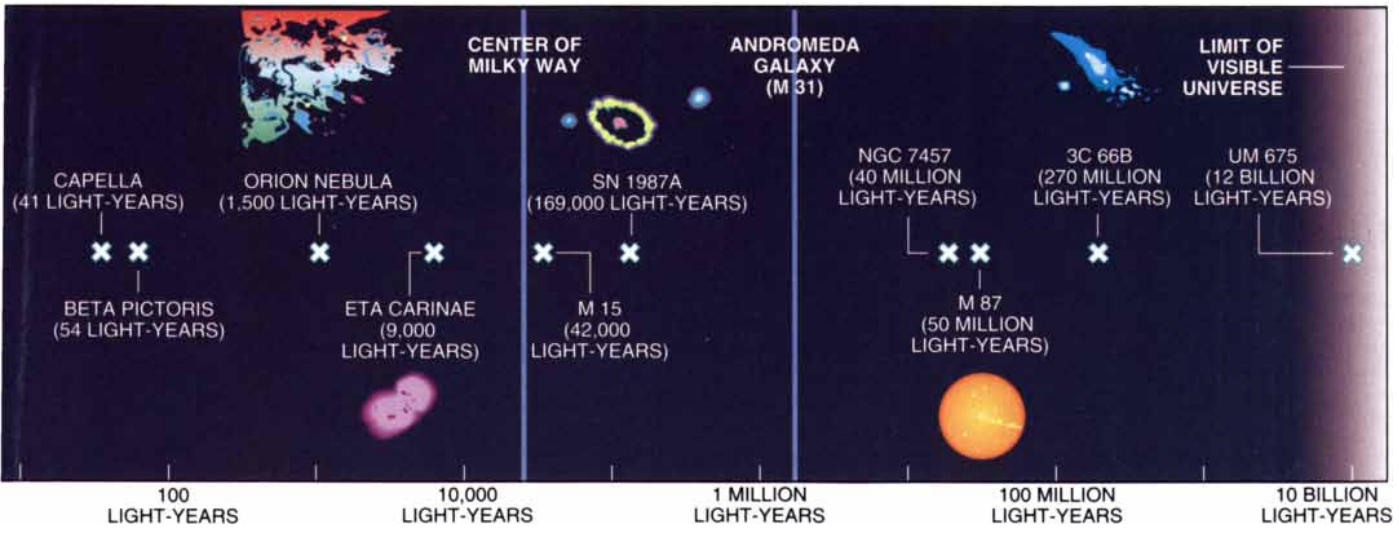
One likely black hole candidate was the bright cluster M 15, located 42,000 light-years away in the constellation Pegasus. Although the hole itself would be invisible, vast quantities of radiation ought to blaze from its immediate environs, where matter under extreme stress and tidal friction grows tremendously hot before vanishing forever. Therefore, a hole should produce a characteristic bright point of light at the center of the cluster. Until now, no telescope could resolve the core in sufficient detail to disclose such a "brightness spike." *Hubble* can discern details in M 15 as small as about 0.02 light-year, close to the theoretical diameter of a black hole having 1,000 times the mass of the sun.

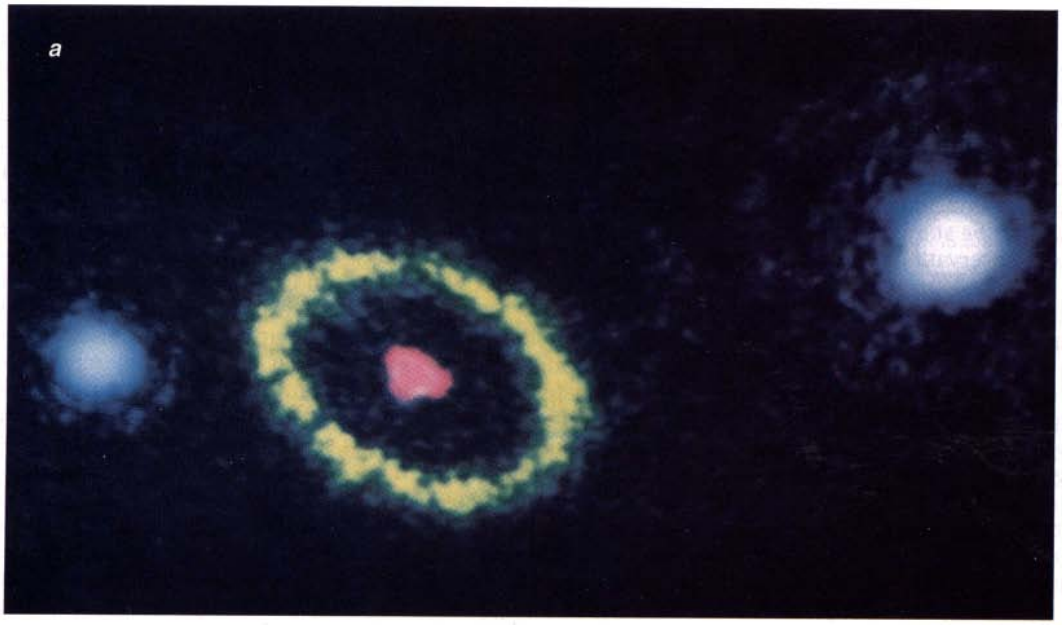
Tod R. Lauer of Kitt Peak National Observatory searched for such a brightness spike in M 15. When he failed to find it, he and his colleagues turned to another technique. *Hubble* was able to resolve the bright red giant stars in the outskirts of M 15, enabling the researchers to subtract them out of the image. What remained was a core region containing thousands of faint stars spread out over a surprisingly large radius of about 0.4 light-year, 10 times that predicted by the black hole models. The *Hubble* results strongly suggest that M 15 does not harbor a black hole at its center. This finding comes as a relief to those of us made uncomfortable by the popular tendency to invoke an invisible black hole to explain every powerful object in the universe.

Astronomers have been especially eager to obtain *Hubble* views of the remnant of SN 1987A, the bright supernova that appeared in 1987 in the Large Magellanic Cloud, a satellite galaxy of the Milky Way. On August 23, 1990, *Hubble*'s Faint Object Camera transmitted a 28-minute exposure of SN 1987A. The image that appeared on our computer screens at the Space Telescope Science Institute showed a remarkable luminescent ring of matter 1.4 light-years across surrounding the supernova remnant. Most of us in the room were astounded by the existence of the ring. Our colleague Nino Panagia at the institute was not; he had actually expected the formation of a peculiar outer structure.

The intriguing aspect about the supernova ring is that it looks elliptical, not round. Its shape implies that the feature is not a three-dimensional shell (shells exist around many planetary nebulae; because of perspective effects, they often resemble circular rings). It appears to be a genuine circular torus of material inclined 43 degrees to our line of sight, giving it an elliptical appearance. Such a formation could not have been produced by the supernova itself. Rather the ring must be a ghostly relic of the expelled outer layers of the progenitor red giant star.

Panagia thinks that thousands of years before the explosion, a gentle stellar wind carried off the star's outer envelope, mostly in the equatorial direction. A subsequent, faster wind compressed the material into a gaseous ring. Ultraviolet radiation from the supernova explosion heated and ionized the gas, causing it to glow. Within a few





decades the ring should disintegrate when it is disrupted by debris from the supernova that is now moving outward at an average velocity of 10,000 kilometers per second. *Hubble* will continue to monitor the protean structure of the remnant of SN 1987A.

Hubble observations of the supernova have led to a vastly improved knowledge of the distance to the Large Magellanic Cloud. The images show very precisely the angular size of the ring. The *International Ultraviolet Explorer* satellite monitored the timing of when the near and far edges of the ring first began to glow; this information, when combined with the well-known speed of light, yields the ring's true diameter. Simple trigonometry then reveals that the distance to the supernova, and hence to the surrounding galaxy, is 169,000 light-years. This estimate is accurate to within 5 percent, more than three times better than earlier measurements. Such information will be important for calibrating the distance scale to other, more remote cosmic objects.

Unfortunately, *Hubble*'s general ability to measure galactic distances has been severely compromised. Its optical flaw makes it impossible for the telescope to distinguish individual Cepheid variable stars in faraway galaxies. These stars are of tremendous interest because their brightness fluctuates in a regular manner: the period of variation is related to their absolute luminosity. Observations of Cepheids can therefore provide an unambiguous measurement of the distance of a galaxy. The study of Cepheids will be an important task for *Hubble* when it is repaired in 1994.

Many people mistakenly think that because of *Hubble*'s impaired light-gathering ability, it cannot study distant celestial objects. Nothing could be farther from the truth. The space telescope has made substantive observations of objects lying nearly at the limits of the visible universe. It has also enabled optical astronomers to study at an unprecedented level of resolution the cores of galaxies beyond our local galaxy cluster; the result has been many remarkable and often unexpected findings.

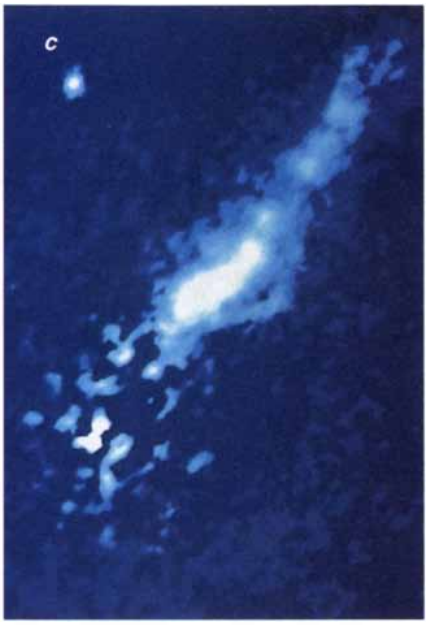
One of *Hubble*'s earliest targets outside the Milky Way was NGC 7457, an elliptical galaxy about 40 million light-years away. The galaxy was chosen as a seemingly normal test subject. But when Lauer and his colleagues used the Wide Field and Planetary Camera to explore the central regions of NGC 7457, they were surprised by what they saw. A significant fraction of the galaxy's light arises from a point-like source, no more than 10 light-years across, lying at the very heart of the nucleus. Stars there must be packed together at least 30,000 times as tightly as the stars in the sun's galactic neighborhood, hundreds of times the stellar density that astronomers theoretically expected.

The central brightness spike may denote the location where vast quantities of material—perhaps entire stars—spiral into a black hole having millions of times the mass of the sun. Alternatively, the bright region might be something less exotic but still unanticipated, such as an exceptionally rich cluster of stars. Researchers working with *Hubble*'s spectrographs will soon attempt to measure the orbital velocity of gas and stars in the core, thereby indicating the total amount of matter present there and helping to determine the true nature of the central object.

Hubble has also produced corroborating evidence that a huge black hole may indeed exist where astronomers did expect to find one: in the giant elliptical galaxy M 87, located in the Virgo galaxy cluster, roughly 50 million light-years away. M 87 strongly emits radio waves and X rays. A gigantic jet of ionized gas (thousands of times the length of the jets from Eta Carinae) points outward from the galaxy's center. Theorists speculated that a massive black hole might be the central engine driving all this activity.

Lauer, working with Sandra M. Faber of the University of California at Santa Cruz, C. Roger Lynds of the National Optical Astronomy Observatories and several other collaborators, called on the Wide Field and Planetary Camera to help settle the question. They found that, as with NGC 7457, stars crowd together in the central region of M 87 hundreds of times more tightly than they would in a normal galaxy. If a black hole is in fact responsible for M 87's dense and overly bright core, it must have a mass a few billion times that of the sun.

F. Duccio Macchetto of the European Space Agency is interested in the violent processes occurring in even more distant active galaxies. He turned the Faint Object Camera to collect ultraviolet radiation from the galaxy 3C 66B, which sits 270 million light-years from the earth. *Hubble* revealed the details of 3C 66B's extraordinary jet of glowing plasma. The jet extends 10,000 light-years from



SUPERNOVA 1987A (*a*) is captured in this false-color *Hubble* image. A ring of matter 1.4 light-years across (*yellow*) surrounds the debris from the supernova (*pink*). M 87, a giant elliptical galaxy, displays an unusually bright, dense core and a huge jet of ionized gas (*b*). Both features may indicate the presence of a massive black hole in the center of the galaxy; matter falling in would glow brilliantly before vanishing. A twisted jet (*c*) extends 10,000 light-years from the nucleus of the galaxy 3C 66B. The galaxy was electronically subtracted to highlight the jet. The ultraviolet radiation seen here is emitted by electrons in the jet spiraling through magnetic fields at nearly the speed of light.

the center of the galaxy, twice the length of M 87's gaseous protrusion.

Macchetto exploited computer image processing to make the jet more visible by subtracting out the image of the host galaxy (this is possible because the jet is brightest at ultraviolet wavelengths, at which the galaxy is faint). He and his co-workers then corrected for *Hubble*'s spherical aberration. They were thus able to glimpse gaseous filaments, bright knots and odd kinks in the jet material, details never before seen through an optical telescope. The jet exhibits an odd, braided structure consisting of two plasma strands situated 500 light-years apart.

The observed features closely correspond to those identified by their radio emission. But visible radiation from the jet is produced by high-speed electrons that lose their energy far more rapidly than do the relatively sluggish electrons that produce the radio jet. The most energetic, light-emitting electrons exist in regions that have been recently disrupted. In comparison to radio astronomy studies, *Hubble*'s data trace out much more recent behavior of the potent forces that produced the huge jet.

Further *Hubble* observations of active galaxies and of their more energetic cousins, quasars and Seyfert galaxies, will show how energy travels outward along the jets. *Hubble* studies will also help define the role of magnetic fields in channeling matter (mostly electrons moving at nearly the speed of light) from the cores of galaxies into intergalactic space. A better knowledge of active galaxies will help determine whether black holes can account for their prodigious energy output or if astronomers need to come up with new, perhaps even more exotic, explanations for these celestial powerhouses.

Hubble is also helping test and refine the big bang theory, which forms the foundation of modern cosmology. The theory states that the present universe, including all matter and all space, exploded outward from a single point roughly 15 billion years ago. If the big bang is correct, most of the helium in the universe was created in the moments after the birth of the universe. Since then, however, some additional helium has been synthesized in the interiors of stars via nuclear fusion.

Margaret E. Burbidge of the University of California at San Diego sought to measure the abundance of helium near the quasar UM 675, which lies some 12 billion light-years from the earth. Because of its great distance, humans now see UM 675 as it was 12 billion years ago, when the universe was one fifth its present age. The big bang theory predicts that UM 675 should contain nearly as much helium as do modern, nearby objects. If the theory is wrong, the helium abundance in UM 675 might be close to zero. *Hubble*'s Faint Object Spectrograph showed a clear signature of helium, lending credence to the big bang.

In another experiment, Jeffrey Linsky of the University of Colorado and his colleagues attempted to measure the cosmic abundance of deuterium, a heavy version of the element hydrogen. Theory implies that the amount of deuterium created immediately after the big bang reflects the overall density of the universe. Linsky and his co-workers used *Hubble*'s High-Resolution Spectrograph to observe the spectrum of the bright star Capella, situated 41 light-years away in the constellation Auriga. The exact shape of the spectrum indicates the amount of radiation absorbed by hydrogen and by deuterium atoms between Capella and the earth.

Linsky's analysis of the spectrum suggests that the universe contains only one tenth the amount of ordinary matter necessary to halt the present expansion. Many cosmologists speculate that exotic, undiscovered particles may add considerably to the total mass of the universe. If not, the *Hubble* results imply that the universe is infinite and that its expansion will continue for the rest of eternity.

Despite a plethora of optical and mechanical shortfalls, *Hubble* is proving a powerful scientific research tool. The results from its first two years of operation offer only a small taste of what the telescope should be capable of if it receives an optical fix in 1994. After centuries of being condemned to watching stars twinkle and dance in the earth's turbulent atmosphere, optical astronomers have finally entered a new age of space-based research. The *Hubble Space Telescope,* I hope, is only the first step.

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Lipoprotein(a) in Heart Disease

A remarkable protein that transports cholesterol and binds with blood clots can raise the risk of a heart attack. Comparisons between it and other blood proteins may explain why

by Richard M. Lawn

Coronary heart disease is the leading cause of death in the U.S. and many other Western industrialized countries. Most cases of coronary heart disease, in turn, are caused by a more fundamental malady: atherosclerosis, the accumulation of fatty deposits in artery walls. As these atherosclerotic deposits, or plaques, grow, they sometimes trigger the formation of clots that block the flow of blood. If a clot obstructs one of the narrow coronary arteries that nourishes the heart, the result is a myocardial infarction, or heart attack.

Some causes of atherosclerosis and coronary heart disease are now clear. High blood pressure, diabetes, smoking and other factors seem to increase the likelihood of premature coronary heart disease. Diets rich in cholesterol and saturated fats contribute to the elevation of lipid (fat) levels in the blood and to the progression of atherosclerosis. An individual's genetic makeup plays a role: some people can eat and drink enormous amounts of dietary fat over time without developing high blood cholesterol, and many with unusually high blood cholesterol levels never acquire coronary heart disease. To the profound dismay of both physicians and patients, heart attacks can also strike those who have a "safe" risk profile.

The fairly recent discovery of a particle in the blood that accounts for much of the previously unattributable risk for coronary heart disease has therefore stirred great excitement. That particle is lipoprotein(a). This amalgam of proteins, cholesterol and other lipids is exceptionally abundant in the blood of many persons whose vulnerability to coronary heart disease cannot be laid to other obvious causes. Dietary changes and other measures that can lower most risk factors have no effect on lipoprotein(a) levels. Researchers are still unsure about how lipoprotein(a) contributes to heart disease; the preliminary results of genetic and biochemical studies suggest that, in part, atherosclerosis and heart attacks may be unfortunate side effects of the particle's possible involvement in the repair of torn blood vessels.

One key to understanding lipoprotein(a) and atherosclerosis lies in the body's system for the intake, synthesis and distribution of fats. Fatty substances that are not electrostatically charged tend to be insoluble in water-based liquids, such as blood. The body overcomes this hindrance with an array of particles that enclose cholesterol and other fats and coat them with charged molecular groups to facilitate their transport. These particles, or lipoproteins, consist of uncharged and detergentlike lipid molecules as well as protein components called apolipoproteins.

In human blood the major cholesterol-carrying particle is low-density lipoprotein (LDL). It consists of about 2,000 molecules of cholesterol, 1,000 molecules of phospholipid and one large protein on the surface called apolipoprotein B-100. High levels of LDL are so firmly established as a risk for coronary heart disease that many people refer to it as "bad cholesterol." That epithet distinguishes it from the "good cholesterol" in high-density lipoproteins (HDLs), the blood levels of which are inversely related to the risk of coronary heart disease.

Despite the stigma it bears, LDL plays a vital role in transporting cholesterol throughout the body. Cholesterol is an essential component of all cell membranes; also, the adrenal glands and gonads use it to manufacture steroid hormones, such as testosterone. To obtain cholesterol, cells take up LDL from the blood using LDL receptors, which bind to the apolipoprotein B-100 on the lipoprotein's surface.

Michael S. Brown and Joseph L. Goldstein of the University of Texas Health Science Center at Dallas received the Nobel Prize in 1985 for elucidating the metabolism of LDL [see "How LDL Receptors Influence Cholesterol and Atherosclerosis," by Michael S. Brown and Joseph L. Goldstein; SCIENTIFIC AMERICAN, November 1984]. They found that a genetic deficiency in LDL receptors (found in about one person in 500) leads to elevated blood cholesterol and an enhanced risk for coronary heart disease. Diets high in cholesterol and saturated fats, they realized, could simulate this defect in genetically normal persons: such diets signal the body to produce fewer LDL receptors.

This biochemical response makes intuitive sense, because cells bathed in high concentrations of cholesterol should reduce their array of receptors to avoid overloading on that substance. Unfortunately, a decrease in the number of LDL receptors prolongs the circulation of LDL particles in the blood-

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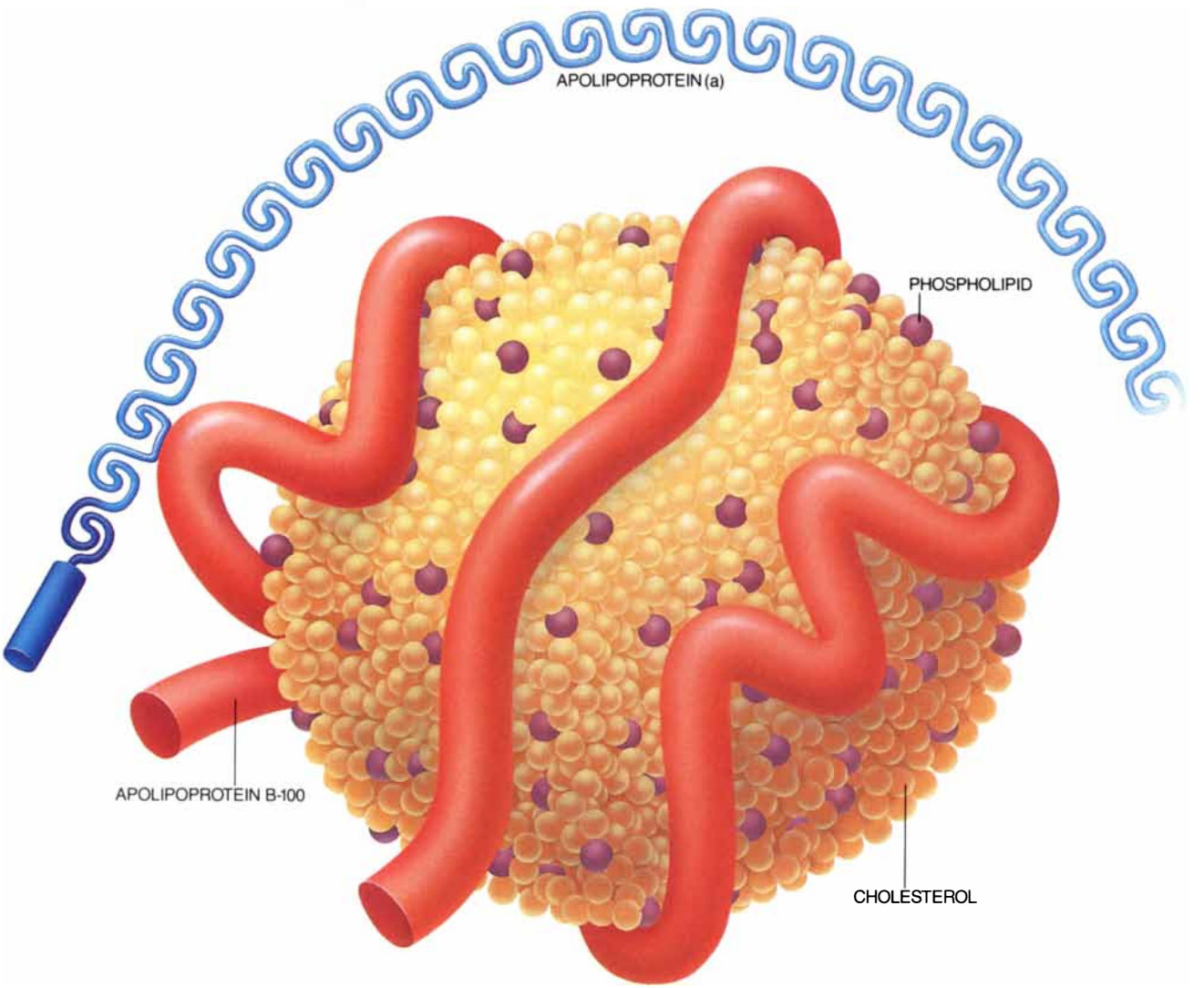
stream—an outcome that increases the chance that the particles and the cholesterol they contain will be incorporated into atherosclerotic plaques. High-density lipoprotein does not cause such problems, because, unlike LDL, it favors the delivery of excess cholesterol from peripheral sites to the liver for elimination. These contrasting mechanisms provide a rationale for the association of risks for coronary heart disease with high LDL levels and low HDL levels.

Studies of LDL and related molecules led to the discovery of lipoprotein(a) about three decades ago. During the early 1960s, Kåre Berg of the University of Oslo was searching for variant forms of beta-lipoproteins, a class of molecules that includes LDL. Using immunologic methods, researchers had already found variations among humans in several other blood proteins, and it seemed plausible that variants of LDL with interesting properties might also be present. Berg injected beta-lipoproteins from several human subjects into rabbits, then tested the affinities of antibodies from the immunized rabbits.

Telltale reactions indicated to Berg that some of the rabbit antibodies recognized a beta-lipoprotein present in only about a third of the human samples. He called this distinct class of molecules lipoprotein(a). Berg's further pioneering studies revealed that the presence of lipoprotein(a) was an inherited trait. Later, he, Gosta Dahlén of the Central Hospital in Boden, Sweden, and their co-workers showed that individuals bearing lipoprotein(a) had a higher incidence of heart attacks than did a control population.

When more sensitive assays were developed to measure lipoprotein(a) concentrations accurately, investigators realized that nearly everyone carries some lipoprotein(a) but that its concentration varies nearly 1,000-fold among individuals. A person's lipoprotein(a) concentration is remarkably stable throughout his or her lifetime, unlike the levels of LDL and HDL, which can vary widely in response to changes in diet, exercise, age or pharmaceutical intervention.

Many experimental trials have now confirmed a positive correlation between lipoprotein(a) and atherosclerosis. Using chemical-extraction techniques and dye-linked antibodies, researchers have detected lipoprotein(a) in atherosclerotic plaques. Many studies have



LIPOPROTEIN(a) is a particle in the blood that when present in large quantities raises the risk of coronary heart disease. One portion of the particle consists of phospholipids, cholesterol and apolipoprotein B-100 and is identical to the low-density lipoproteins that transport cholesterol. The remaining piece, apolipoprotein(a), which is linked to apolipoprotein B-100 at a single point, gives this particle its distinctive properties.

also shown high levels of the protein to be associated with heart attacks, strokes, the narrowing of arteries and the reclosure of vessels after coronary artery bypass surgery. According to some medical experts, approximately one quarter of all heart attacks in men younger than 60 years occurs in those who have inherited high blood concentrations of lipoprotein(a). Most of the genetic component of coronary heart disease that is not attributable to any of the traditional risk factors rests with levels of lipoprotein(a).

As part of the ongoing Framingham Heart Study, which has monitored the health of thousands of people since 1948, investigators have assessed the condition of the family members of heart attack victims. They concluded that a high level of lipoprotein(a) ranks among the most prevalent inherited risks for heart attacks. Furthermore, a given quantity of lipoprotein(a) in the blood seems to confer as much added risk as does 10 times that quantity of LDL. Berg's search for a variant LDL-like particle has uncovered a lipoprotein with distinctive and seemingly dangerous properties.

Lipoprotein(a) turns out to be quite similar in structure to LDL: it contains cholesterol, phospholipid and one molecule of apolipoprotein B-100. Its distinguishing feature is the presence of one additional large protein, dubbed apolipoprotein(a), that is chemically linked to apolipoprotein B-100. Chemical treatments that break the bond between the two proteins produce a free apolipoprotein(a) and a particle that looks and behaves like LDL. The structure of the apolipoprotein(a) component is therefore the key to the distinctive behavior of the lipoprotein(a) particle.

In 1987 my group at Genentech, in collaboration with the laboratory of Angelo M. Scanu of the University of Chicago, cloned the gene for human apolipoprotein(a). We determined its DNA sequence and were able to deduce the amino acid sequence of the protein. Luckily, that string of amino acids was almost identical to that of a protein with well-understood properties: about 80 percent of the amino acids in apolipoprotein(a) coincide with those of plasminogen.

Plasminogen is the precursor of a blood protease, an enzyme that cleaves other proteins. Its target is fibrin, the main protein component of blood clots. Because plasminogen is not an active protease itself, it can circulate through the blood without destroying clots indiscriminately. Under the appropriate conditions, such as those found at the sites of healing wounds, enzymes called plasminogen activators alter part of the plasminogen molecule and turn on its fibrin-cutting activity.

The presence or absence of plasminogen at a blood clot associated with an atherosclerotic plaque could spell the difference between the benign repair of the vessel injury and a full-fledged heart attack. Indeed, precisely because plasminogen is critical to the healing process, physicians now infuse heart-attack patients with plasminogen activators to hasten the breakup of blood clots.

Because of its resemblance to plasminogen, some researchers speculated that apolipoprotein(a) might provide the long-sought link between lipoprotein levels and the incidence of blood clots. They immediately began to compare the properties of apolipoprotein(a) and plasminogen in the hope of determining why the two proteins were so similar and how that likeness might figure in the genesis of atherosclerosis and coronary heart disease.

The similarity of apolipoprotein(a) to plasminogen is rooted in an economy inherent to protein evolution. Useful, novel proteins are not always built from scratch, resulting from the chance assembly of thousands of DNA bases into a functional gene. Instead many proteins are apparently built from components that evolved earlier. The advent of rapid techniques for sequencing genes and protein molecules has enabled researchers to scrutinize thousands of sequences. When geneticists compare a new protein sequence with the data banks of those already known, it is becoming the rule, not the exception, for them to recognize similarities in whole or in part.

On the basis of these homologies, or sequence similarities, genes and the proteins they make can be grouped into families and superfamilies. Some members of a group may share only the few components necessary to fold the proteins into roughly the same shape; others may be so nearly identical throughout that their functional differences are minor.

For example, one of the first analyzed gene families consisted of the globin genes, which encode the subunits of hemoglobin. Humans have five homologous globin genes arranged in tandem on one chromosome. This cluster probably arose through repeated duplications of part of that chromosomal DNA. The spare copies of the ancestral globin gene gradually mutated, and some survived because of their functional advantages. The globins evolved specialized differences: some that bind oxygen more strongly, for example, are expressed only during prenatal development because they enable the fetal hemoglobin to derive oxygen from the maternal circulation.

In many instances, proteins evolve through the exchange of parts of genes that make functional domains, or modules [see "Proteins," by Russell F. Doolittle; SCIENTIFIC AMERICAN, October

ATHEROSCLEROTIC PLAQUE almost completely obstructs this coronary artery. Blood clots associated with such plaques can trigger heart attacks. Lipoprotein(a), which is often deposited in these plaques, seems to enhance atherosclerosis.

1985]. In most of the genes in complex organisms, regions that encode protein domains are separated by noncoding regions; the synthesis of a protein involves the assembly of these separate domains into a complete structure through the splicing of an intermediate molecule, messenger RNA. This modular genetic architecture facilitates protein evolution because genes can swap discrete domains that confer a particular binding affinity, enzymatic activity or structural feature.

Plasminogen and apolipoprotein(a) are part of an extended superfamily that has been built up through the acquisition and loss of functional modules in duplicates of genes. All the family members, including nearly a dozen proteins involved in blood clotting, have a domain homologous to trypsin, a protease of broad specificity that breaks down dietary protein. That homology suggests that those proteins and trypsin evolved from a common ancestral protein. Aside from their trypsinlike domain, some of these proteins also share other modules with one another and with nonprotease proteins in other groups. By comparing sequences and counting the changes that occurred since a gene or gene domain was duplicated, molecular biologists have been able to draw family trees that portray the possible evolutionary relations among the proteins.

In addition to its trypsinlike domain, plasminogen has five modules known as kringles, structures in which the amino acid chains are interconnected by three disulfide bonds. (They are called kringles because they are commonly drawn in a form resembling the Danish pastry of that name.) The kringle structural motif occurs in several other proteases, as well as in some proteins that have no catalytic function.

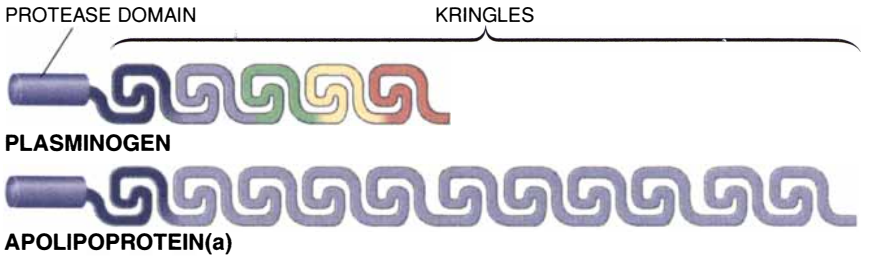
Each plasminogen kringle is distinctive. Some contain binding sites for fibrin and help plasminogen find its preferred substrate for clot digestion. One has a binding site for a regulatory protein that prevents activated plasminogen from working indiscriminately.

The sequences of plasminogen and apolipoprotein(a) match closely at one end, but then a gap appears in the homology: apolipoprotein(a) lacks the parts that correspond to kringles 1, 2 and 3, as well as the so-called preactivation region of plasminogen. Instead apolipoprotein(a) has multiple repeats of a domain resembling plasminogen kringle 4; in the apolipoprotein(a) gene we cloned in 1987, that kringle is repeated more than 30 times.

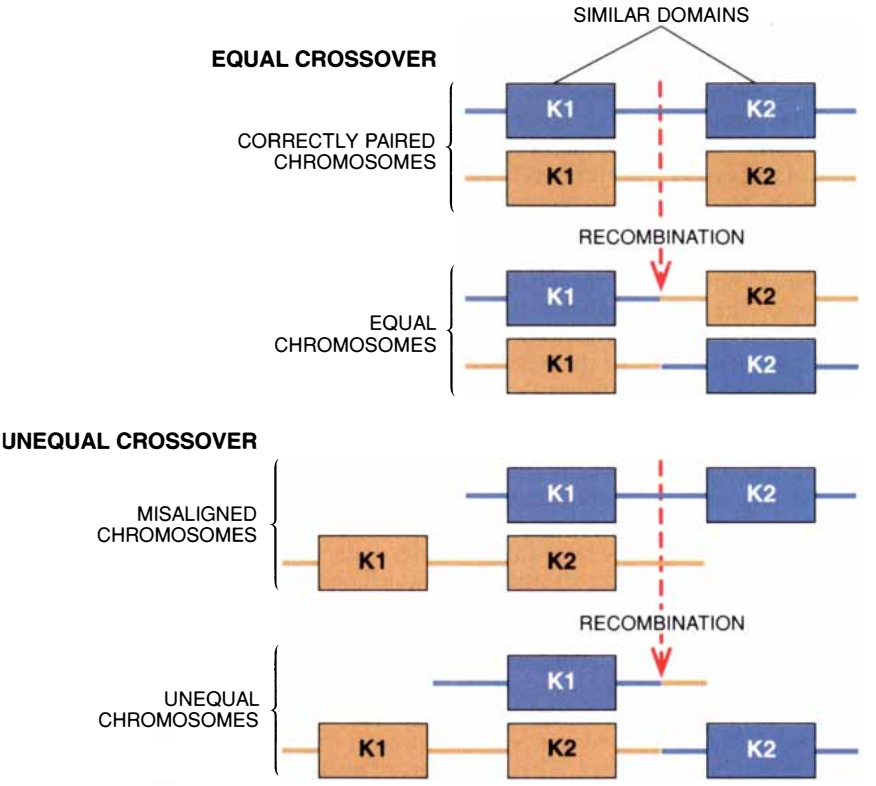
It is easy to imagine apolipoprotein(a) evolving in several steps, beginning with the duplication of the plasminogen gene (or of a gene that was the common precursor to both of them). Segments of the gene that encoded parts of plasminogen, including kringles 1, 2 and 3, were deleted. Mutations led to amino acid substitutions that altered the functional characteristics of the remaining protein domains. Successive rounds of sequence duplication also extensively multiplied the region encoding kringle 4.

As Gerd Utermann of the University of Innsbruck noted, the size of apolipoprotein(a) differs considerably among individuals. Several groups have confirmed that those differences result almost entirely from variations in the number of repeated kringle domains. The apolipoprotein(a) gene originally cloned, which had 37 repeated kringles, turns out to be one of the largest commonly found variants.

The high degree of homology among the copies of kringle 4 is suggestive. Many proteins contain internally re-



KRINGLE DOMAINS and other similarities between apolipoprotein(a) and plasminogen, a blood protein that dissolves clots, suggest the molecules are closely related. Apolipoprotein(a) lacks three of the kringle domains found in plasminogen. Two other kringles and a protease domain appear in both proteins; apolipoprotein(a) has between 10 and 40 copies of one of these kringles.



CROSSOVER OF DNA between chromosomes during meiotic cell division can produce multiple copies of gene sequences, such as those that make the kringles in apolipoprotein(a). Usually, the corresponding genes on paired chromosomes align perfectly and exchange equal amounts of DNA. If two sequences on one strand are similar, however, the first copy from one chromosome may then pair with the second copy from the other, causing a misalignment. The resulting unequal recombination event produces a chromosome with an extra copy of a sequence.

peated domains, but the copies tend to diverge widely as mutations accumulate. The five kringles in plasminogen, for instance, were probably very similar at first but now differ in about 70 of their 114 amino acids. In contrast, more than 20 of the repeated kringle domains in apolipoprotein(a) are identical in all their amino acids and all 342 corresponding bases of DNA. Many kringles have therefore probably been added to the gene quite recently, by a process known as out-of-register homologous recombination.

Recombination occurs during meiosis, the cell division mechanism that produces sex cells, when paired chromosomes are held in precise alignment by their corresponding DNA sequences. Breakage and rejoining of the DNA strands, or other enzymatic processes with the same outcome, commonly swap parts of one chromosome for those of its partner. This process of homologous recombination retains the overall structure of each chromosome. If the chromosomes contain repeated sequences, however, a misalignment can occur. The first repeated sequence of one chromosome may pair with the second sequence on the other chromosome. Recombination between the out-of-register chromosomes will then produce one chromosome with an extra copy of the repeated domain and one chromosome with a corresponding deletion. This random mechanism offers a likely explanation for the large inherited differences in the size of apolipoprotein(a) molecules.

Working from assumptions about how rapidly mutations accumulate in DNA, some investigators have estimated that apolipoprotein(a) and plasminogen began diverging in sequence only about 40 million years ago. That date corresponds to the timing of the split between Old World and New World monkeys. In keeping with that finding, the initial searches for apolipoprotein(a) in various species did not detect the protein in animals other than Old World monkeys, the great apes and humans. This conclusion fascinated scientists with an interest in molecular evolution, but it was a setback for those hoping to study the mechanisms of atherosclerosis in rodents and other small laboratory animals.

In 1988, however, P. M. Laplaud of the Laboratory of Medical Biochemistry in Limoges, France, found high levels of a protein resembling human apolipoprotein(a) in the European hedgehog. This spiny insectivore is only distantly related to humans—its line of descent diverged from our ancestors' line about 80 million years ago. That discovery calls the history of apolipoprotein(a) back into question. Further cloning and sequencing of apolipoprotein(a) genes from different species may solve the riddle of their origin.

The sequence of apolipoprotein(a) offers some tantalizing leads concerning the protein's normal physiological role and its part in accelerating atherosclerosis. One attractive speculation is that lipoprotein(a) assists with the healing of blood vessel wounds. When a vessel is torn or punctured, fibrin-rich clots temporarily stem the leakage of blood. Healing, however, depends on the growth of new cells, which need cholesterol as a component of their membranes.

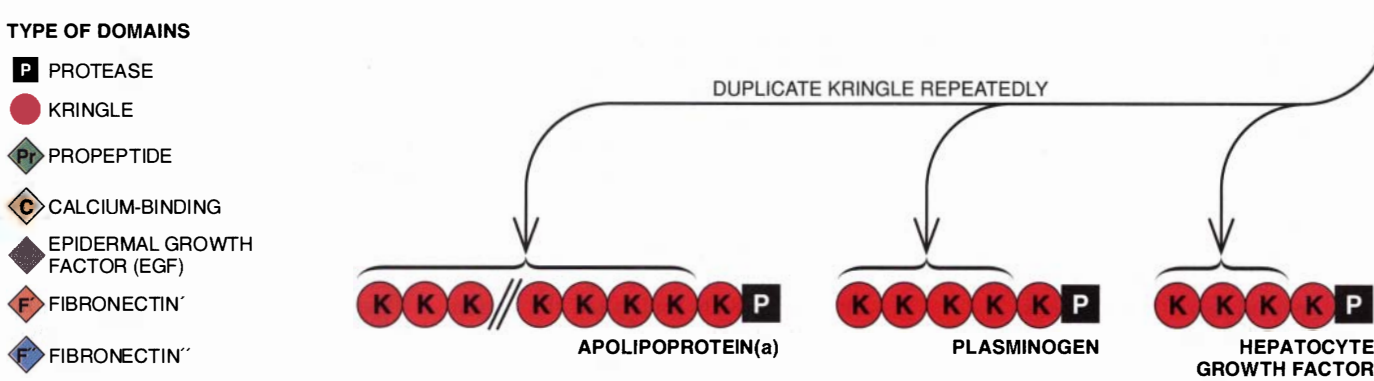
Apolipoprotein(a), a plasminogenlike protein bound to cholesterol-carrying LDL, could conceivably offer some selective advantage in wound repair. If the protein retained the fibrin-binding ability of unactivated plasminogen, it would help deliver cholesterol to the right place at the right time. Such a beneficial role for apolipoprotein(a) is not inconsistent with its pathological effects: the protein might have evolved at a time when our primate ancestors had far lower levels of cholesterol in their blood than do modern humans who eat large amounts of fat. Natural selection would not have been shaped by our current desire to avoid death from heart disease at the ripe old age of 40.

Attempts to confirm this and related hypotheses have met with mixed results. Early studies indicated that apolipoprotein(a) binds fibrin less well than plasminogen does. More recently, however, Peter Harpel's group at Cornell University and several other laboratories have found that the partial degradation of a fibrin clot unmasks sites that bind well with apolipoprotein(a). These sites would help associate lipoprotein(a) with a blood clot at the stage of wound healing when the clot begins to dissolve. As several laboratories have shown, some molecules in the vessel wall, including components of the matrix material between cells (such as elastin, fibronectin, collagen and glycosaminoglycans), bind to lipoprotein(a) more avidly than to LDL. These results suggest lipoprotein(a) might be able to assist with wound healing even though it promotes atherosclerosis when it is present in excess.

Another means by which lipoprotein(a) might enter the vessel wall is inside macrophage cells. Macrophages, which are part of the immunologic defense against pathogens, dispose of microscopic debris in the body. Their specialized features enable them to ingest invading microbes, sloughed-off parts of dead cells and toxic particles, including lipids and proteins oxidized by chemical reactions within the tissues.

Yet macrophages can do harm. If

PROTEIN FAMILY TREE shows a hypothetical, simplified reconstruction of the evolutionary relations within an extended group of molecules that includes apolipoprotein(a) and plasminogen. All the proteins are derived from an ancestral protease. Molecules with new properties arose through the addition, deletion or duplication of functional domains in the proteins and also through the gradual accumulation of amino acid substitutions through mutations (*not shown*).



overwhelmed by too much oxidized LDL, they fail as scavengers and become lipid-laden foam cells. These cells can become stuck in blood vessels and release growth factors that promote cell multiplication, which could thicken the artery wall. Lipoprotein(a), particularly after oxidation, can stick to macrophages and promote their transformation into foam cells.

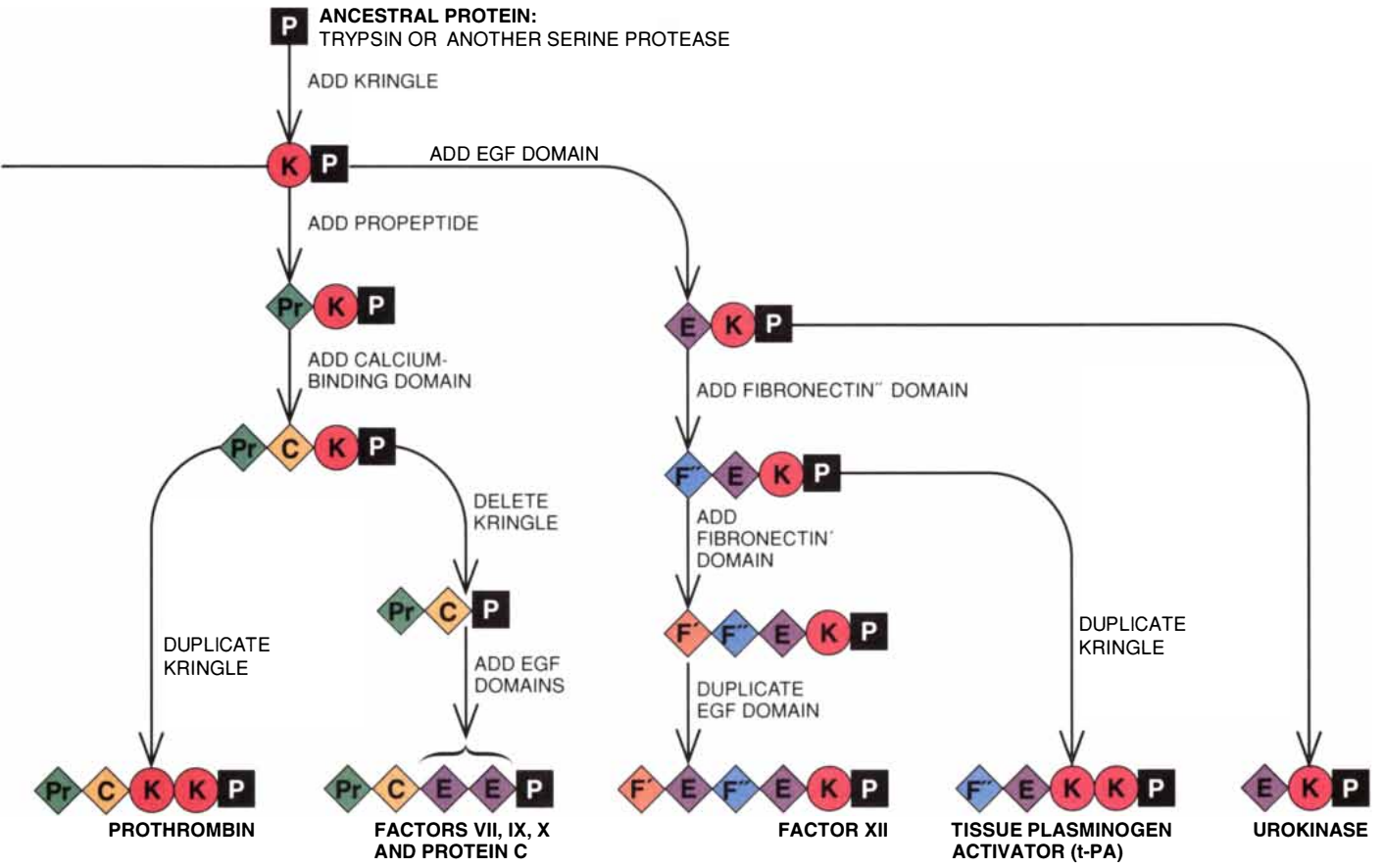
Lipoprotein(a) may also promote the growth of atherosclerotic plaques more directly. Two groups in Japan have recently characterized a protein, called hepatocyte growth factor, that stimulates the multiplication of many types of cells. It, too, resembles plasminogen in sequence, although not as closely as does apolipoprotein(a). If apolipoprotein(a) can promote cell division as hepatocyte growth factor does, it may cause the atherosclerotic proliferation of cells in the vessel wall.

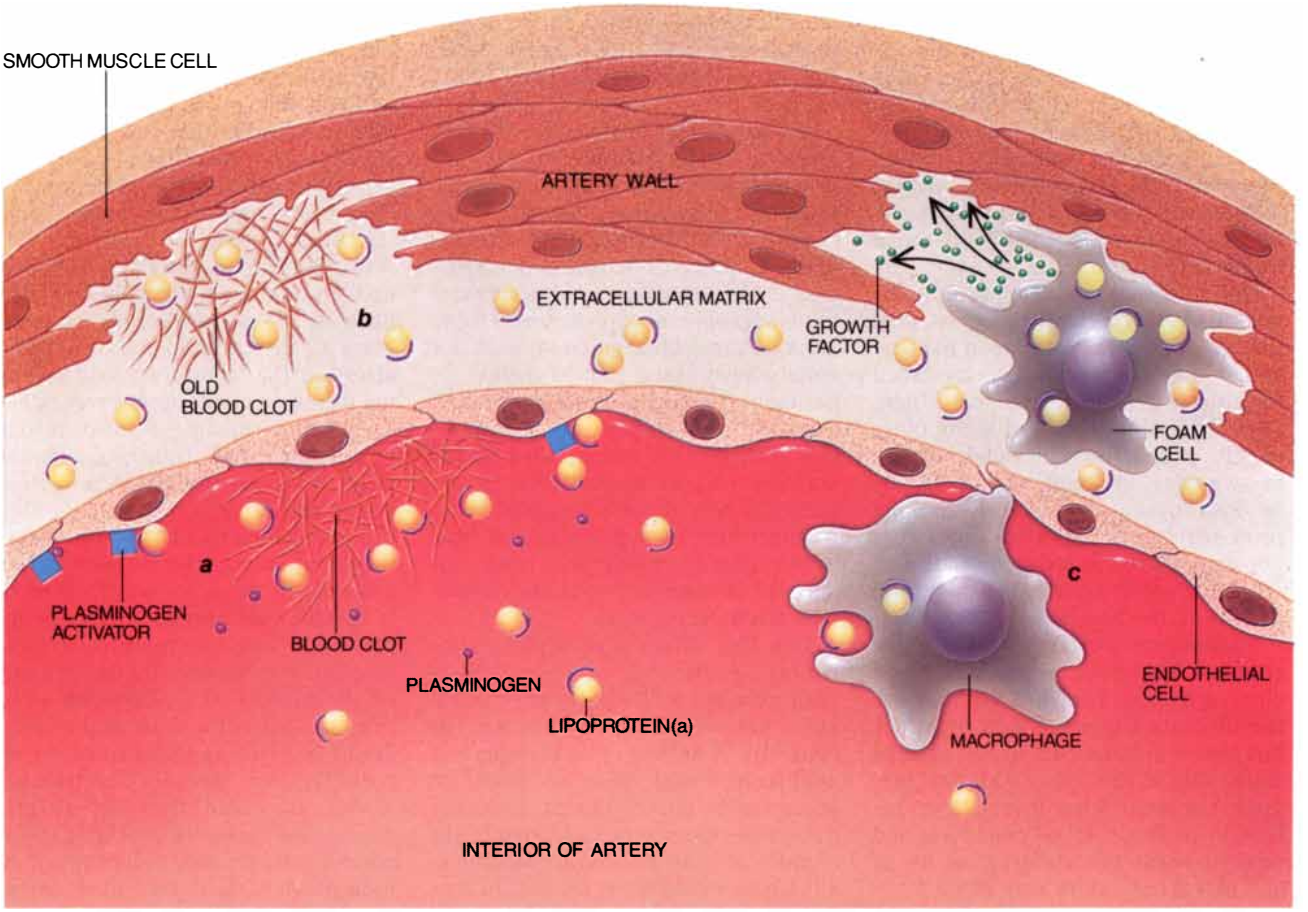
Apolipoprotein(a) may also promote coronary heart disease by helping blood clots to persist. The clots not only are the ultimate trigger of a heart attack but also may take part in the gradual thickening of the artery wall that precedes the event. Some investigators believe microscopic blood clots form and dissolve many times during the life of a vessel. These clots may often leave residues that are incorporated into the vessel wall each time it undergoes repair. Such deposits may act as signals for cell growth during the wound-healing response.

Any factor responsible for either increasing the formation of blood clots or impeding their dissolution could consequently play a dual role in causing heart attacks. Apolipoprotein(a) cannot dissolve fibrin, as activated plasminogen can. Yet because of its resemblance to plasminogen, apolipoprotein(a) might serve as a molecular stand-in for it. Scientists have found that in certain experimental settings, apolipoprotein(a) can compete with plasminogen for access to fibrin, to binding sites on cell surfaces and to plasminogen activators. Any one of these competitive activities could keep plasminogen from performing optimally and upset the delicate balance between clot formation and disintegration.

This idea offers a satisfying explanation for the link between high lipoprotein(a) levels and heart disease, but a note of caution is in order. The competition between plasminogen and apolipoprotein(a) does not seem to occur under all conditions, including many physiological ones. Moreover, the amount of plasminogen in the bloodstream far exceeds the amount of apolipoprotein(a), so the effect of the competition may be small. Nevertheless, only a slight prolongation in the time needed to dissolve a clot may crucially affect the course of a disease—like atherosclerosis—that takes years to develop. The possibility that apolipoprotein(a) inhibits the breakdown of clots is still an intriguing area for further investigation.

Experiments to test all these hypotheses are under way, but they are complicated by the difficulties of re-creating all the components of a human artery in the laboratory. One promising means of clarifying the role of apolipoprotein(a) in atherosclerosis is to develop appropriate transgenic animals. Genetic engineers should be able to insert the gene for human apolipoprotein(a) into rodents or other creatures and induce them to express large amounts of the protein in their blood. If species that normally lack apolipoprotein(a) become more susceptible to plaque formation in the presence of the human gene, that fact would firmly establish the cause-and-effect relation between apolipoprotein(a) and coronary heart disease. The transgenic animals could then act as good models for the development of atherosclerosis in humans. Recent results do indicate that transgenic mice harboring the human apolipoprotein(a) gene





LIPOPROTEIN(a) PROMOTES HEART DISEASE according to several possible mechanisms. By competing with plasminogen for binding sites on blood clots and plasminogen-activator enzymes (*a*), lipoprotein(a) may slow the breakdown of clots that trigger heart attacks. Remnants of old clots within the artery wall and lipoprotein(a) bound to the extracellular matrix may also signal the cells lining the arteries to grow inappropriately (*b*). Macrophage cells that consume too much lipoprotein(a) become foam cells, which release growth factors that encourage atherosclerosis (*c*).

are more prone to the development of atherosclerosis.

While scientists are unraveling the complexities of lipoprotein(a) and atherosclerosis, what can be done in the interim for the quarter of the population that has inherited high levels of the protein and is at risk for coronary heart disease? An advisable first step would be to identify those people through widespread screenings for lipoprotein(a) levels. At present, research centers and some large clinics are generally the only places equipped to conduct lipoprotein(a) assays, but the availability of the tests will probably widen.

Checking the levels in coronary heart disease patients who show none of the other risk factors might be a particularly fruitful way to identify individuals with high lipoprotein(a) levels. Also, because lipoprotein(a) levels are inherited, it would be prudent to examine the close relatives of those with elevated lipoprotein(a) and of patients with premature coronary heart disease.

In the realm of treatment, diet and drug manipulations can reduce LDL levels and the risk for heart disease, but they have far less effect on lipoprotein(a). In one of the more dramatic demonstrations of the insensitivity to diet, Scanu and his co-workers switched rhesus monkeys from low-fat to extremely high fat diets: the monkeys experienced as much as a 10-fold leap in their LDL levels but almost no change in their lipoprotein(a) levels. Of all the cholesterol-lowering drugs now available, only high doses of niacin have been reported to lower blood levels of lipoprotein(a). That effect was not seen in every case, however, and some patients do not tolerate the high doses of niacin well.

Today the wise course of action appears to be, in effect, to treat what is treatable. Because the risk factors for heart disease are usually additive, individuals with high lipoprotein(a) levels would do well to control for the other known risk factors, such as LDL cholesterol, cigarette smoking, hypertension and obesity. They can take comfort in the knowledge that many people with high levels of lipoprotein(a) never acquire coronary heart disease and that in parts of the world where other predisposing factors are few, atherosclerosis is a rare disease. Given the many questions that still remain about the association of lipoprotein(a) with heart disease, the topic should remain exciting for years to come.

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Biotechnology has already created plants that withstand pests and fruits that resist spoilage. Recent advances confirm its environmental soundness and commercial viability

by Charles S. Gasser and Robert T. Fraley

Modification of crop plants to improve their suitability for cultivation has persisted for at least 10,000 years. Early farmers produced better crops simply by saving the seeds of desirable plants. During the past century, plant breeding has become more rigorous in its approach. Significant improvements in crops have resulted from the successful crossbreeding of different individuals of the same species. More recently, researchers have made advances in crossing sexually incompatible species of the same family. Now there exists a promising method of developing superior plants: genetic engineering. By using recombinant DNA techniques, biologists can direct the movement of specific and useful segments of genetic material between unrelated organisms.

That approach can add a significant degree of diversity to the total repertoire of traits from which the plant breeder can choose. In the laboratory, plants can now be made to withstand insects, viruses and herbicides. Fruits can be made to resist spoilage, and grains may become more nutritious and economical.

Biologists created the first transgenic plants less than 10 years ago. Since then, researchers have applied genetic engineering to more than 50 plant species. The technique has helped investigators gain critical insights into the fundamental processes that govern the development of plants, and the first commercial introductions of such genetically modified plants are now only a few years away.

CHARLES S. GASSER and ROBERT T. FRALEY collaborated on research in crop improvement at the Monsanto Company in St. Louis for five years. Gasser, now assistant professor at the University of California, Davis, received his Ph.D. in molecular biology from Stanford University. He is currently using genetic engineering methods to study plant development. Fraley, vice president of technology for Monsanto, received his doctorate from the University of Illinois. He has made pioneering contributions in gene transfer in plants and is deeply interested in the commercial development of engineered crops to address, in particular, food production in developing countries.

Although genetic engineering is more complex than traditional plant-breeding practices, it is just as safe. In both methods, new DNA enters the plant's genome and is stably maintained and expressed. A recent National Academy of Sciences report concluded that "crops modified by molecular and cellular methods should pose risks no different from those modified by classical genetic methods for similar traits." This past February the White House stated that genetically engineered products should not be subject to additional federal regulations, because they do not pose any unreasonable risk.

In this article, we shall describe the methods used at present to engineer plants genetically. We shall also outline the rationale of and progress in the current applications.

The first practical—and still the most widely used—system for genetic engineering of plants relies on an innate ability of the plant pathogen *Agrobacterium tumefaciens*. This bacterium can transfer a portion of its DNA into plant cells. It does so by introducing a set of genes into one or more of its own DNA fragments. These fragments, called transferred DNA (T-DNA), then integrate into chromosomes of infected plant cells and induce the cells to produce elevated levels of plant hormones. These hormones cause the plant to form novel structures, such as tumors or prolific root masses, that provide a suitable environment and nutrient source for the *Agrobacterium* strain. This bacterial infection is called crown gall disease.

For the bacterium to be an effective vehicle for DNA transfer, its disease-causing genes had to be removed. This alteration is known as disarming. Researchers at the Monsanto Company and Washington University and groups directed by Jozef Schell of the Max Planck Institute for Plant Breeding in Cologne and by Marc van Montagu of the State University of Ghent in Belgium first accomplished the task in 1983. They relied on traditional DNA recombination to delete the genes that cause tumors. Disarming thus eliminates the bacterium's ability to cause disease but leaves the mechanism of DNA transfer intact [see "A Vector for Introducing New Genes into Plants," by Mary-Dell Chilton; SCIENTIFIC AMERICAN, June 1983].

The first engineered gene, constructed with *Agrobacterium* in the early 1980s by groups at the Max Planck Institute in Cologne and at Monsanto, made plant cells resistant to the antibiotic kanamycin, a compound that inhibits plant growth. The engineering of kanamycin resistance represented a breakthrough for two reasons. First, it showed that foreign genes and proteins could be expressed in plants. Second, it demonstrated that kanamycin resistance is useful as a "marker." Because only a small number of cells take up, integrate and express introduced DNA, marker genes help investigators to identify those cells into which genes have successfully been introduced.

Because plant cells are totipotent—that is, the undifferentiated cells can generate a whole organism—complete, reproductively competent plants can emerge from the transformed cells. Most methods today rely on the cells of explants, or small pieces of plant, for genetic engineering. Our colleague Robert B. Horsch of Monsanto popularized the use of a common paper hole punch to cut disks from leaves for *Agrobacterium*-mediated techniques. (He used to carry a punch in his coat pocket, always ready to give an impromptu demonstration of the leaf-disk transformation method.) *Agrobacterium*-mediated gene transfer is now routinely used in hundreds of industrial and aca-

demic laboratories around the world. At Monsanto alone, more than 45,000 independent transgenic plant lines have been produced in this way.

Although the method is simple and precise, many plant species, including such critical grain crops as rice, corn and wheat, are not natural hosts for *Agrobacterium* and so are not readily transformed by the method. As a result, extensive efforts have been mounted to develop alternative systems.

One of the first was introducing free DNA into plant protoplasts. Protoplasts, plant cells that have had their cell walls removed by enzymes, must be used because the pores of cell walls are too small to allow the easy passage of DNA. The only barrier in protoplasts is the plasma membrane. Polyethylene glycol, a thick organic polymer, can penetrate the plasma membrane to transport DNA. It is the most commonly used chemical delivery agent. Electroporation can also carry DNA across the plasma membrane. In this process, short, high-voltage pulses briefly produce pores in the protoplast membrane. The DNA molecules can enter through these spaces.

Because these procedures do not rely on any special biological interaction, they are, in principle, general methods of transforming cells. But the regeneration of plants from isolated protoplasts has proved problematic in many species, especially the critical cereal grains. Corn and wheat respond very poorly, usually yielding infertile plants.

As a result, investigators have been searching for methods that introduce DNA into intact plant cells, those that still have their walls. A fairly obvious way is simply injecting the DNA. But microinjection has not been effective for several reasons. The fine needle tips break easily and clog frequently. Transforming cells one at a time is tedious, difficult work that would be inappropriate to a commercial operation. Furthermore, once DNA enters a cell, its incorporation into the genome of the recipient is by no means a certainty. A technician might have to inject DNA

GENETICALLY ENGINEERED RESISTANCE to the Colorado potato beetle *(Leptinotarsa decemlineata)* is shown in this false-color, infrared aerial image of test beds planted in a field recently irrigated by a center-pivot system at Hermiston, Ore. The beetles defoliated fields of ordinary potato plants, leaving behind wet ground (*green*), but avoided plants that were able to produce their own insecticide (*red*). The white patches are wheat plants kept dry for an unrelated experiment.

into at least 10,000 cells just to ensure that one of them will take up the new gene.

To increase the efficiency of gene delivery, John C. Sanford of Cornell University envisioned a way to bombard many plant cells with genetic material. He surmised that small metal particles, about one or two microns in diameter, could first be coated with DNA. Sufficiently accelerated, the particles could penetrate the walls of intact cells and thus deliver the DNA. Because small holes in cell walls and membranes rapidly close by themselves, the punctures are temporary and do not irreversibly compromise the integrity of the cells. Although the particles remain in the cytoplasm, they are too small to interfere with any cellular functions.

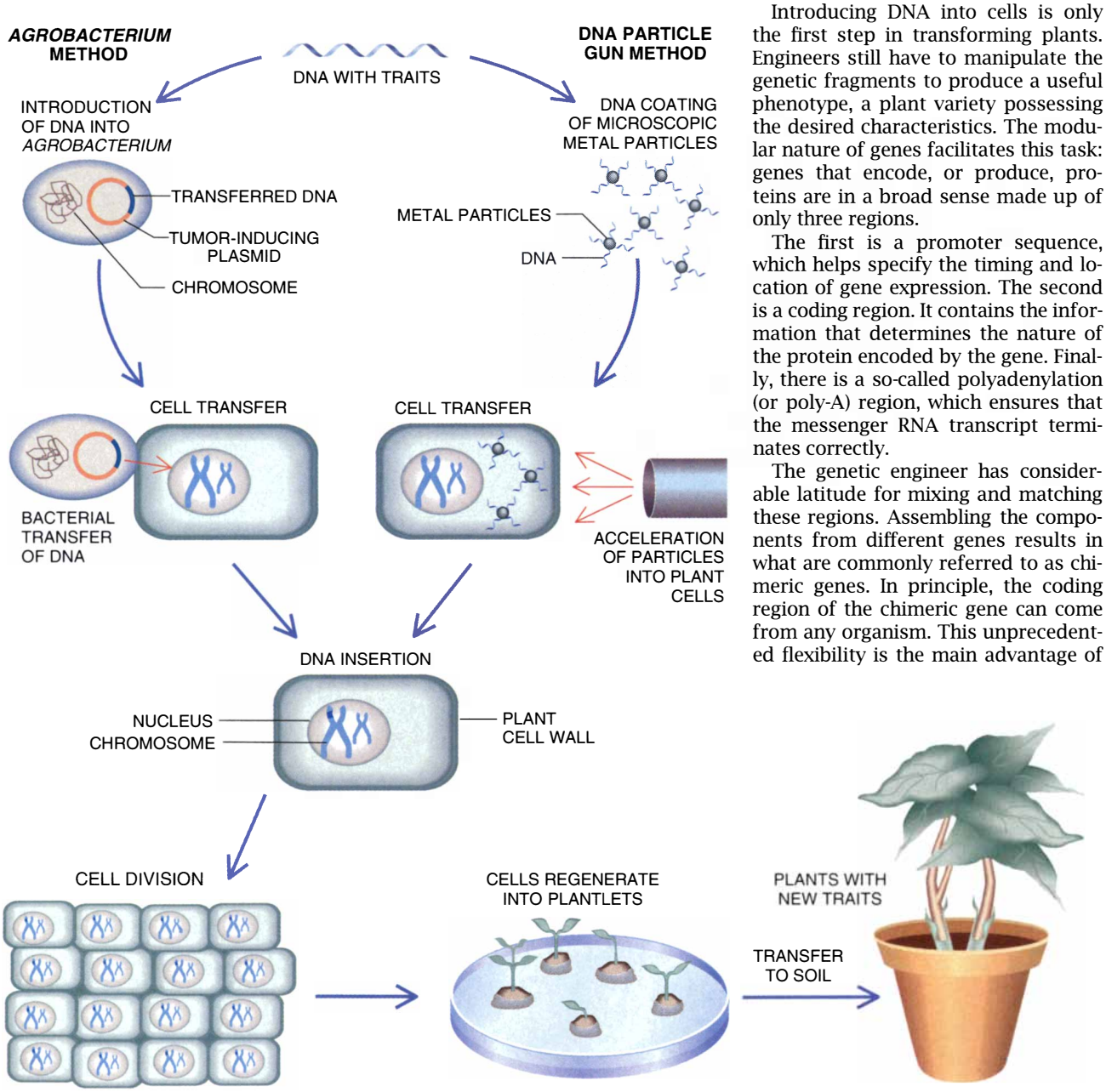
In 1987 Sanford and his co-worker Theodore M. Klein constructed a practical device that used tungsten particles to bombard plant cells. Their DNA particle gun, as it is called, uses a .22-caliber blank cartridge as the motive force. Researchers at Agracetus in Middleton, Wis., have developed a similar gun using gold particles propelled by the vaporization of a water droplet.

Both these particle guns have produced transgenic plants. Last year a group at DeKalb Plant Genetics in Groton, Conn., and a collaboration between Charles L. Armstrong of Monsanto and Michael E. Fromm, then at the U.S. Department of Agriculture in Albany, Calif., independently developed efficient, consistently functioning particle gun systems for the transformation of corn. Even more recently, we have collaborated with Indra Vasil's laboratory at the University of Florida in Gainesville to transform wheat plants.

Introducing DNA into cells is only the first step in transforming plants. Engineers still have to manipulate the genetic fragments to produce a useful phenotype, a plant variety possessing the desired characteristics. The modular nature of genes facilitates this task: genes that encode, or produce, proteins are in a broad sense made up of only three regions.

The first is a promoter sequence, which helps specify the timing and location of gene expression. The second is a coding region. It contains the information that determines the nature of the protein encoded by the gene. Finally, there is a so-called polyadenylation (or poly-A) region, which ensures that the messenger RNA transcript terminates correctly.

The genetic engineer has considerable latitude for mixing and matching these regions. Assembling the components from different genes results in what are commonly referred to as chimeric genes. In principle, the coding region of the chimeric gene can come from any organism. This unprecedented flexibility is the main advantage of



TRANSGENIC PLANTS are now commonly created by two methods. In the *Agrobacterium*-mediated technique, DNA with the desired trait is inserted into the tumor-inducing plasmid of the bacterium. The bacterium infects the plant cell and transfers the DNA. In the particle gun method, metal particles coated with DNA are fired into the plant cell. In either case, the plant cell incorporates the DNA into its chromosome and then divides and regenerates into full plants.

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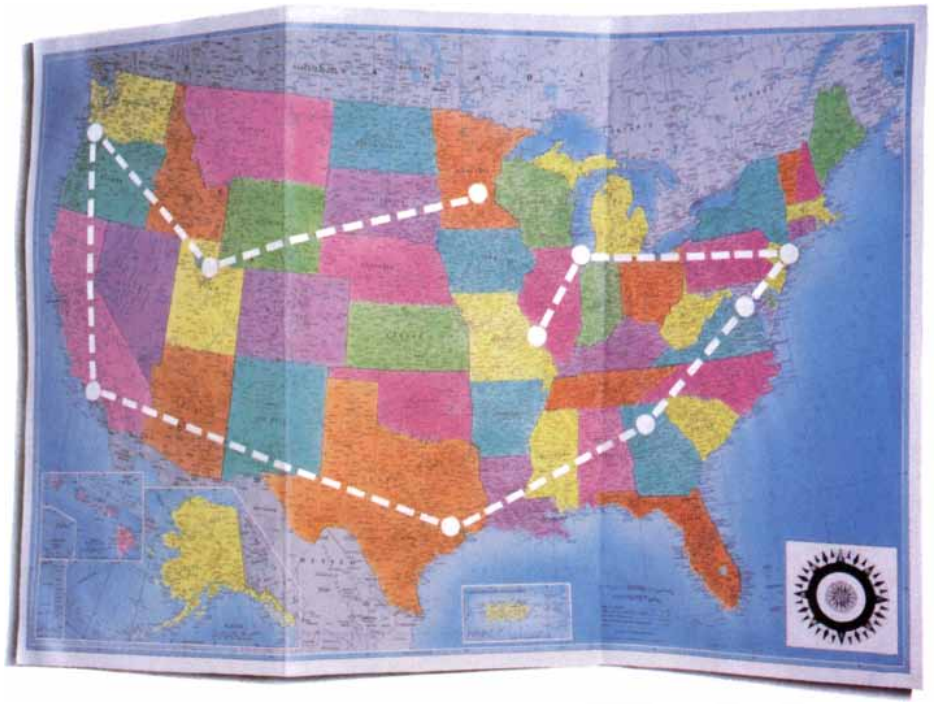

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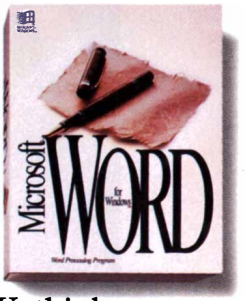

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genetic engineering over more traditional methods, which can transfer genes only between closely related species. Furthermore, by choosing various promoters, researchers can target gene expression to specific organs such as leaves, roots, seeds and tubers and, in many cases, to specific cell types within these complex tissues.

One of the most promising traits gene transfer offers is resistance to diseases. Exciting results have been achieved in creating plants resistant to viruses, an important matter because currently no direct way to treat virus-infected crops exists. Most infections reduce crop yield, but occasionally some prove catastrophic. Good farming practices, such as rotating crops and removing weeds and crop litter, can contain viruses, but only partially. Insecticides are sometimes used to control the pests responsible for transmitting the virus.

Genetic work on virus resistance builds on previous basic research in plant biology. It had long been observed that infection of a plant with a mild strain of a virus protected it from subsequent infection of a more virulent strain. Apparently, the replication of the mild virus strain interferes with a virulent strain's ability to infect. Investigators have applied "cross-protection" to shield greenhouse-grown tomatoes against contagion by intentionally infecting them.

Roger N. Beachy and his co-workers at Washington University reasoned that a single component of the virus might be responsible for the protection. Collaborating with Stephen Rogers of Monsanto and one of us (Fraley), the investigators constructed a vector to introduce and express in tobacco and tomato plants the coat protein of the tobacco mosaic virus (TMV). Plants so modified were then inoculated with a heavy concentration of the virus. The plants were found to be strongly resistant to infection, thus confirming Beachy's hypothesis of viral protection.

Subsequent experiments have shown that the expression of the TMV coat protein confers resistance only to strains of TMV and a few other closely related viruses. Still, the mechanism appears to be generally applicable; expression of the coat protein gene of almost any plant virus, at a sufficiently high level, protects against infection by that virus. Workers have now engineered effective tolerance to more than a dozen different plant viruses in a broad range of crop species.

Resistance to insect predation is another important goal for genetic engineering, especially in cotton, potato and corn plants. During the past three decades, gardeners and farmers have relied on the bacterium *Bacillus thuringiensis* (*Bt*), which produces an insecticidal protein. Most commonly used preparations of *Bt* are highly specific to the caterpillar larvae of lepidopteran insects—moths and butterflies—which are major pests. The *Bt* proteins bind to specific receptors located on the gut membranes of the target insects. The binding interferes with ion transport in the epithelial cells of the gut, thus disrupting the insect's ability to feed. These natural insecticides have no toxicity to mammals or even to any other species of insects.

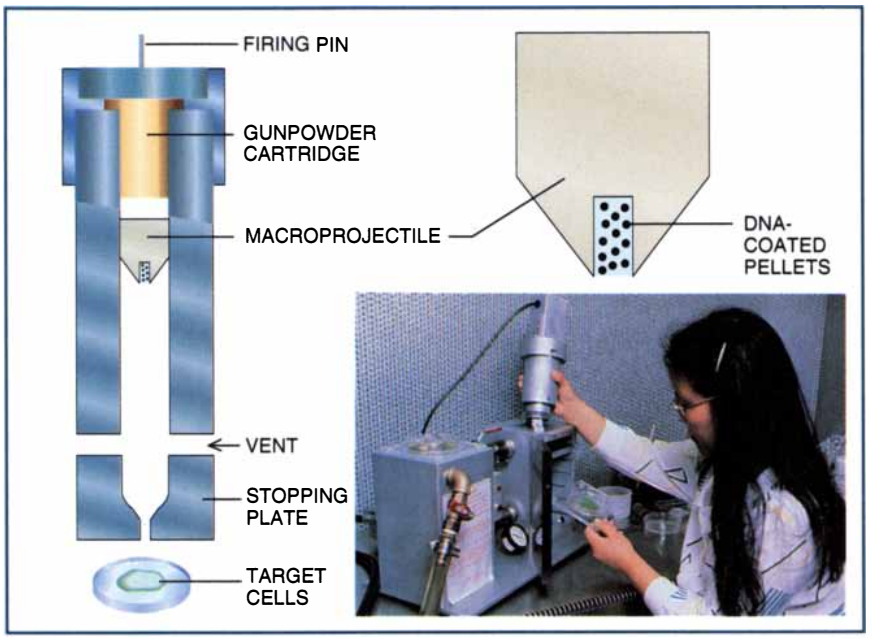
The usefulness of the *Bt*-based insecticides is often limited by the ease with which they are washed from plants. Furthermore, their effectiveness in the field lasts only briefly. In the mid-1980s genetic engineers at several companies, such as Plant Genetic Systems in Ghent, Belgium, Agrigenetics in Middleton, Wis., Agracetus and Monsanto, succeeded in isolating from the bacterium genes for the insecticidal proteins. They used the particle gun and *A. tumefaciens* to insert the genes into tomato, potato and cotton plants. At first, the genes expressed poorly; the *Bt* proteins the plant produced killed only the most sensitive laboratory insects.

Monsanto scientists David A. Fischhoff and Frederick J. Perlak made improvements. They redesigned the original bacterial gene to mimic more closely the plant DNA sequences. The changes dramatically enhanced insect control. Two years of field testing have confirmed that the presence of these *Bt* genes within cotton plants effectively controlled all major caterpillar pests, including the bollworm. These genetically engineered plants should reduce the use of insecticides on cotton by about 40 to 60 percent.

Scientists have screened extensively for naturally occurring *B. thuringiensis* strains that are effective on insects other than caterpillars. One such strain has led to the redesign of a gene that is effective against the Colorado potato beetle. In the summer of 1991, Russet Burbank potato plants expressing a beetle-control gene were tested at several sites from Maine to Oregon. Researchers found the potato plants to be essentially immune to beetle damage.

Bt may continue to offer additional genes for the control of plant pests. Scientists at Mycogen Corporation in San Diego have now discovered *Bt* genes active against plant parasitic nematodes, and *Bt* genes active against mosquitoes have been identified. Some researchers are trying to produce the mosquitocidal protein in algae as a means to control malaria.

The target specificity of the *Bt* pro-



DNA PARTICLE GUN developed by John C. Sanford of Cornell University fires tungsten pellets coated with DNA into plant cells. The pellets are held by a plastic macroprojectile, which is accelerated by a gunpowder charge. The plate stops the macroprojectile; momentum sends the pellets into the target. The vents allow air in front of the projectile to escape. In the photograph, a technician readying the device holds the "gun barrel" in her right hand; the cells to be transformed are in her left.

A substance abuse program at work can save employers money on insurance.

tein and its localization within the tissues of the plant ensure that the protein is active only against attacking insects. In contrast to topical insecticides, proteins in the plant obviously cannot be washed off. Extensive toxicological testing of *Bt* proteins and experience gained from more than 30 years of using *Bt*-based products confirm their safety. In fact, many researchers refer to *Bt* as the world's safest insecticide. Furthermore, the *Bt* protein, which makes up less than 0.1 percent of the total protein in the modified plants, breaks down in exactly the same fashion as any other protein—both in the soil and the digestive tract.

Besides the threat from viruses and insects, crops face a challenge from weeds. Weeds that compete for moisture, nutrients and sunlight can reduce a field's potential yield by 70 percent. Moreover, weed material in the harvest significantly reduces the value of the crop, and weeds serve as a habitat for pests.

In most cases, a combination of herbicide and careful cultivation effectively controls weeds. But because a herbicide has a limited spectrum of activity, affecting only a small portion of the weeds, several kinds of chemicals are often used during the growing season.

Genetic engineering may offer a partial alternative to such weed control. The strategy is to create plants that can tolerate exposure to a single, broad-spectrum, environmentally safe herbicide. In contrast to views expressed by some critics of genetic engineering, the use of herbicide-tolerant plants will actually reduce the overall amount of herbicide applied.

There are two general approaches to engineering herbicide tolerance. Researchers at Monsanto and at Calgene in Davis, Calif., have been working to enable plants to tolerate glyphosate, the active ingredient of a herbicide called Roundup. Roundup is a broad-spectrum compound that can control broadleaf and grassy weeds. The compound kills plants by inhibiting the action of EPSP synthase. This enzyme is necessary for the production of the aromatic amino acids that a plant needs if it is to grow.

Genetic engineers are especially interested in Roundup because it is one of the most environmentally attractive herbicides. It does not affect animals, because animals do not have an aromatic amino acid pathway. Furthermore, it degrades rapidly in the environment into harmless, natural compounds.

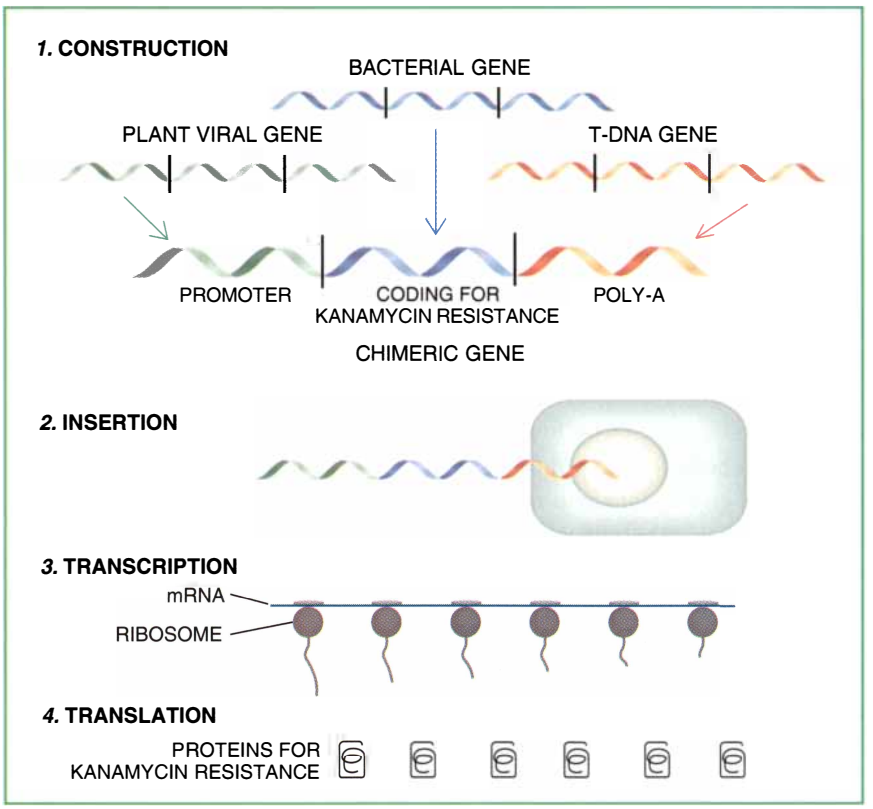
The first step in developing Roundup tolerance took place in 1983, when groups headed by Luca Comai and David M. Stalker of Calgene and Rogers and Ganesh Kishore of Monsanto isolated the genes for EPSP synthase from bacteria and plants. They also identified variants of the genes that produce proteins that have reduced sensitivity to Roundup. Later, investigators were able to construct genes that produced higher amounts of these proteins in plants. The genes were subsequently introduced into tomato, soybean, cotton, oilseed rape and other crops. As demonstrated by field tests performed during the past three years in the U.S., Canada and Europe, the crops were able to tolerate treatment with Roundup at levels that effectively controlled weeds. Researchers at Du Pont have used a technically similar approach to engineer plants that can tolerate certain kinds of sulfonylurea herbicides.

Scientists at Plant Genetic Systems and at the German company Hoechst took another approach to herbicide tolerance. From the microbe *Streptomyces hygroscopicus*, they isolated a gene for an enzyme that inactivates a herbicide called Basta, which affects the glutamine synthase pathway in weeds and thus interferes with their growth. But crop plants that have the gene inactivate Basta before damage can occur. Field tests performed on the Basta-tolerant plants demonstrate the effectiveness of the protection.

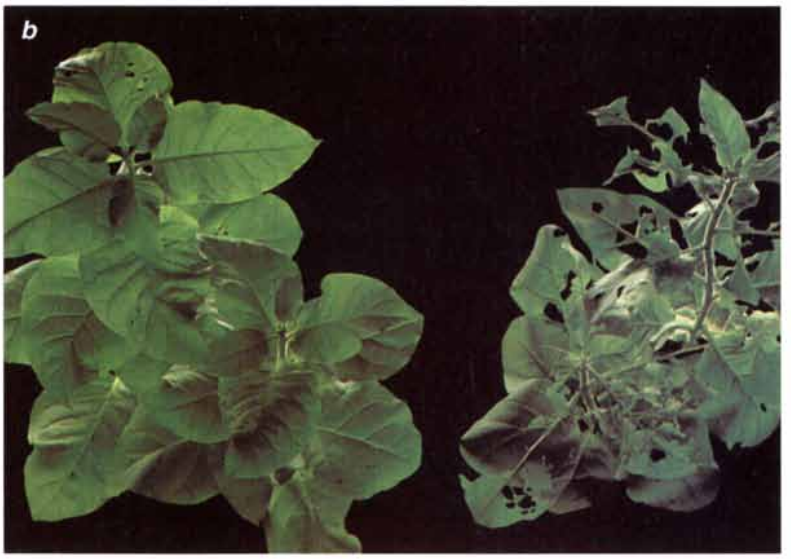
Engineered herbicide tolerance offers the farmer an alternative that is lower in cost and more effective than conventional weed-management measures. Careful selection of broad-spectrum herbicides should lead to an overall decrease in the use of weed-control chemicals and should enable farmers to replace existing herbicides with environmentally more attractive products.

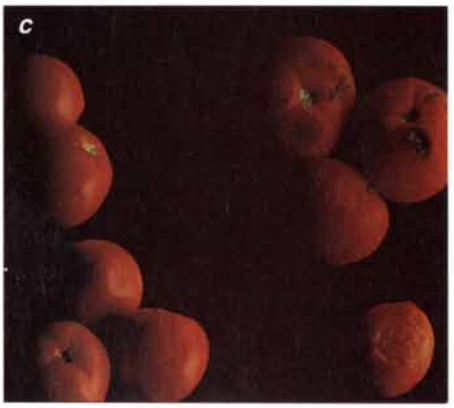
Additional advances in the simplicity and breadth of genetic engineering techniques and increasing knowledge of plant biology promise to extend greatly the beneficial changes that gene transfer can confer. For example, researchers have already identified and isolated several genes that play a role in the biosynthesis of ethylene, the signal molecule that triggers the ripening of fruits. Delayed spoilage would allow harvesting at a later stage than is currently practical, which may improve the flavor and even the nutritional value.

To increase the shelf life of fruit, re-



CHIMERIC GENES can be constructed from the genes of different organisms. Here the chimeric gene for kanamycin resistance is assembled from diverse sources: the promoter region of a plant virus, the coding region of an *E. coli* bacterium and the poly-A site from the transferred DNA (T-DNA) of *Agrobacterium* (*1*). After the chimeric gene is inserted into a plant cell (*2*), it is transcribed into messenger RNA (mRNA) (*3*). The ribosomes translate the mRNA to produce the proteins (*4*).





GENETICALLY ENGINEERED SPECIES

ALFALFA	CRANBERRY	PAPAYA	SPRUCE
APPLE	CUCUMBER	PEA	STRAWBERRY
ASPARAGUS	EGGPLANT	PEPPER	SUGARBEET
BROCCOLI	FLAX	PLUM	SUGARCANE
CABBAGE	GRAPE	POPLAR	SUNFLOWER
CARROT	HORSERADISH	POTATO	SWEET POTATO
CAULIFLOWER	KIWI	RASPBERRY	TOBACCO
CELERY	LETTUCE	RICE	TOMATO
CORN	MUSKMELON	RYE	WALNUT
COTTON	OILSEED RAPE	SOYBEAN	WHEAT

GENETICALLY TRANSFORMED CROPS, shown to the left of their ordinary counterparts in each photograph, include herbicide-tolerant cotton plants (*a*), insect-resistant tobacco plants (*b*) and tomato plants whose fruits resist spoilage (*c*). The list identifies familiar plant life in which genetic engineering has successfully been demonstrated.

searchers developed two genetic methods. The first is inserting so-called antisense versions of the ripening genes. Antisense molecules bind with specific messenger RNA to turn off the genes. Athanasios Theologis of the USDA in Albany, Calif., and Don Grierson of the University of Nottingham have shown that fruits of tomato plants with the antisense genes resist softening. In a different approach, Monsanto scientists Kishore and Harry Klee have introduced a gene into tomato plants that induces them to manufacture an enzyme. This enzyme degrades the precursor compounds that form ethylene, thus retarding spoilage.

Genetic engineers may also be able to fashion healthier foods: genes for proteins that have superior nutritional properties have been isolated. It should be possible to insert these genes into crops. Plants could also be tailored to produce specialty chemicals such as starches, industrial oils, enzymes and even pharmaceuticals. Preliminary trials are now under way.

More than 400 field tests of engineered plants have now been conducted in the U.S. and Europe. The tests confirm the inherent safety and commercial validity of these approaches, and crops containing these traits should be available to farmers during the mid-1990s. Still, there are some limitations. In practical terms, genetic engineers can only modify traits expressed by no more than three to five genes. Furthermore, some crops do not respond to current gene-transfer methods, and isolating useful genes is sometimes difficult.

Yet to many in plant biotechnology, these challenges seem less likely to delay commercialization than are nontechnical issues. Genetically modified crops are being developed at a time when both public and political support for agricultural research is in general tepid. Concerns about food safety, the environmental impact of agriculture and a rapidly changing farm infrastructure have combined with a lack of understanding of new technologies to overshadow the long-term need for economical, high-quality food products. World food production will have to increase threefold during the next 40 years to meet the needs of an estimated nine billion people. Biotechnology is one of the few new solutions to this problem.

Another important advantage of the genetic engineering of plants is that it provides the very latest technology to farmers in a very traditional package—the seed. Even the most impoverished nations will thus have access to the benefits without the need for high-technology supplies or costly materials. Although not a panacea, biotechnology promises to become an important component of agriculture around the world.

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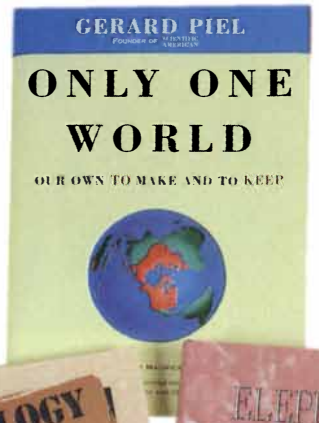

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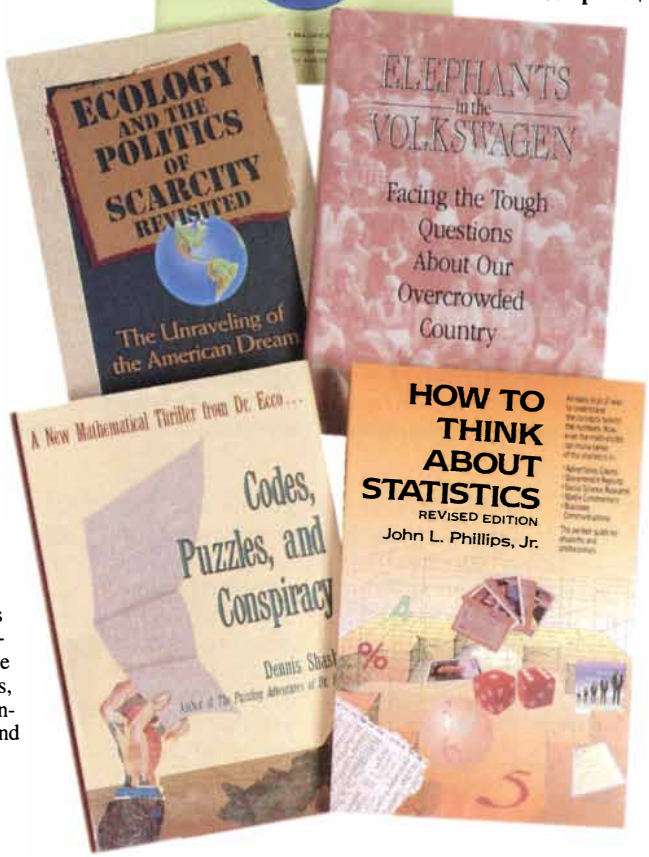

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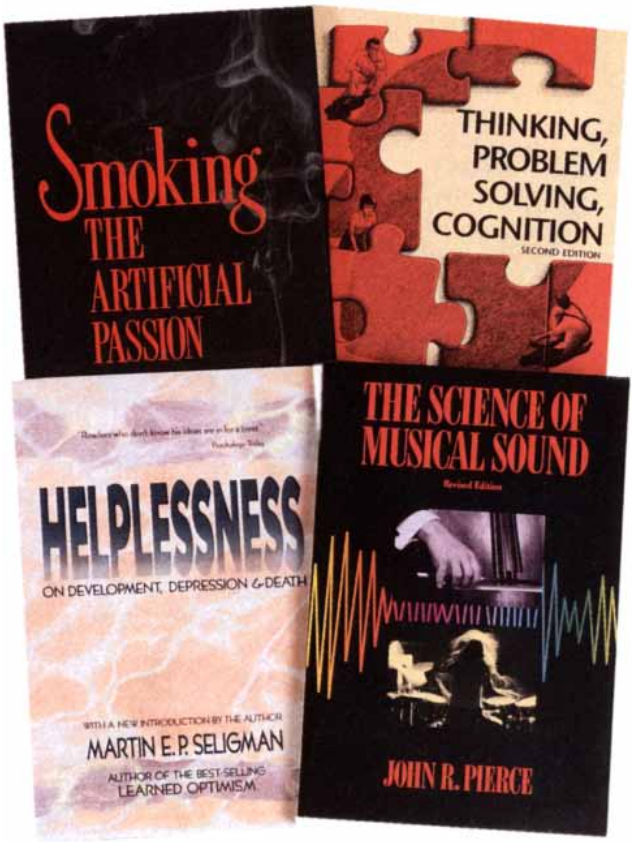

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The Codex Mendoza

This magnificent pictorial book, compiled by Aztecs at the instigation of their Spanish conquerors, constitutes an eyewitness account of a rapidly vanishing civilization

by Patricia Rieff Anawalt and Frances F. Berdan

When Hernan Cortés and the conquistadors who accompanied him subjugated the Aztecs in 1521, they found in these native Americans a combination of simple technology and impressive cultural achievements. The Aztec Empire was vast and populous, spanning Central Mexico from sea to sea and encompassing some 20 million people. About a tenth of that population lived in the capital of Tenochtitlán, which equaled or surpassed in size most of the cities of Europe. Today, under the name of Mexico City, it is fast becoming the largest metropolis in the world.

The Mesoamericans employed a pictographic writing system that comes down to us in a few remaining books made of fig-bark paper or deerskin. The manuscripts were used to record genealogies, histories and tribute tallies and to serve as ritual, divinatory and calendrical manuals. Hundreds of these Mesoamerican codices, as they now are known, went up in flames soon after the Conquest, victims of the zealotry of proselytizing priests. Yet only a few decades later some Spanish friars began commissioning native artists to record selected aspects of the quickly vanishing civilization.

None of these colonial codices is more magnificent or informative than the Codex Mendoza, prepared on 71 folios of Spanish paper in Mexico City around 1541 to acquaint Charles V of Spain with his exotic new subjects. The manuscript apparently was produced at the instigation of Mexico's first Spanish viceroy, Antonio de Mendoza, who wanted to obtain a firsthand account of Aztec life while the last pre-Conquest natives still lived.

FOUNDING OF TENOCHTITLÁN in 1325 is depicted on the first folio of the Codex Mendoza. The city's place glyph, an eagle on a cactus, remains modern Mexico's emblem. The burning temples, teetering atop stepped pyramids (*bottom*), represent the conquest of two nearby city-states.

The compilation of the Codex required teamwork, as the document itself reveals. The hand of a single master painter is apparent on all the pictorial pages; other hands, undoubtedly those of his assistants, prepared the pigments and applied the color in flat washes. Informants who had lived the best part of their lives under Aztec rule interpreted the pictures in Nahuatl (pronounced "NA-hwat"), the Aztec language that served as the lingua franca of Mesoamerica. These comments were then translated into Spanish and transcribed on each facing page by a Spanish priest.

Viceroy Mendoza remarked in a letter, dated October 6, 1541, that the priest compiling the pictorial had drawn on the knowledge of "many lords of each province" and that among them there had been considerable diversity of opinion. The resulting indecision frustrated the harried scribe, who on the last page of the codex apologizes for certain hastily corrected errors and complains that he had not had enough time to finish his work properly: "It was the fault of the Indians, who were slow in coming to agreement."

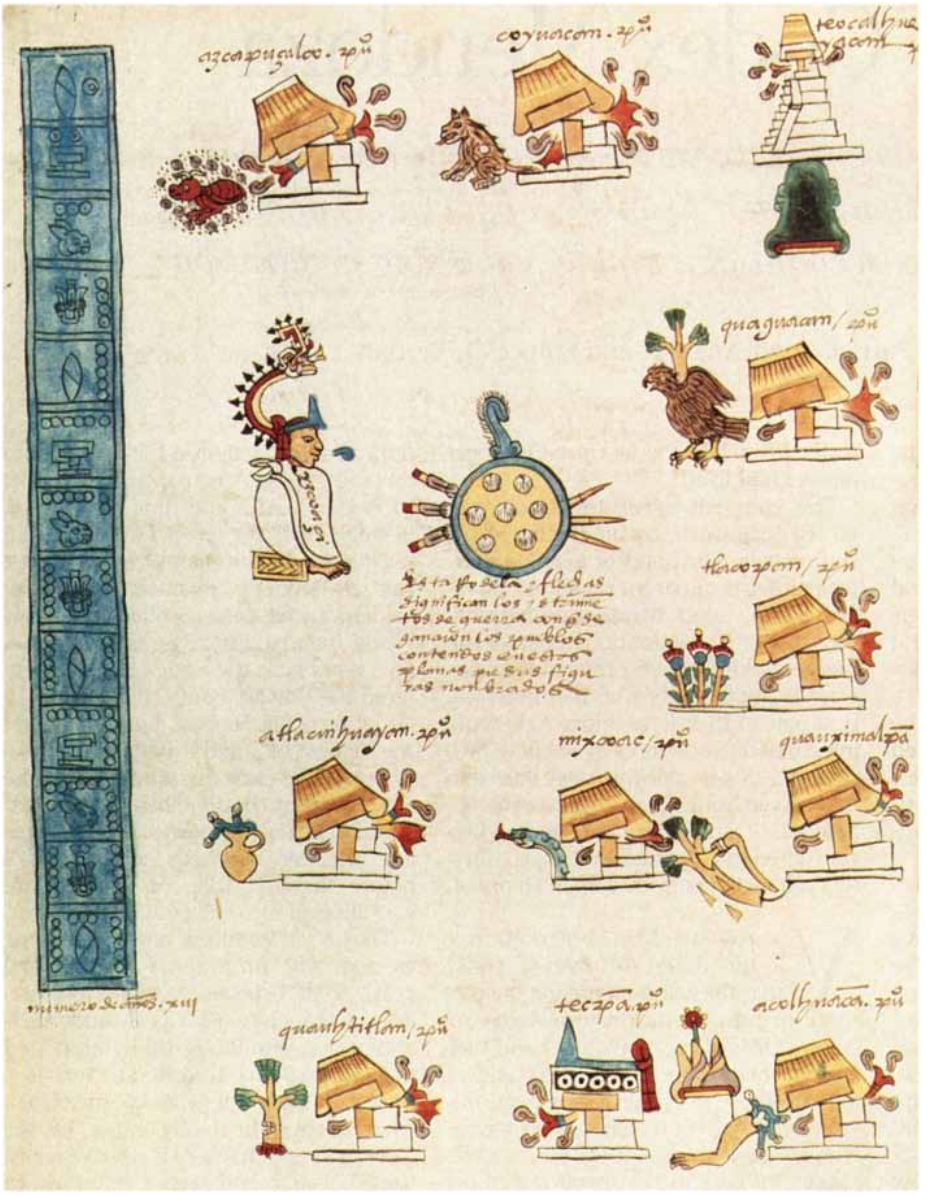
Time was short because the scribe had to ship the document before hurricane season. Accordingly, he rushed to prepare the folios for transport on a mule train, which then jostled down some 250 muddy miles of twisted trail that descended 7,000 feet to the port at Veracruz, whence departed the annual treasure fleet.

The Codex Mendoza never reached Spain. En route, the galleon carrying the manuscript was captured by a French man-of-war, and all its booty was taken to the Court of Henri II of France. There the document came into the possession of the king's geographer, Andrés Thevet, a cleric whose signature appears three times in the 71 folios.

After Thevet's death, Richard Hakluyt, chaplain to the English ambassador in France, acquired the Codex Mendoza for 20 French crowns and took it to England. At some time after 1616, it came into the possession of Samuel Purchas, a compiler of travel books. His son sold the manuscript to John Selden, a well-known collector of New World manuscripts, who died in 1654. Five years later the Codex Mendoza entered the University of Oxford's Bodleian Library. Sir Thomas Bodley had set the highest of standards for the collection that he gave his alma mater: he was adamant that no "baggage books" should clutter its shelves. It was a decade after Sir Thomas's death in 1613 before the first folio of Shakespeare was allowed into the Bodleian.

The Codex Mendoza, now safely come to rest, was forgotten for some 170 years. Such respected New World scholars as Francisco Clavigero and Alexander von Humbolt—both interested in Mexican native-tradition pictorials—knew nothing of the manuscript's whereabouts. It finally came to the world's attention in 1831, after Viscount Kingsborough had seen a reference to

PATRICIA RIEFF ANAWALT and FRANCES F. BERDAN collaborate in the study of Aztec culture. They have also researched present-day Nahuatl-speaking weavers for five field seasons with funding from the National Geographic Society. Anawalt directs the Center for the Study of Regional Dress in the Fowler Museum of Cultural History, a division of the University of California, Los Angeles, where she earned her Ph.D. in 1975. She has served on the President's Cultural Property Advisory Committee since 1984. She has written widely on Mesoamerican textile arts, past and present. In 1988, as a Guggenheim Fellow, she established a data bank of textile motifs from the Aztec period. Berdan received her Ph.D. from the University of Texas at Austin in 1975. She has written six books and many articles on Aztec culture and early colonial Mexico.



VICTORIES OF ITZCOATL (*left*) are commemorated in the place glyphs of the 11 communities the emperor conquered during his 14-year reign. They surround the ruler, who sits facing Tenochtitlán's martial emblem, a shield with a design of down balls backed by three darts and a spear-thrower. The curling glyph in front of the ruler's mouth represents speech.

TRIBUTE TALLY of Tochtepec (*right*), a province along the Atlantic Gulf coast, contains 22 place glyphs (*counterclockwise, from upper left*). The textile ideograms at the top are accompanied by a counter indicating that 2,800 must be sent annually. Beneath them appear a feathered warrior suit with a quetzal-bird back device, shields, a yellow-feather back device, diadems and necklaces of gold, strings of greenstone beads, as well as various colors of tropical feathers and bundles of cacao beans.

it in an account of the holdings of Thevet. Kingsborough was so impressed with the Codex that he featured it as the initial manuscript in his massive nine-volume *Antiquities of Mexico* set, published between 1831 and 1848.

A century later a beautiful but ill-fated Codex Mendoza was edited by James Cooper Clark and published by Waterlow and Sons Limited. Sadly, almost the entire run was blown up in the London Blitz of 1940. (A new four-volume edition has just been completed by the authors and will be published by the University of California Press this month.)

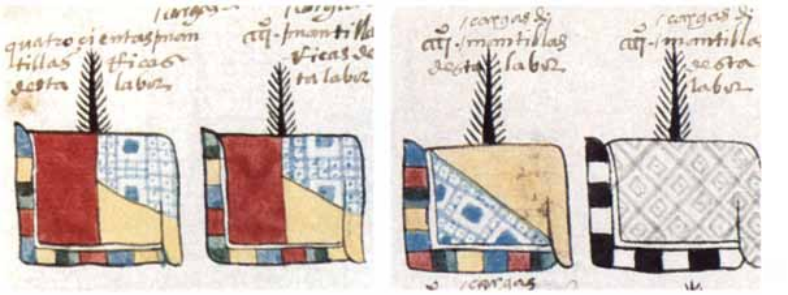
The Codex Mendoza falls into three parts. The first 19 folios give the history of the conquests of the Mexica of Tenochtitlán, as the Aztecs referred to themselves. The next 37 folios tally tribute from the empire's 38 provinces (some of which took up more or less than a single folio). The final 15 provide an ethnographic account of the Aztec life cycle.

Although Tenochtitlán predominated, the people of two other cities—Texcoco and Tlacopán—also participated as lesser partners. In the 1940s Robert H. Barlow of the University of California at Berkeley referred to this arrangement as the Triple Alliance Empire. The term "Aztec," on the other hand, was first employed in 1813 by von Humbolt, who derived it from "Aztlan," the Mexica's mythical home. Thirty years later William H. Prescott popularized Humbolt's neologism in his book *The Conquest of Mexico*.

The first pictorial page of the Codex Mendoza depicts the Aztecs' founding of Tenochtitlán in 1325 [*see illustration on page 70*]. It represents both fact and legend. According to their migration myth, the Mexica had originally lived as nomadic hunter-gatherers in the deserts of northern Mexico. Then, early in the 12th century, they began migrating southward, becoming the last in a series of such wanderers to arrive in the Valley of Mexico. The only place left for them to settle was an unpromising island, but there they found the omen their god had promised: an eagle perched on a cactus growing out of a rock. This site inspired the place glyph of Tenochtitlán, "Among the Stone-Cactus Fruit," which, with the addition of a snake in the eagle's mouth, serves as Mexico's national emblem.

This swampy island grew into a metropolis of 200,000 people by 1519, at which time it had developed discrete regions divided by crisscrossing canals. The pictorial anachronistically shows well-defined quarters, one of which contains a skull rack—the Codex Mendoza's only overt reference to the Aztecs' practice of large-scale human sacrifice.

This initial folio is bordered by a calendrical account of the 51-year reign of the migratory bands' leader, Tenoch. At the bottom of the page, two vignettes lay claim to quite improbable conquests. They imply that the Mexica, in their impoverished early years, managed to conquer Colhuacan and Tenayucan, two settled and powerful 14th-century communities in the Valley of Mexico. The symbol of conquest, a burning temple teetering atop a stepped pyra-



EXCLUSIVE DESIGN, attesting pride of descent, appears in tribute textiles (*above*) shown in the Codex Mendoza. The same design of dotted squares can be seen in the cloak of King Nezahualpilli of Texcoco (*right*), depicted in the Codex Ixtlilxochitl. The 11 provinces entitled to contribute such textiles limn the boundaries of earlier kingdoms (*far right*), whose rulers traced their lineages to the venerated Toltecs.

mid, has been placed next to each conquered community's place-name.

Such place glyphs reveal several levels of complexity in Aztec writing. At its simplest, the system is pictographic: a picture of a man hunting means only that, a hunter. The next stage of abstraction is the ideographic: an image conveys an idea. An ideogram of a footprint indicates a path and hence a direction or journey. The most abstract level is the phonetic: here characters represent sounds rather than images or ideas. Rebus writing applies this principle, as do many Aztec place-names.

For example, the place glyph *Tochpan* is formed by combining *tochtli,* rabbit, with a suffix to denote a place. In Nahuatl the word *pan* means "on, on top of, over." But pictorially, the sound-alike suffix is taken from *pantli,* flag or banner. The result of combining *tochtli* and *pantli* is the rebus form of a flag atop a rabbit: *Tochpan,* "Place of the Rabbit." (Rabbits carried religious connotations linking them to the moon, fertility and inebriation.)

Many of the Codex Mendoza's place glyphs appear in the history section, where they represent the conquests that constituted the significant events in a monarch's reign. These 19 folios are actually victory chronicles rather than secular histories. The Codex presents the reigns of the nine Aztec rulers identically. Each emperor sits facing the martial symbol of Tenochtitlán, a shield decked with balls of down and backed by three darts and a spear-thrower. The years of the emperor's rule are to his back; his conquered communities surround him.

Whereas the history section emphasizes the expansion of the empire's domain, the following section on tribute indicates its wealth. Political scientists classify the Aztec realm as a tribute empire because the central authority did not permanently occupy any of the 38 provinces, nor did it compel their populations to relocate.

This approach to empire building reflects the Mesoamerican view of warfare, in which the point was not to destroy the enemy but to subordinate him. As the glyph for conquest indicates, the strategy centered on burning the other side's principal temple. That feat was taken as a sign that the gods had spoken and hence that hostilities should cease and bargaining over tribute should begin.

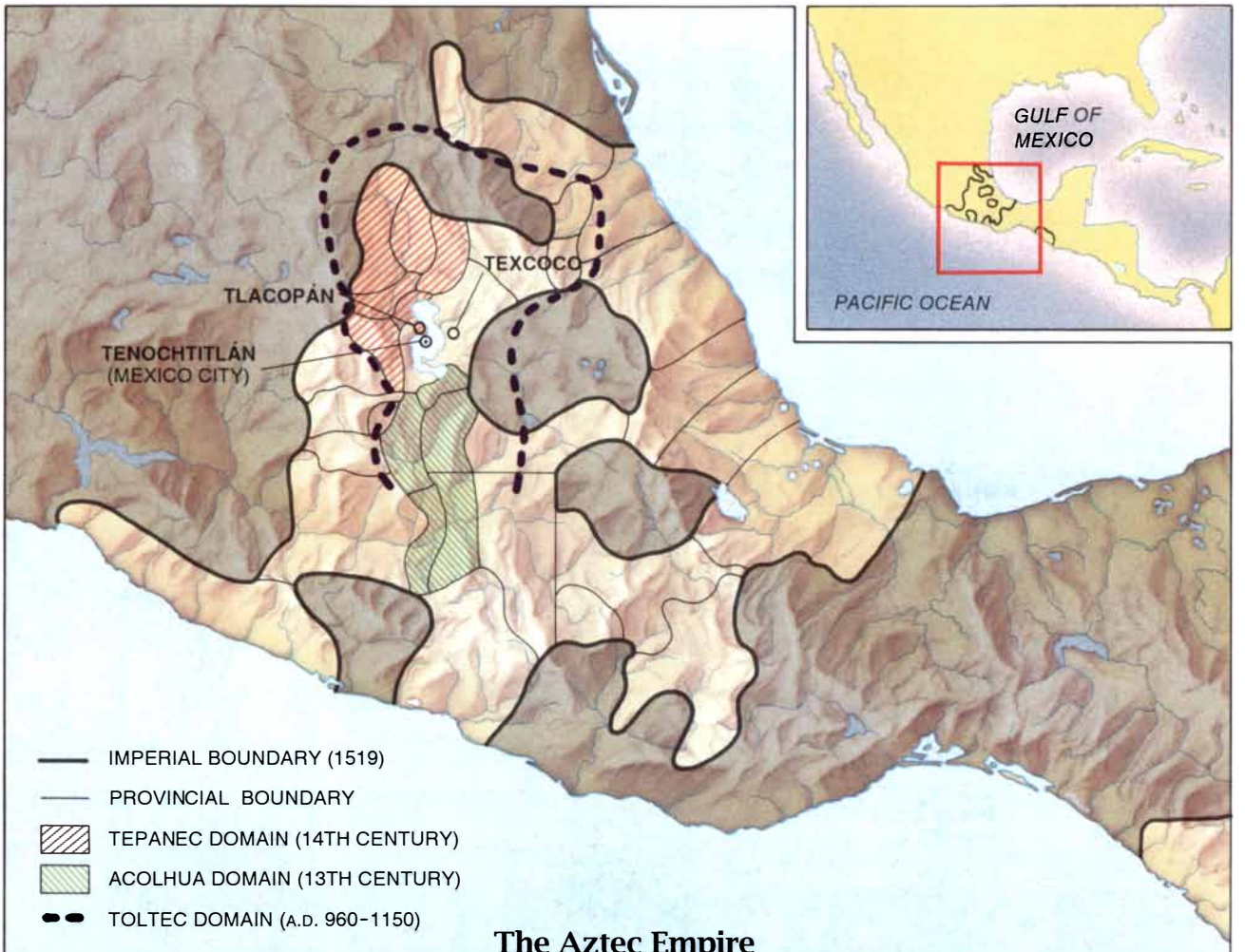
With each successful conquest, the Aztecs gained territory, subjects and economic resources in the form of tribute. The management of these goods required a formal accounting system. We now know that part 2 of the Codex Mendoza represents the tribute sent to Tenochtitlán in the years just prior to European contact, from 1516 to 1518.

The tribute to be paid by each province is depicted in a set format. The place glyphs of the tribute towns line the margins. Each province was known by the name of the first community listed. The rectangular ideograms at the top represent textiles. They are followed by the elaborate feathered costumes that served as the uniforms of the Aztec military [*see top of illustration on preceding page*]. Below this flamboyant martial apparel, bins of foodstuffs often appear, including maize, beans and amaranth seeds, as well as such exotic items as jaguar pelts, live eagles, bales of cacao and smoking tubes.

The most precious items were greenstone jewelry and shimmering quetzal feathers [*see bottom of illustration on preceding page*]. One might wonder how the quetzal population could survive the demands of the luxury trade. The Aztecs, unlike Europeans of the day, conserved their resources. They would trap the bird, pluck its long tail feathers and release it to produce more feathers and more quetzals, too.

The conquistadors' eyewitness accounts make it clear that the Aztecs' remarkable feather warrior costumes and towering back devices were actually worn into combat as psychological reinforcement. Each warrior costume carried an elaborate supernatural symbolism; to don this apparel was to invoke the power and protection of the deity involved.

Eleven styles of warrior costumes appear in the tribute tallies, each representing the religious affiliation of a particular corps within the Aztec fighting force. The battle attire most frequently pictured on the imperial tribute rolls is the *cuextecatl,* the Huaxtec warrior costume [*see illustration on page 78*]. This suit, whose main characteristic is its pointed headpiece, was paid in tribute from 20 culturally and geographically diverse provinces but, strangely, not



The Aztec Empire

The Aztec Empire was ruled by three city-states in the Valley of Mexico: Texcoco, Tlacopán and, preeminently, Tenochtitlán. In 1519 the imperial domain stretched from sea to sea and from what is now north-central Mexico to the borders of Guatemala. Beyond the highly urbanized Valley of Mexico, imperial power became attenuated. In the hinterlands, the emperor ruled through alliances—at times established by marriage—and by threats of reprisal against whoever might rebel.

The Triple Alliance was a tribute empire, regularly receiving goods from its conquered regions. Not all the provinces were contiguous: some parts of central and southern Mexico remained independent of Aztec control, either because their defensive strength was too great or their economic value was too small to justify conquest.

Typically, defeated rulers were allowed to retain local power, although they served thenceforth as the emperor's vassals. Among them were the nobles who governed the 11 provinces the Aztecs had carved from two earlier realms, the Acolhua, of the 13th century, and the Tepanec, of the 14th. These nobles traced their lineages through the ruling houses of the two prior kingdoms and thence to the royal bloodline of the Toltec Empire, which had collapsed in A.D. 1150. In commemoration of this prestigious heritage, the nobles of the 11 provinces displayed the Toltec genealogical marker on their tribute textiles.

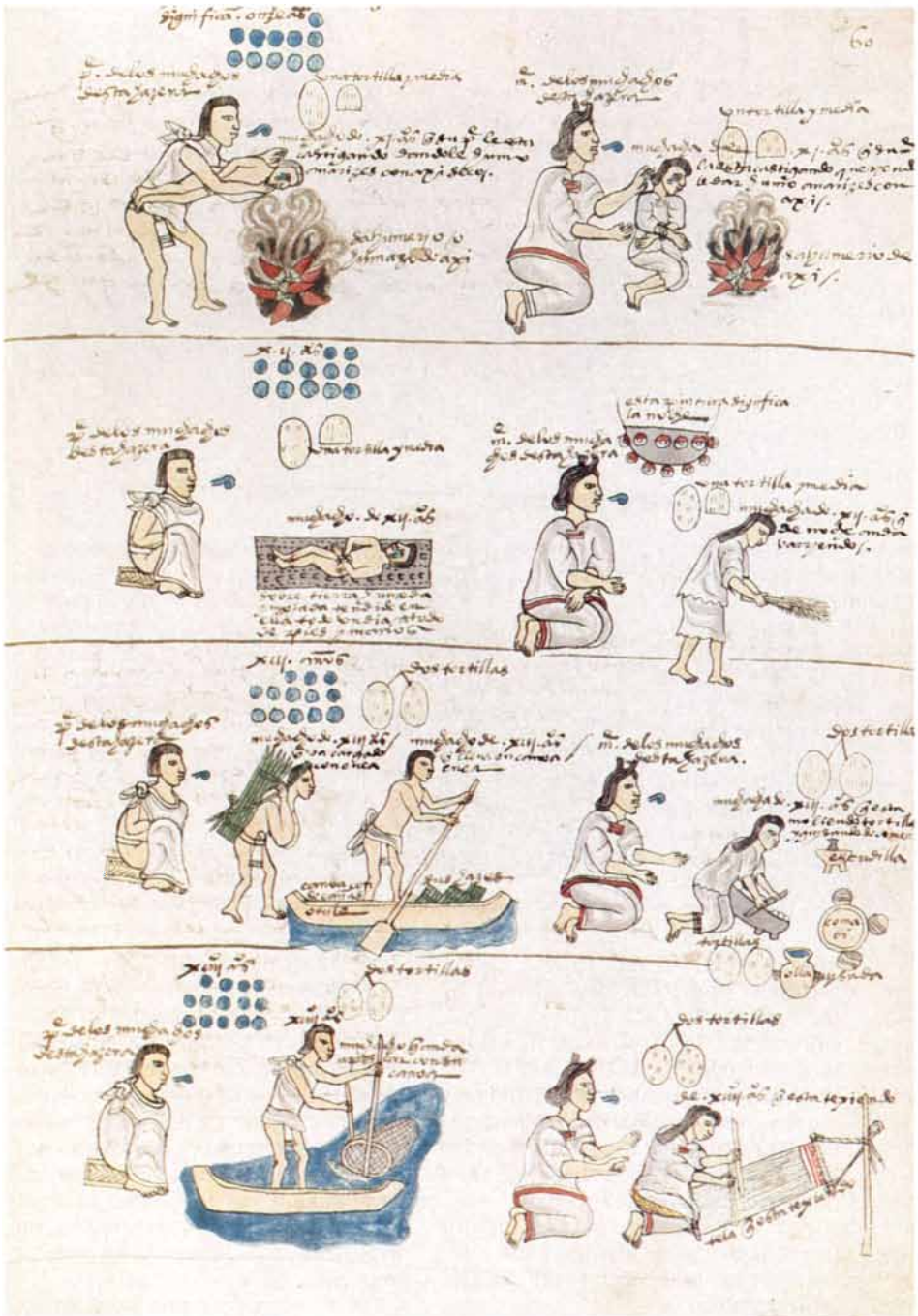
from the Huaxtec region. A portion of the Huaxteca became the Aztec provinces of Tziccoac and Oxitipan. Perhaps the *cuextecatl* was so prominent among the forms of Aztec military attire because it represented the first step up from the entry-level warrior costume, a thickly padded, cotton armor—one so effective that the Spanish conquistadors quickly adopted it. When a young warrior took his first captive in battle, he earned the right to wear the *cuextecatl* over his protective armor.

All of the *cuextecatl*'s Huaxtec-derived imagery—pointed hat, rosette, cotton eardrops—apparently was adopted by the Mexica after the Emperor Axayacatl's victory in the Huaxtec region (he reigned from A.D. 1470 to 1481). The Huaxteca was unusually fertile and productive, renowned for its excellent cotton and abundant foodstuffs and for the erotic and licentious behavior of its populace. This verdant tropical world, part of what the Aztecs called the Hot Lands, held a particular fascination for the more inhibited denizens of the arid central plateau.

Quite fascinating to the Aztecs was the Huaxtecs' penchant for strong drink. Their costume bears a characteristic emblem of this trait in its crescent-shaped nose ornament. The crescent was a symbol of the gods of pulque, Mesoamerica's most important intoxicant, made from the fermented juice of the maguey plant. Today some Mexicans still drink pulque, but they have given up the Aztec custom of strengthening the drink with a root having hallucinogenic properties.

The Aztecs were ambivalent toward

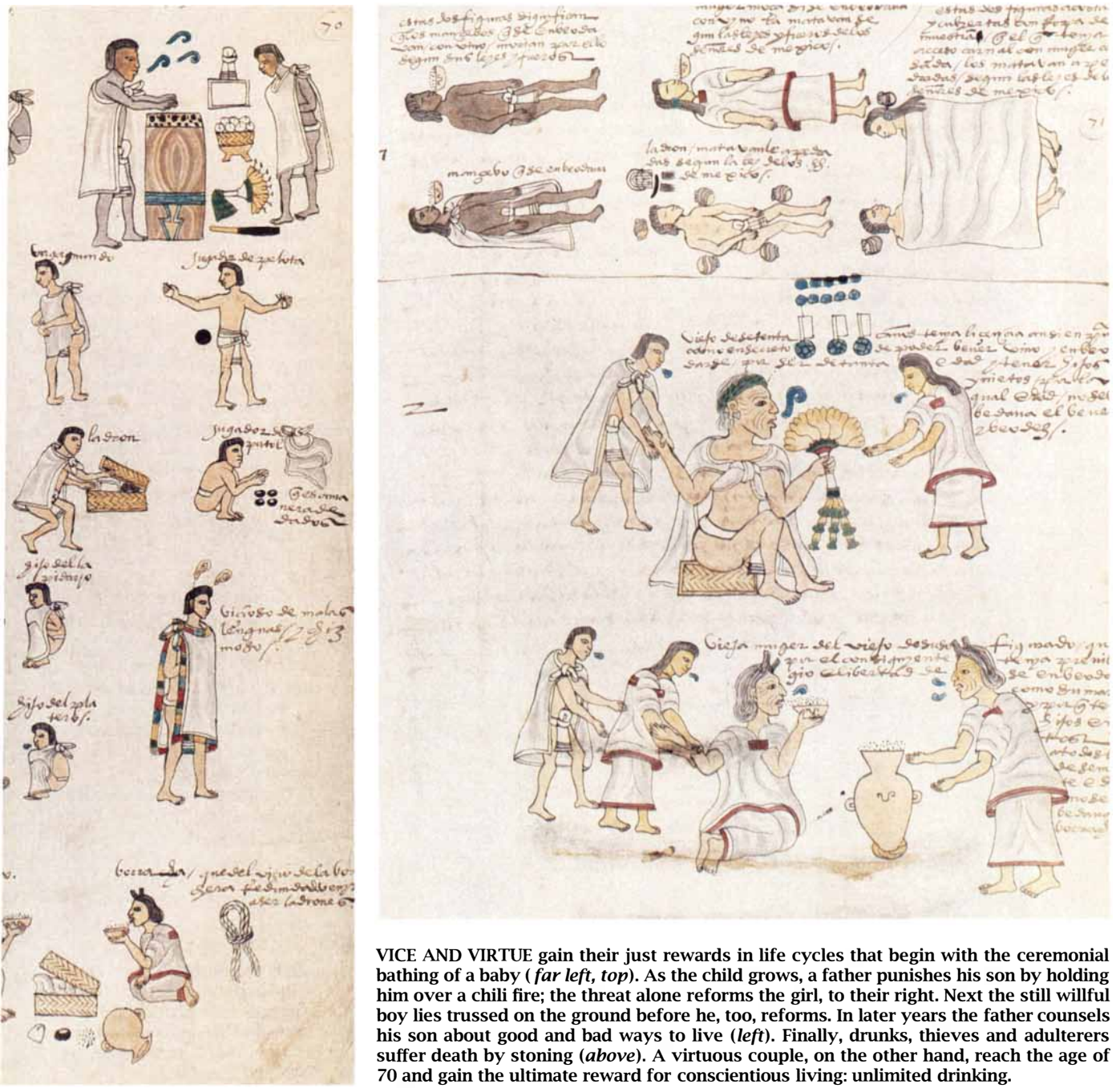
strong drink and drunkenness, acknowledging the felicitous aspects of inebriation but surrounding it with strict prohibitions. Their laws carefully limited the imbibing of pulque to ritual contexts, at least until citizens had reached the age of 70, when they were allowed to drink freely [*see illustration on opposite page*]. Whether many could have reasonably hoped to live to so ripe an age remains an open question. After the Conquest, the Aztecs contended that their longevity had been much greater before the coming of the Spanish, although their practice of cremation has left little evidence with which to judge the matter.



The problems involved in controlling the alcoholic intake by the rest of the populace must have been severe, judging from the stringent measures taken: the Spanish chronicles assert that infraction meant death. Yet the association of the rabbit—the Aztec symbol of inebriation—with the revered pulque cult suggests approval of the uninhibiting effects of the drink on procreation. The underlying message of Aztec symbolism invariably is the maintenance of fertility.

The appearance of the cult of the pulque gods along the Gulf coast is particularly intriguing because the type of maguey from which the fermented drink is made does not grow at those low altitudes. Tochpan and Tochtepec's emphasis on pulque-associated designs implies an ancient, pre-Aztec introduction of maguey products and their accompanying motifs into these areas. Gulf coast cloaks carrying pulque jug designs were worn in official ceremonies by the Mexica of Tenochtitlán. This practice suggests that the relatively new Aztec Empire sought validity through incorporation of an older culture's iconographic tradition.

The Codex Mendoza tribute tallies contain an even better example of this phenomenon. A set of tribute textiles contains a pattern of repeating blue-and-white squares, each with a dot in the middle. This pattern, created by the tie-dying technique known today as plangi, must have carried tremendous significance because it marked the official mantle of Aztec rulers [*see illustration on page 74*]. The key to the meaning of this design lies in the geographic distribution of the 11 Aztec provinces that featured parts of the motif on the textiles they paid in tribute. Not only are these territories contiguous, their borders also closely outline portions of two pre-Aztec kingdoms. Both had been founded in the wake of the venerable Toltec Empire, whose collapse in A.D. 1150 had stripped its nobles of



VICE AND VIRTUE gain their just rewards in life cycles that begin with the ceremonial bathing of a baby (*far left, top*). As the child grows, a father punishes his son by holding him over a chili fire; the threat alone reforms the girl, to their right. Next the still willful boy lies trussed on the ground before he, too, reforms. In later years the father counsels his son about good and bad ways to live (*left*). Finally, drunks, thieves and adulterers suffer death by stoning (*above*). A virtuous couple, on the other hand, reach the age of 70 and gain the ultimate reward for conscientious living: unlimited drinking.

their patrimony but not their prestige.

The parvenu Acolhua and Tepanec—who, like the later Mexica, began as nomads—therefore sought to legitimize their conquests by marrying into the house of the small city-state of Colhuacan, whose leadership could still claim pure Toltec descent. They thus earned the right to pass the tie-dye marker of royal Toltec lineage to both female and male descendants. The Aztec rulers' official capes were genealogical statements, heraldic devices that declared the Aztecs' legitimate claim to the prestigious and essential Toltec heritage.

The ethnographic part of the Codex was the only one of the three that has no pre-Hispanic model. It depicts the Aztec life cycle, beginning with the ritual naming of a newborn child, which includes symbols denoting possible future occupations. For boys, the first image is a shield with arrows; all Aztec males were trained as warriors before becoming farmers or specializing by craft or profession. A display of craft specializations follows; for girls, however, only a broom, spindle and workbasket are portrayed [*see top left illustration on page 76*].

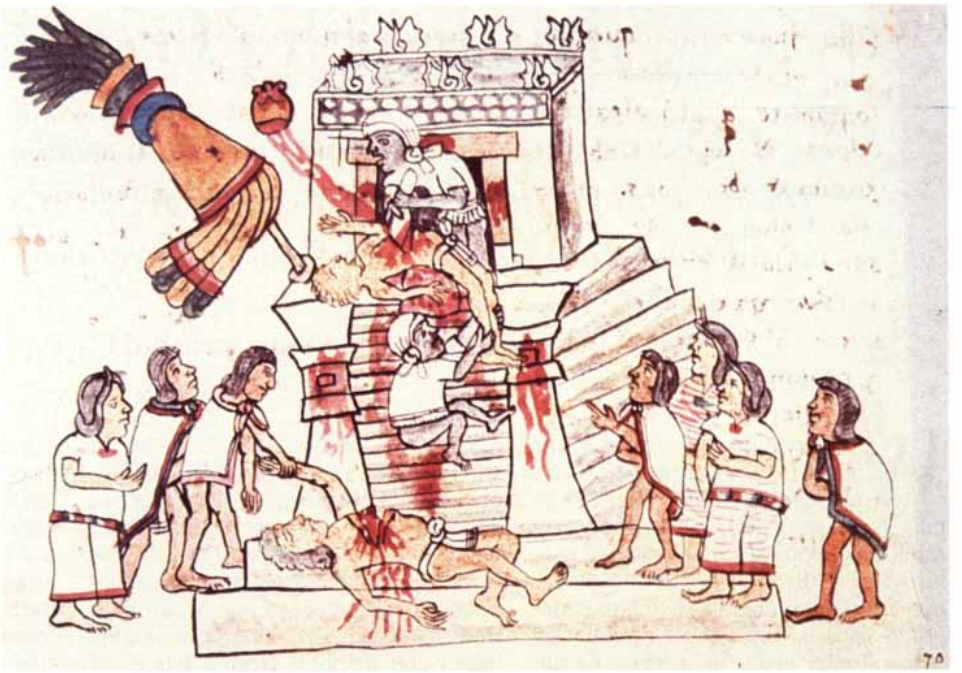
Subsequent folios cover ages three through 15, each year noted by a turquoise-blue dot. The proper amount of food per meal is symbolized by its tortilla ration: half a maize cake at the age of three, two by 13. Such limits on food, like those applying to strong drink, reflect an almost Spartan emphasis on self-denial, discipline and the other martial virtues. And, as in the case of the Spartans' child-rearing practices, the emphasis on punishment increases as the children grow older.

Every parent was obligated to inculcate the Aztec code of obedience, moderation, modesty and diligence. Misbehavior at the ages of eight or 10 resulted only in hands being struck with a stick or the jabbing of maguey spines into the flesh, but as the children grew older the punishments became increasingly severe [*see illustration on page 76*]. In the depiction, the boy, still willful at 11, is held over the acrid smoke of a chili fire. The girl is also threatened with this cruel practice but apparently sees the error of her ways. In the subsequent vignettes, she dutifully sweeps, grinds corn and weaves on the backstrap loom. The son, meanwhile, remains intractable through age 12, and hence he is bound and forced to sleep on the damp ground. By 13, however, he, too, is helping with family chores, carrying reeds and industriously catching fish from Lake Texcoco.

The child-rearing folios are followed by illustrations of the two types of training offered boys. Noble youths had an intellectual, priestly and military curriculum, whereas the education of commoners concentrated on practical skills as well as warrior training. Females, who married around the age of 15, appear infrequently in subsequent folios.

The primary aim of male education was to produce intrepid warriors, an end to which the flamboyant military attire served as an incentive. If the strategic point of war was lim-

MILITARY PROMOTIONS came with each prisoner captured. The red-clad warrior at the bottom right has passed through all the ranks to become an honored general.



HUMAN SACRIFICE is depicted in the Codex Magliabechiano, compiled in the Valley of Mexico sometime before 1566. A palpitating heart appears at the left; the body of a prior victim has already been rolled down the stairs.

ited to burning the enemy's major temple, the tactical goal was also limited: one typically sought not to kill but merely to capture enemies, so that they might later be offered to the gods. Such sacrifices were always highly ritualized affairs.

When a soldier overwhelmed his foe, he recited the formula, "He is as my beloved son," and the captive responded, "He is as my beloved father," thus accepting his fate as the god's elect. Later, on the apex of a stepped pyramid, the waiting priests would cut out the victim's heart and offer it to the deities. At the point of death, the sacrificial victim was thought literally to become a god, a great honor in the eyes of both the Aztecs and their foes, with the assurance of the most glorious of afterlives.

It should be noted that sacrificial captives furnished only part of the gods' ritual gift. Most blood offerings came from self-sacrifices periodically required of every Aztec man, woman and child. People would draw blood from fleshy parts of the body and offer it to the various deities on their designated feast days. Most important of all were offerings in sustenance of the sun god, on whom the fate of the world was thought to depend.

Warfare, by meeting religious obligations, providing upward mobility for warriors and extending the power of the state, became so formalized that neighboring states would arrange dates for their battles. As a consequence of this highly stylized warfare, the Spanish would surely have gained the upper hand even without the technological advantages of cavalry against foot soldiers, steel against obsidian and guns against spear-throwers.

The final folios describing the life cycle present what the Aztecs deemed the just rewards of virtuous and worthless lives [*see illustration on page 77*]. In this pictorial, a father explains to his son not only the merits of working hard at one of the crafts but also the pitfalls that await the foolishly idle—the rootless vagabond whose sadly twisted limbs bear the mark of a vengeful goddess's attack; a fanatic ball player, a young man who literally bets his shirt in the game of patolli; a sneak thief; a gossip; and a young couple who drink to excess and become thieves.

At the end, drinkers, a thief and an adulterous couple lie dead, executed by stoning, whereas a worthy older couple of 70 years basks in the solicitous care of their grandchildren. The old man sings loquaciously as he enjoys a flower bouquet; the grandmother and her aged friend appear to have given themselves over completely to the pleasures of drink; both the foaming jug and cup bear the crescent-shaped symbol of the pulque gods.

Rich as this information is, one wishes for still more descriptive detail. For example, with the exception of the military attire, the clothing throughout the ethnographic section is shown with neither design motifs nor color decoration, a far cry from the eyewitness accounts of Aztec apparel and many of the textiles depicted in the Codex Mendoza's tribute tallies.

But in this final part of the Codex, the Spanish were asking for something that probably had never been seen before in the New World: a depiction of the culture and life cycles of a people. This the master painter did as well as his own pre-Hispanic mode would allow. His brilliant effort, recorded only 20 years after the arrival of the Europeans, represents a fascinating adaptation of the indigenous style to an Old World theme. Considering the many other changes the Aztecs had already undergone after the Conquest, this was one of the mildest adjustments that the Spanish required of their subjects.

Of all the cultural traumas precipitated by Columbus's discovery of the Americas, none was more dramatic than Cortés's conquest of the Aztec Empire, a true War of the Worlds. Here were met two cultures of comparable social complexity and artistic achievement, each completely unknown to the other. Their cataclysmic encounter resulted in the total destruction and subjugation of one of history's most exotic and vulnerable civilizations. Fortunately for us, a glimpse of that doomed world is beautifully memorialized in the magnificent Codex Mendoza.

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Single Electronics

Is electric current the motion of individual electrons or the continuous flow of a fluid of charge? Recent experiments confirm both ideas and may lead to novel electronic devices

by Konstantin K. Likharev and Tord Claeson

What is the smallest amount of electric charge that can sit on the head of a pin? The answer may surprise. A pin, like almost everything else, consists of electrons, protons and neutrons. Each proton holds one fundamental unit of charge (denoted as +e), and each electron carries a similar negative charge (–e); the neutron has no charge. It may seem that the total charge on the head of the pin could be found by counting the number of protons, subtracting the number of electrons and ignoring the neutrons. Using this logic, the smallest nonvanishing amount of charge should be +e or –e. But recent experiments demonstrate otherwise. They clearly show that the charge on the head of a pin can be equal to a fraction of the charge of an electron, for example, +0.5e or –0.1e.

Whereas counting the number of angels on a pin has yet to yield anything of practical value, measuring charge in small structures has provided fascinating tests of physics as well as several potential applications for electronics. The tests were performed with extremely small devices, typically about 30 billionths of a meter in width, which is comparable to the diameter of a virus. By studying the behavior of such minuscule components at temperatures of a fraction of a degree above absolute zero, researchers have developed a better understanding of how electric charge moves through materials. Whereas charge passes through thin insulators in discrete amounts (like water dripping from a faucet), it travels through ordinary conducting materials in a continuous way (like water flowing in a pipe).

These discoveries have led to the invention of various novel devices that control the movement of individual electrons in solids. The single-electronic devices may serve as transistors and other computational elements. Although the technology is still in its infancy, we believe it will play a major role in the future of electronics.

The field of single electronics emerged from investigations of a device known as a tunnel junction [*see illustration on page 82*]. It consists of two electrodes—pieces of a conducting material—separated by a thin layer of an insulating material, as thin as about one nanometer (a billionth of a meter). Although electrons move freely in conductors, they do not readily enter insulators. Yet according to the laws of quantum mechanics, electrons have a small chance to pass, or tunnel, through the thin insulating layer.

If a voltage is applied across the junction, electrons will prefer to tunnel in one particular direction through the insulator. Hence, they will carry some electric current through the junction. The magnitude of the current depends on both the thickness of the insulating layer and the material properties of the conducting electrodes.

By the middle of the 1980s physicists understood many properties of tunnel junctions. A few physicists suspected, however, that tunnel junctions would exhibit interesting behavior if they were made smaller than 100 nanometers or so.

In early 1985 Dmitri Averin and one of us (Likharev) tried to predict the behavior of very small tunnel junctions with superconducting electrodes. (Superconductivity is a property of some materials cooled to temperatures close to absolute zero. Notably, superconductors do not resist the flow of electric current.) Averin and Likharev hoped to tackle the problem by applying ideas of quantum theory. They derived some equations that described the device, but the equations were so complicated that they could not have been solved without a struggle.

It was decided, therefore, to examine the easier case of a small tunnel junction with electrodes made from ordinary conductors. For this problem, the equations could be readily solved and gave a completely unexpected result. They showed that if a constant electric current is passed through a junction, it will induce a voltage that oscillates periodically in time. Most remarkably, these periodic oscillations would have a frequency simply equal to the current divided by the charge of an electron. The frequency is totally independent of any other parameters of the system. A more careful examination of the equations has shown that each oscillation represents the response of the device as a single electron tunnels through the insulating layer. The phenomenon is now known as single-electron tunneling (SET) oscillations.

To understand this effect, one must appreciate how electric charge moves through a conductor, say, an ordinary aluminum wire. An electric current can flow through the conductor because some electrons are free to move through the lattice of atomic nuclei. Despite the motion of the electrons, any given volume of the conductor has virtually no net charge because the negative charge of the moving electrons is always balanced by the positive charge of the atomic nuclei in each small fraction of the conductor. Hence, the important quantity is not the charge in any given

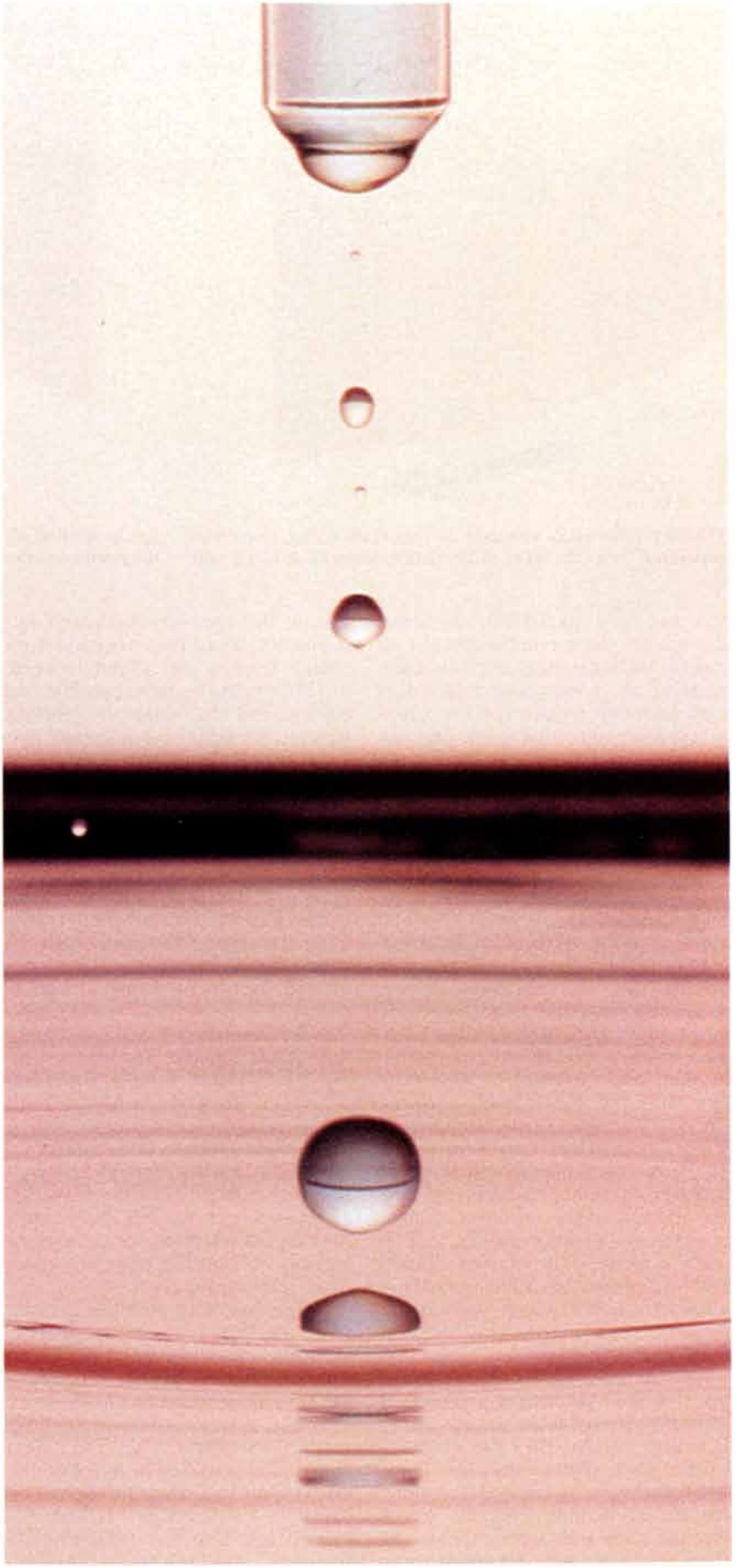
KONSTANTIN K. LIKHAREV and TORD CLAESON have collaborated for several years to develop single electronics. Likharev, who is now professor of physics at the State University of New York at Stony Brook, spent most of his career at Moscow State University. He first entered the institution as an undergraduate, then earned his Ph.D. there and stayed on as a research scientist. For three years, Likharev directed the Laboratory for Cryoelectronics at the university. Since 1982 Claeson has been professor of physics at Chalmers University of Technology in Göteborg, Sweden. He obtained his undergraduate degree and Ph.D. from Chalmers, and he has helped to establish a Swedish facility for fabricating nanometer-scale, solid state devices.

volume but rather how much charge has been carried through the wire. This quantity is designated as the "transferred" charge. What is most surprising, this charge can have practically any value, even a fraction of the charge of a single electron.

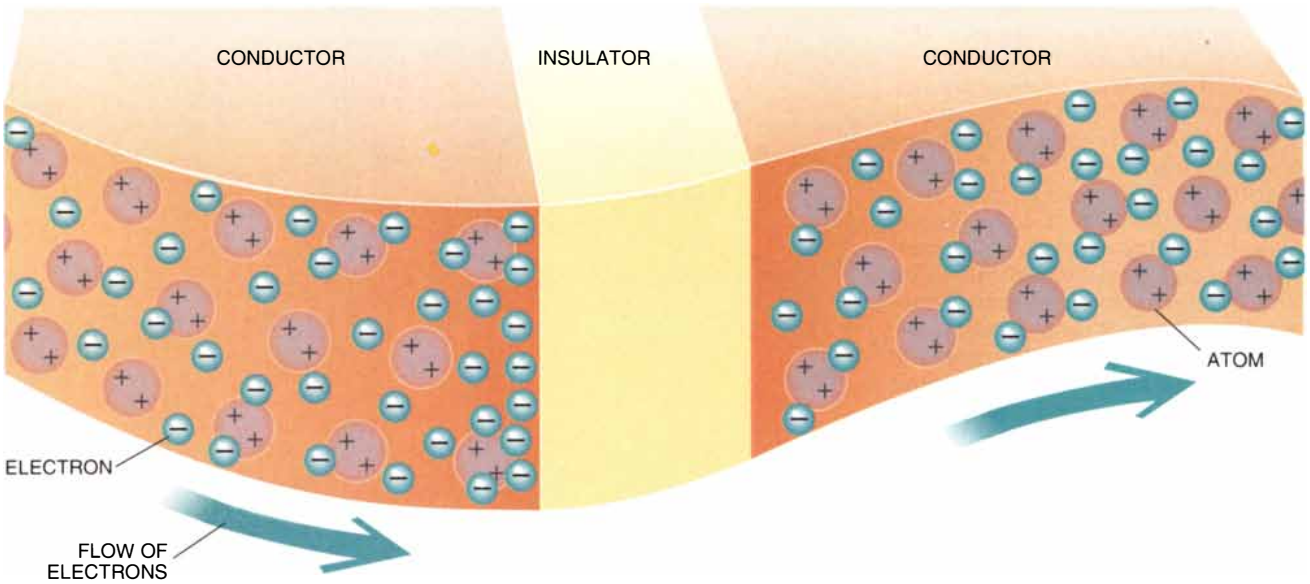
Although this concept may seem counterintuitive at first, it can be explained in simple terms. The transferred charge actually has little to do with counting single electrons or protons. This charge is proportional to the sum of shifts of all the electrons with respect to the lattice of atoms. Because the electrons in a conductor can be shifted as little or as much as desired, this sum can be changed continuously, and therefore so can the transferred charge.

If an ordinary conductor is interrupted by a tunnel junction, electric charge will move through the system by both a continuous and a discrete process. As the transferred charge flows continuously through the conductor, it will accumulate on the surface of the electrode against the insulating layer of the junction (the adjacent electrode will have equal but opposite surface charge). One can imagine this surface charge Q as a slight continuous shift of the electrons near the surface from their equilibrium positions. On the other hand, quantum mechanics shows that the tunneling can only change Q in a discrete way: when an electron tunnels through the insulating layer, the surface charge Q will change exactly by either +e or –e, depending on the direction of tunneling. The interplay between continuous charge flow in conductors and discrete transfer of charge through tunnel junctions leads to several interesting effects.

These phenomena can be observed when the tunnel junctions are very small and the ambient temperatures are very low. (Low temperatures reduce thermal fluctuations that disturb the motion of electrons.) In this case, if the charge Q at the junction is greater than +e/2, an electron can tunnel through the junction in a particular direction, subtracting e from Q. The electron does so because this process reduces the electrostatic energy of the system. (The energy increases in proportion to the square of the charge and does not depend on the sign of the charge.) Likewise, if Q is



WATER DROPLET forms at the end of a glass pipe and falls—a process analogous to the way charge moves through single-electronic devices.



TUNNEL JUNCTION consists of two conducting electrodes separated by a thin layer of insulating material. When a voltage is applied to the device, electric charge creeps through the insulator, creating a weak current.

less than $-e/2$, an electron can tunnel through the junction in the opposite direction, adding e to Q, and thus again decrease the energy. But if Q is less than $+e/2$ and greater than $-e/2$, tunneling in any direction would increase the energy of the system. Thus, if the initial charge is within this range, tunneling will not occur. This suppression of tunneling is known today as the Coulomb blockade.

Curiously, physicists first noticed and studied Coulomb blockade more than 40 years ago. In the 1950s and 1960s Cornellis Gorter of the Kammerling Onnes Laboratory, Hans-Rudi Zeller and Ivar Giaver of the General Electric Research Center and John Lambe and Robert Jaklevich of the Ford Motor Company observed this effect in thin metallic films and explained it. Meanwhile Igor Kulik and Robert Shekhter of the Kharkov Institute of Low Temperature Physics devised its comprehensive theory for one particular system. It seems, however, that until the mid-1980s no one appreciated the concept of continuous charge transfer in metals, and no one was aware of the simple condition for the Coulomb blockade. Once these ideas were understood, it was straightforward to discover new phenomena in small tunnel junctions.

For example, what happens if the junction is connected to a source of constant current? If the surface charge Q is zero initially, then the system is within the Coulomb blockade limits, and tunneling is suppressed. Therefore, the current flowing from the source through wires will start to change the charge Q continuously. For convenience, assume that the deposited charge rate is positive rather than negative. If the charge reaches and slightly exceeds $+e/2$, tunneling becomes possible. One electron will then cross the junction, making its charge slightly greater than $-e/2$. Hence, the system is within the Coulomb blockade range again, and tunneling is not possible. The current continues to add positive charge to the junction at a constant rate, and Q grows until it exceeds $+e/2$ again. The repetition of this process produces the single-electron tunneling (SET) oscillations: the voltage changes periodically with a frequency equal to the current divided by the fundamental unit of charge, e.

In this respect, charge flows through the tunnel junction like water leaking from a faucet. Initially, the charge collects in the junction just as water forms a droplet on the faucet. And indeed, when enough charge builds up, some of it pushes through the junction just as when the droplet reaches a certain size, it will fall. Yet whereas the water droplets can vary in size, the amount of tunneling charge is quantized; it always equals e.

With a couple of plausible assumptions, the formula for the frequency of SET oscillations can be derived from classical physics, because it describes behavior of electrons as particles. Nevertheless, a deep connection exists between SET oscillations and one type of oscillations predicted by quantum theory. In many situations, the electron behaves like a wave rather than a particle. The electron wave has a characteristic frequency, which is equal to the energy of the electron divided by Planck's constant. In 1962 Brian Josephson (then a student at the University of Cambridge) showed that in large tunnel junctions with superconducting electrodes, this relation can be observed experimentally as a fundamental relation between applied voltage and the frequency of oscillations in the current flowing through the junction. In the mid-1980s James Lukens and his co-workers at the State University of New York at Stony Brook used these "Josephson junctions" to demonstrate that the Planck-Bohr-Josephson relation is accurate to at least 16 decimal places. We believe the classical equation for SET oscillations will prove to be equally exact.

To produce SET oscillations, physicists must fabricate tunnel junctions of a very small area and cool them enough to ensure that the thermal energy does not influence tunneling. For example, the device must be cooled to temperatures of about a tenth of a degree above absolute zero if the junction is 100 nanometers in length and width.

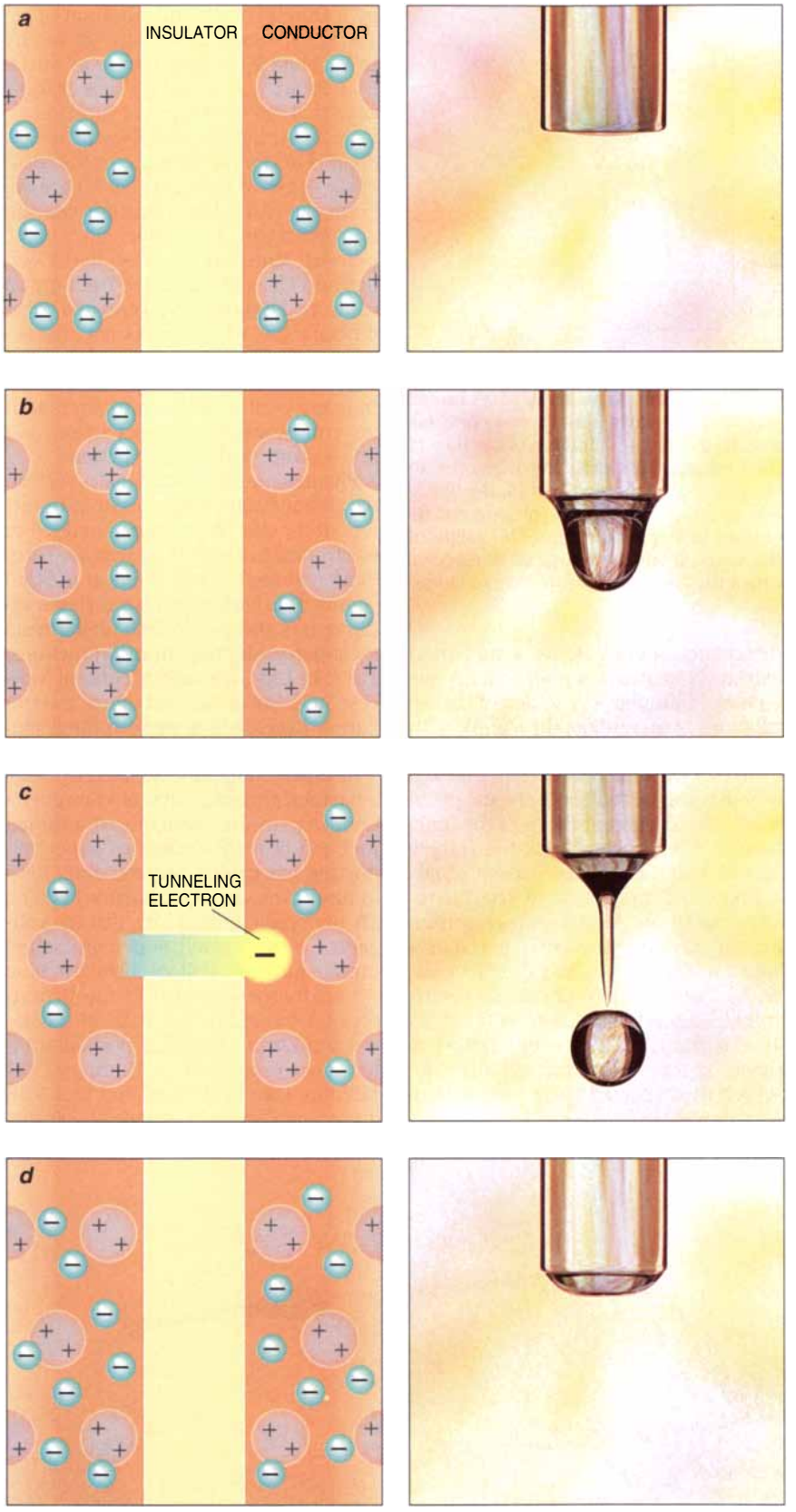
Low-temperature refrigeration and small-scale fabrication are not the only experimental problems that must be overcome. To apply current and voltage to a tunnel junction, one must attach metallic wires to it. Unfortunately, the wires pick up quantum fluctuations of the electromagnetic fields that exist everywhere. These fluctuations can jam the single-electron effects completely. One of the simplest ways to eliminate the jamming is to connect several tunnel junctions in series (end to end). In

such an arrangement the junctions defend one another from the fluctuations. This idea was implemented in 1989 by a team of Swedish and Soviet scientists. The team—which included Per Delsing of Chalmers University of Technology in Sweden, Leonid Kuzmin of Moscow State University and the authors—made the junctions by modifying the so-called suspended mask technique for nanofabrication. Several investigators contributed to the invention of the technique, which was perfected by Gerald Dolan of AT&T Bell Laboratories.

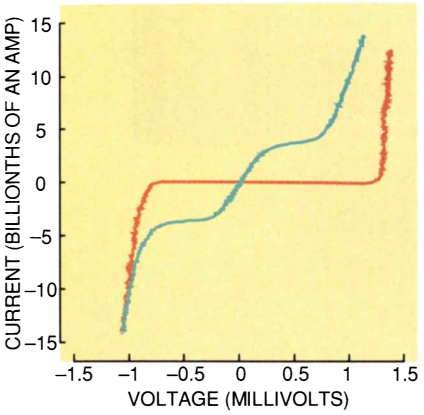
To start, an insulating substrate should be coated with two layers of special organic materials, both thinner than one micron. We used a copolymer of polymethylmethacrylate (PMMA) and polymethacrylic acid (PMAA) for the bottom layer, whereas the top layer was pure PMMA. The coated substrate is then placed into the vacuum chamber of a scanning electron microscope. Although the instrument is mainly designed for imaging applications, it is useful for device fabrication because it produces a beam of electrons a few nanometers in diameter, and the beam has enough energy to break polymer bonds. A computer directs the beam to sweep over the polymer coating in a desired pattern. In our experiments the pattern was a chain of closely located rectangular windows, 200 by 80 nanometers. The sample is then developed in toluene, which removes PMMA from the exposed regions and the underlying copolymer from a somewhat larger area. This process leaves a PMMA layer with open windows that is suspended above the substrate.

At this stage, the sample is placed into another vacuum chamber and is subjected to a beam of aluminum atoms. This beam deposits a thin aluminum film on the PMMA layer and on the parts of the substrate under the open windows. (These aluminum islands will ultimately become the first conducting layer of the tunnel junction array.) Then a small amount of dry oxygen is allowed into the chamber, forming a very thin layer of aluminum oxide on the surface. (The aluminum oxide will become the insulating layer of the junction.) The oxygen is pumped out again, and a second layer of aluminum is deposited from another angle. In this way, the islands of the first and the second layer overlap, forming an array of tunnel junctions, each close to 80 by 60 nanometers.

As our team began fabricating arrays of tunnel junctions, we also considered how we might best measure SET oscillations. The expected power of the oscillations would be very low. To make



SINGLE-ELECTRON tunneling through a small junction is similar to a water droplet falling from a glass pipe. Initially, the interface between the electrode and the insulator has no charge (*a*). As electrons flow into the electrode, charge builds up on the surface of the conductor (*b*). When enough charge collects there, an electron will pass through the insulator and thereby diminish the surface charge (*c*). The process will repeat (*d*) if the charge is replenished.



CURRENT through an array of 25 tunnel junctions is nearly zero (*orange line*) between –0.8 and +1.2 millivolts because of the Coulomb blockade. Yet when the array is exposed to microwaves, the blockade is suppressed, and the current increases in steps (*blue line*). The height of the steps equals the charge of an electron times the frequency of the microwaves.

direct measurements, we would need extremely sensitive high-frequency detectors. A simpler way to detect the oscillations is to irradiate the sample with microwaves. The radiation interacts ("mixes") with the SET oscillations in a way that can be easily observed. Specifically, as the current through the junctions increases from zero, the voltage should increase until the current equals e times the frequency of the microwave radiation. As the voltage continues to increase, the current remains constant for a while and then increases. As a result, a plot of current versus voltage should show horizontal steps at a current equal to the frequency times +e (or –e). In July 1989 we observed the expected steps [*see illustration above*].

Our results were soon confirmed by a Dutch-French collaboration of researchers working at Delft University of Technology and the Center of Nuclear Research at Saclay. These groups used two different types of junction arrays, in which the microwave field is applied to central electrodes rather than at the edges of the array. With these devices, the current to frequency relation was tested with an accuracy close to 0.1 percent. Moreover, in 1990 Bart Geerligs and Hans Mooij of the Delft group confirmed a theory by Averin and Arcadii Odintsov, which shows how the accuracy might be improved. We believe that in the near future the current to frequency ratio will be measured with an error below at least one part per million—and probably much better.

Phenomena similar to single-electron oscillations should also occur in tunnel junctions that have superconducting electrodes. In 1982 Allen Widom, Terry Clark and their collaborators at the University of Brighton first suggested a rudimentary theory for such phenomena in superconducting tunnel junctions. Then, in 1984, Alexander Zorin of Moscow State University and one of us (Likharev) developed a more refined and realistic theory.

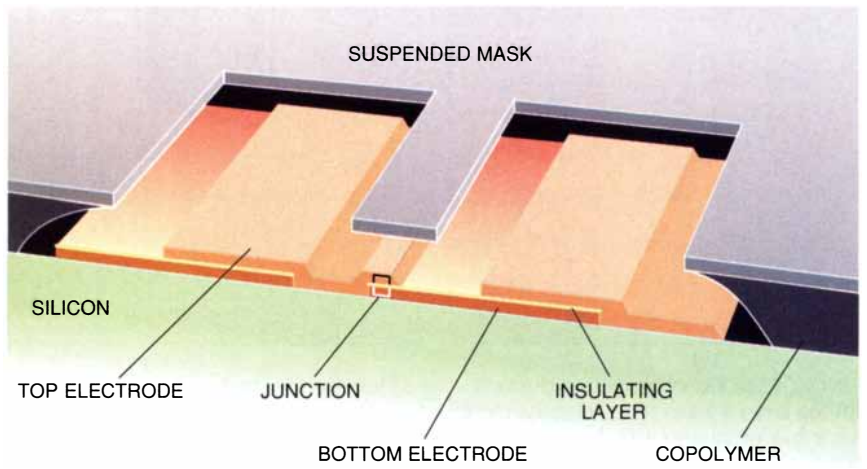
In superconductors, each electron has a partner, forming what is known as a Cooper pair. Consequently, if a tunnel junction is made from two superconducting electrodes, the electrons tend to tunnel through the insulator in pairs. Theory predicts, therefore, that the voltage of a very small superconducting tunnel junction will oscillate in time with a frequency equal to the current divided by 2e (rather than e). Likharev and Zorin called this particular effect Bloch oscillations. In February 1991 Kuzmin, David Haviland and their colleagues at Chalmers found reliable evidence for Bloch oscillations in a small junction formed between two thin films made of a superconducting alloy.

The SET and Bloch oscillations can be considered as the ordering ("correlation") of single-electron or Cooper-pair tunneling events in time. Another type of correlation of these events is also possible and is important for future applications. This type of correlation occurs, for example, in a device consisting of two tunnel junctions that share a middle electrode. If a constant voltage is applied across the device, the tunneling events in each of the junctions should be mutually correlated. Specifically, whenever an electron tunnels through one of the junctions, a second electron passes through the other junction nearly simultaneously.

Most important, as Averin and Likharev showed in 1985, this correlated tunneling can be controlled if electric charge is continuously injected into (or removed from) the electrode that connects the two junctions. If the charge injected into the electrode is close to zero or a multiple of e, the device maintains a considerable Coulomb blockade: no current flows through the junction if the voltage applied to the system is lower than a particular threshold. But if the charge of the middle electrode is either +0.5e or –0.5e (or even +1.5e, +2.5e and so on), the Coulomb blockade is completely suppressed: electrons tunnel through the system, and a current can be induced by even a small applied voltage. Thus, the current through the device can be controlled by changing the charge of the middle electrode just as the current through a usual semiconductor transistor, but this control can be achieved by much weaker charge signals. For this reason, the two-tunnel-junction device is now known as the single-electron transistor.

Fortunately, the correlated tunneling effect is not sensitive to quantum fluctuations of the ambient electromagnetic field, and so the device can be connected easily to a voltage source and measuring instruments. For this reason, Kuzmin and Likharev were able to conduct experiments on the single-electron transistor very rapidly after the device was conceived. On March 6, 1987, they reported their results to a Soviet journal. (They later learned that, on the same day, Theodore Fulton and Gerald Dolan of Bell Labs had submitted a paper on almost similar observations to an American journal.) These two works marked the beginning of experimental single electronics.

During the past five years, physicists have devised many types of single-electron transistors and developed more



TINY TUNNEL JUNCTIONS were made using the suspended mask technique.

complex single-electronic circuits. The behavior of all these circuits can be fully explained using what is now called the Orthodox theory, which the Moscow group formulated in 1985. Hence, the Orthodox theory can be used to analyze possible applications of single electronics.

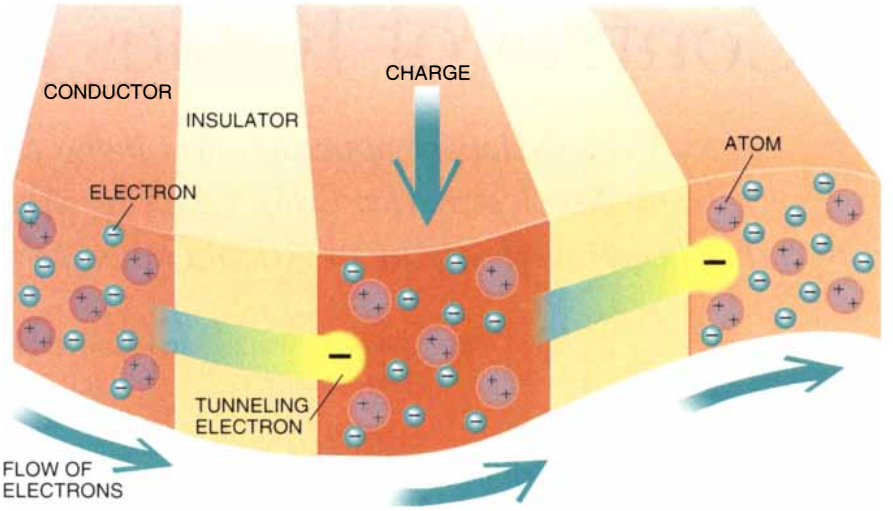
In the near future, we foresee at least three important applications. First, the technology should provide a new standard for measuring small currents. We expect an accuracy of better than one part per billion, about 1,000 times better than existing systems. Second, the technology promises supersensitive electrometers—instruments that would measure charges as small as one ten-thousandth of e, which is almost a million times better than the resolution of commercially available instruments. (Such electrometers have already been used by researchers at Saclay and at Bell Labs to measure single-electron tunneling effects in other devices.)

But the most important prospect for single electronics is its application to digital integrated circuits. Currently computer chips can have a density of some 10 million devices per square centimeter. Although this achievement is impressive, computer designers continue to demand chips with ever higher device densities. But the conventional electronic devices are approaching their limit. Most agree that any further reductions in size will require radically new ideas, and single electronics is ranked highly on this issue.

In circuits based on single electronics, bits of information can be represented as the presence or absence of individual electrons. This technology may make it possible to pack up to 10 billion electronic devices on a one-square-centimeter chip (for that, the dimensions of tunnel junctions could be reduced to about 10 nanometers). Such a circuit would operate at four kelvins, a temperature that is acceptable for some applications. Still, the development of such circuits will require a considerable investment of time and effort.

Conceivably, single-electron circuits could be made even more dense, but such attempts will encounter two problems. First, researchers need to pioneer techniques to fabricate complex structures whose smallest dimension is less than 10 nanometers. Second, they must determine how single-electron effects change as the dimensions of the device decrease to the atomic scale.

To solve this second problem, Averin and Alexander Korotkov of the Moscow State University revised the Orthodox theory in 1989. They recognized that if a device is small enough, the laws of quantum mechanics play a larger role in the system. In such cases, the energies of the electrons are quantized, that is, they can only equal certain discrete values. Yet they showed that the energy quantization does not exclude correlated tunneling, and indeed the effects can coexist peacefully.



SINGLE-ELECTRON TRANSISTOR can switch on or off the flow of billions of electrons per second when the charge on the middle electrode is changed by only half the charge of an electron.

To verify this conclusion, several groups have performed experiments in which electrons are confined within tiny structures made of semiconducting material. Such structures, which are known as quantum dots and quantum wells, can hold a "puddle" of a few hundred free electrons. Both devices allow electrons to tunnel in or out through well-defined energy barriers. In both types of experiments, physicists have observed single-electron effects and energy quantization together, confirming that the phenomena can coexist. Paul McEuen and his colleagues at the Massachusetts Institute of Technology and the IBM Thomas J. Watson Research Center were the first to demonstrate this coexistence in quantum dots; Bo Su and his co-workers at Stony Brook and at Bell Labs have obtained similar results using quantum wells.

Several fundamental issues are still to be solved. For one, investigators have not yet tackled the issue of how energy quantization influences single-electron charging effects in circuits that consist of many quantum dots or quantum wells. A preliminary analysis shows that in such structures an electron can behave simultaneously as a wave and as a particle. If this prediction turns out to be true, it will be very important for fundamental physics.

Another unresolved issue is whether the correlated transfer of electrons requires tunneling. Averin and Likharev have recently given arguments that it does not. Such correlated flows may be achieved in narrow channels, where the electrons can propagate only in one direction. Forthcoming experiments should reveal whether such channels can be fabricated.

Regardless of these new issues, single electronics has already advanced our understanding of how electrons behave in materials. We believe that a contribution has been made as well to what could be called the psychology of physics. The discovery of correlated tunneling has given us an example of a conceptually simple and fundamental effect that remained undiscovered until the mid-1980s. It has shown that Newton's "ocean of undiscovered truth" is still full and is waiting for scientists armed with not much more than a bit of imagination and creativity. This is something to be remembered by adherents of theoretical supersophistication and advocates of multibillion-dollar experiments.

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Control of Rabies in Wildlife

A revolutionary approach now being tested in Europe and North America is the offspring of a research effort that began modestly in an Atlanta laboratory some 30 years ago

by William G. Winkler and Konrad Bögel

On April 13, 1990, at a tavern in Mercedes, Texas, a bat bit the right index finger of a 22-year-old visitor. The man, who did not seek medical attention, seemed well until May 30, when the affected hand began to feel weak. Just six days later he was dead of rabies, having been tormented in the interim by many of its symptoms. Before slipping into a coma, the Texan suffered episodes of rigidity and breath holding; hallucinations; extreme difficulty swallowing (so much so that he refused liquids); frequent spasms in the face, mouth and neck; continuous drooling; and, finally, disorientation accompanied by high fever.

Every year similar horrible deaths await more than 25,000 human beings around the world. That dismal outlook may soon change, thanks to development over the past 30 years of ways to immunize free-ranging animals on their home turf. The current armamentarium includes various edible baits and even a genetically engineered vaccine.

The need to focus on animals arises in part because existing ways to prevent rabies in humans have major drawbacks. The rabies virus, which can cause disease in any mammal, is spread by the bite of an infected animal. It is lethal once symptoms develop but can be blocked by timely administration of a series of vaccine injections soon after an attack. The vaccine, which today may be given in an arm rather than the abdomen, is derived from a killed rabies virus. The inactivated virus prods the immune system to destroy active virus, especially when the injections are combined with application of rabies-specific antibodies to the wound area [see "Rabies," by Martin M. Kaplan and Hilary Koprowski; SCIENTIFIC AMERICAN, January 1980].

Unfortunately, in any year thousands of people who are probably uninfected undergo treatment because they do not know whether the animal that bit them had rabies. These high numbers are disturbing because therapy is costly and because vaccination of any kind carries a risk of side effects. (The expense is a major reason veterinarians and others who are very likely to encounter rabid animals are generally the only people immunized prophylactically.)

Even more distressing, most people who die of rabies are lost simply because they live in impoverished nations. Those who are attacked by infected animals often lack access to therapy or cannot pay for it.

Routine immunization of the animal species most likely to transmit the virus to humans would be a more efficient, health-conscious way to save human lives and, not incidentally, to spare animals from suffering. To an extent, such inoculation is already a reality. In many wealthy nations, including the U.S., periodic injection of pet dogs with vaccine has all but stopped canine transmission to humans. Disease caused by cats can be limited in the same way.

In developing countries, however, obtaining veterinary care can be extremely difficult, which is one reason why dogs continue to account for at least 90 percent of all human deaths from rabies. Another problem is that even where pet rabies is under good control, wild animals—not being very amenable to collection and carting to the local veterinarian—pose a threat.

For these unattended groups, distribution of vaccine-laced baits for animals to eat in the field is showing particular promise. This approach is already halting the spread of rabies by foxes in many parts of western Europe and Canada. More preliminary work suggests rabies in other species can be controlled as well.

Indeed, a vaccine-filled bait for raccoons is now being tested in the U.S. If the results are good, the bait method might finally check an epidemic of raccoon rabies that has been spreading up the East Coast from Florida since the 1950s. If baiting can be perfected for distribution to dogs in developing countries, then the goal of sharply curtailing human cases worldwide would finally seem feasible.

This encouraging state of affairs stands in marked contrast to the situation in the 1960s, when research into vaccinating wild animals started in earnest. By then immunization had already reduced the incidence of dog rabies in the U.S. But infection by foxes, skunks, raccoons and bats—the other significant rabies reservoirs in this country—was a continuing concern. Compared with dogs, those groups have less direct contact with humans, but collectively they are more abundant.

To control rabies in free-ranging animals, health officials in the 1950s had depended on thinning populations that harbored the offending virus. They tried gassing of dens, poisoning, trapping and shooting, among other tactics. The workers reasoned that destruction of enough animals would so reduce a population that any infected individuals would die without tangling with another animal. When diseased creatures disappeared, only healthy ones would remain. Yet the strategy halted the spread of the malady in target groups only some of the time.

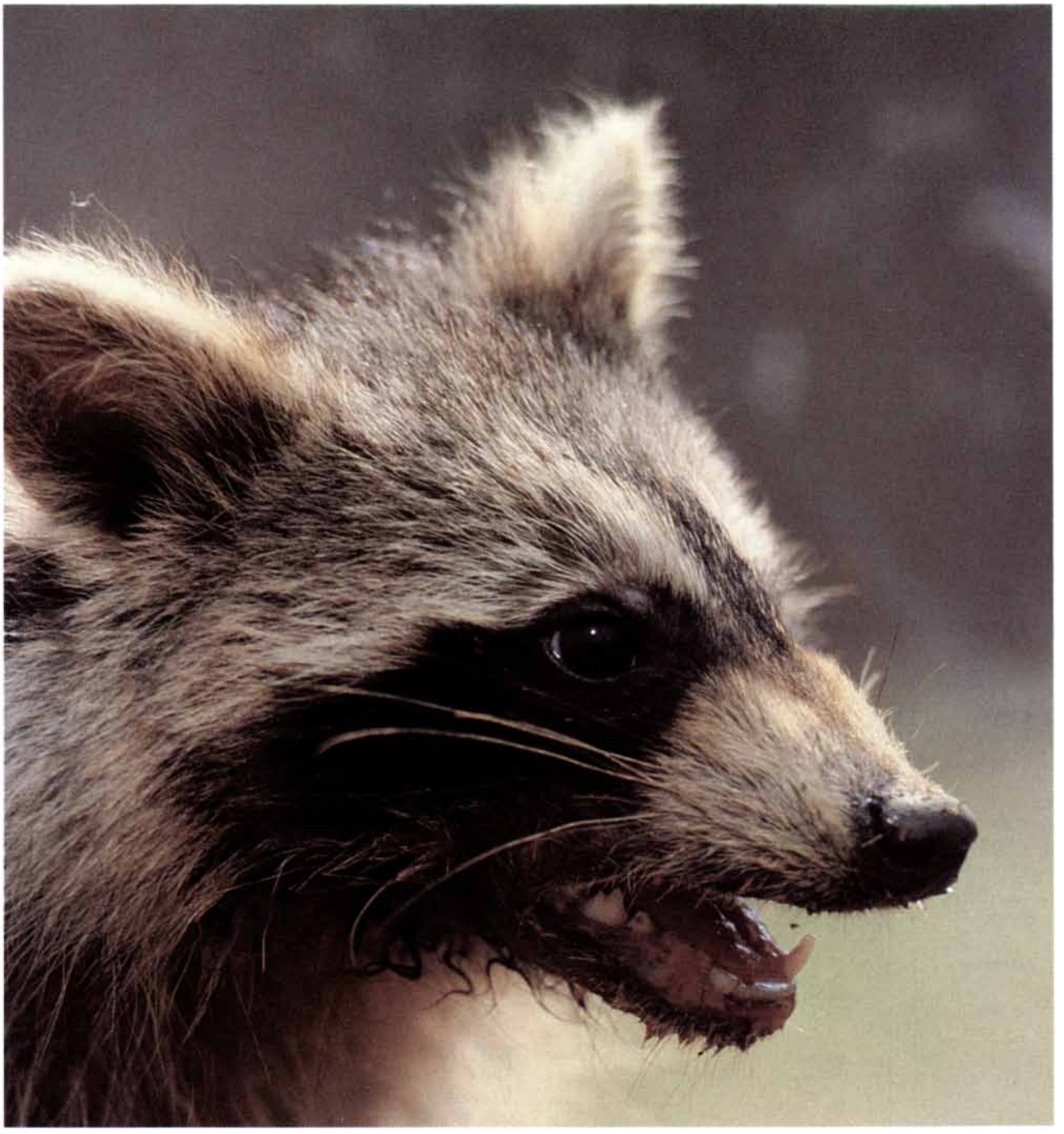
Biologists reviewing some 10 years

WILLIAM G. WINKLER and KONRAD BÖGEL are veterinarians who have devoted their careers to developing ways to prevent and treat diseases of animals. Winkler spent 26 years with the Centers for Disease Control before retiring in 1989. Since then, he has served as a private consultant to national governments and the World Health Organization. Bögel, professor of veterinary microbiology and epidemiology at the University of Munich, retired in January 1992 as chief of the veterinary public health unit at WHO, a position he assumed in 1984. He was a virologist at the Federal Research Institute for Animal Virus Diseases in Tübingen, Germany, before moving to WHO in 1967.

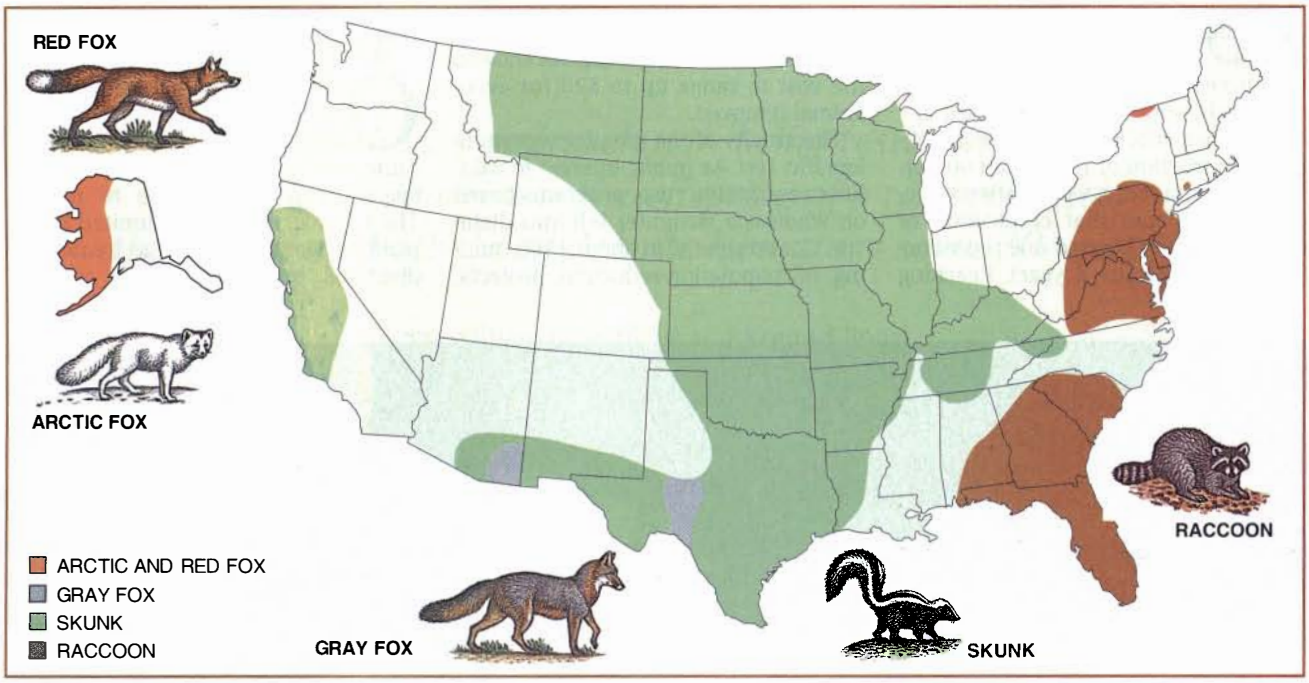
of experience with population-reduction programs for foxes, skunks and raccoons concluded that to improve the success rate, enormous numbers of animals would have to be killed. Because those species reproduce prolifically, destruction of more than 60 percent of a population would often be required to ensure that eradication of rabies persisted beyond one reproductive cycle (typically a year). Reaching that number would be extraordinarily difficult and expensive. A 1960 review of the economics of fox control showed the cost to range up to $26 for every animal removed.

The cruelty of the practice was problematic, too. As public interest in wildlife preservation rose, programs based on wholesale slaughter fell into disfavor. Consequently, in about 1960 funding of population-reduction projects, which had always been minimal, became almost unobtainable.

One of the first alternatives tried in the U.S. was to capture wild animals, inject them with the same vaccines used in domesticated species and return them to nature. The scheme, tested on a limited basis, worked beautifully for the treated individuals, but most animals escaped



RACCOON SUSPECTED OF HAVING RABIES was captured in Virginia in 1983—several years after a rabies epidemic began sweeping through raccoons in the mid-Atlantic states. Investigators are hoping to halt the outbreak eventually by distributing vaccine-laced baits to healthy raccoons. A candidate vaccine-and-bait combination is now being tested in the wild.



trapping. In any event, the technique was far too expensive to merit further consideration.

Then, in late 1961, George M. Baer of the Centers for Disease Control (CDC) in Atlanta began devising ways to entice animals to vaccinate themselves in the field. Today he can rightly be called the father of the self-vaccination concept, but initially his idea aroused doubt.

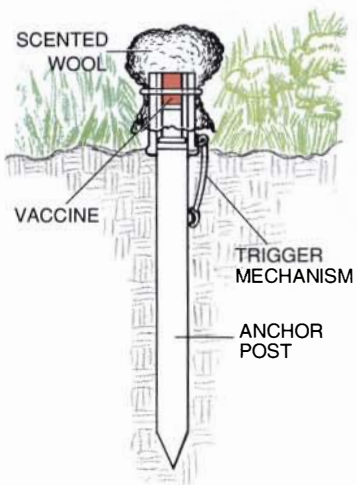
Part of the skepticism stemmed from the fact that, at the time, the most effective commercial products for animals were manufactured from live, albeit weakened, strains of the rabies virus. Certain species, particularly rodents, can acquire rabies from attenuated viruses. Moreover, some scientists feared that after distribution, weakened viruses, which replicate somewhat in the body, might regain the ability to multiply dramatically and thus revert to virulence.

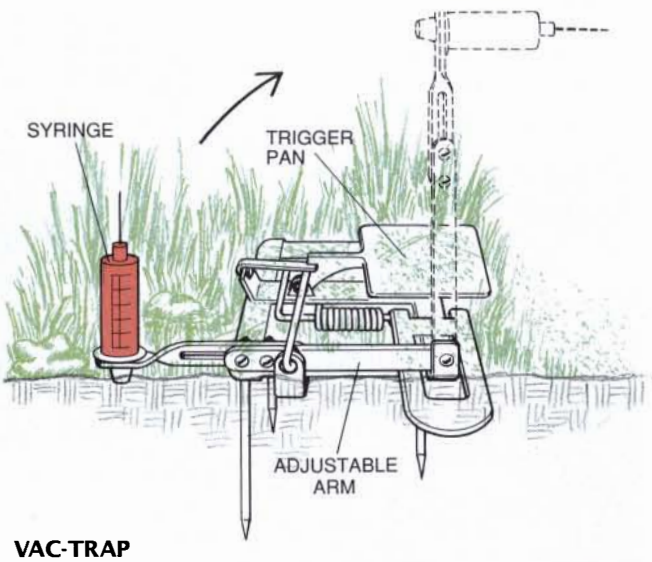
Those concerns would later be addressed, but the first challenge was inventing a practical vaccination method. In Baer's early work, he adapted for vaccine delivery a weapon originally designed to poison sheep-killing coyotes. Called the Coyote Getter, the device consisted of a pipelike gun that was buried so that only the top of the barrel and a small trigger remained above ground. The barrel was covered with scented wool to attract victims. When a coyote put its mouth over the wool

Evolution of Vaccination Methods

COYOTE GETTER

In the early 1960s U.S. investigators substituted a commercial vaccine for the poison in a weapon designed to kill coyotes. When test animals mouthed the wool cover, a jet of vaccine shot into the oral cavity. The jet often damaged the mouth, which could have led wild animals to starve.





VAC-TRAP

The device, shown atop the ground for clarity, was buried just beneath the surface, except for the arm, which rested on the soil. When an animal stepped on the hidden trigger pan, the arm sprang up and jabbed a vaccine-loaded syringe into a side. The American designers field-tested the device in the late 1960s, but it proved too hazardous.

EPIDEMICS OF RABIES (*colored areas*) are raging not only in raccoons but also in foxes and skunks in the U.S. Together with bats, those animals account for about 87 percent of reported cases of animal rabies in the U.S. (Bat rabies occurs throughout the mainland but is not spreading rapidly, so it is not considered epidemic.) Hawaii is rabies free. Raccoon rabies jumped into the mid-Atlantic region (leaving the gap visible in North Carolina) in 1977, probably when hunters began releasing in Virginia 3,500 raccoons from Florida.

and tugged, the trigger released, causing the gun to fire a jet of cyanide into the mouth.

Baer intended to induce immunity by replacing the poison with a commercial vaccine for animals. He hoped viral particles would cross the mucous membranes of the mouth and induce an immune response. Regrettably, the vaccine did not immunize animals adequately by the oral route. Also, the jet often damaged the mouth, rendering test subjects unable to eat for some time, which meant survival in the wild would have been questionable. (Bats were not targets of this or later self-vaccination methods, because most of them feed on insects in flight and do not seek food on the ground.)

Back at square one, investigators then developed several new vaccinating devices, but most of them were too flawed to warrant extensive evaluation outside the laboratory. Eventually, though, the inventors came up with a more practical contraption, called the Vac-Trap.

The device was modeled in part on conventional steel traps that grab the legs after an animal steps on a trigger pan hidden just under the ground surface. In this case, pressing on the pan caused a metallic arm to pivot up and jab a syringe into the target's side. At that point, a vaccine under pressure was injected into muscle.

One of us (Winkler), a veterinarian at the CDC, tested the Vac-Trap for two months in the mid-1960s on San Clemente Island, off the California coast. It immunized 25 percent of the wild foxes and 16 percent of the stray cats on the island; that is, the animals, who possessed no rabies antibodies before treatment, produced high levels after vaccination. And there was no loss of life or identifiable damage to the animals or the environment.

Nevertheless, Vac-Traps could not economically vaccinate 60 to 70 percent of a population, the number required to eliminate rabies in an area. Further, an animal had to enter the trap from a specific angle, or else the syringe might miss the subject's side. Most important, the device was unacceptably hazardous because any creature, including a human, that depressed the trigger pan could be jabbed by a large needle and instantly injected with vaccine. Possible exposure to the attenuated virus was somewhat of a worry, but it was the danger of flying needles that truly sounded the death knell for the Vac-Trap.

The safety problem was underscored for Winkler and his crew late one evening after 130 devices had been set out along the beach. Someone informed the team that the island, which was managed by the U.S. Navy and was often a site of training exercises, would be invaded that night by an "attacking force" of marines. The attackers, unaware of the study, could be struck by the Vac-Trap needles as they crawled up the beach, suffering serious injuries.

When officials on the island were told of the problem, they instructed the scientists to leave the Vac-Traps in place, arguing that the hazards would serve as an additional measure of the invaders' prowess. The next morning, after a harrowing and sleepless night, the researchers were relieved to find that although a number of foxes had been vaccinated, no humans had been hurt. Nevertheless, this demonstration of potential danger convinced even the most optimistic investigators that a safer approach would have to be found.

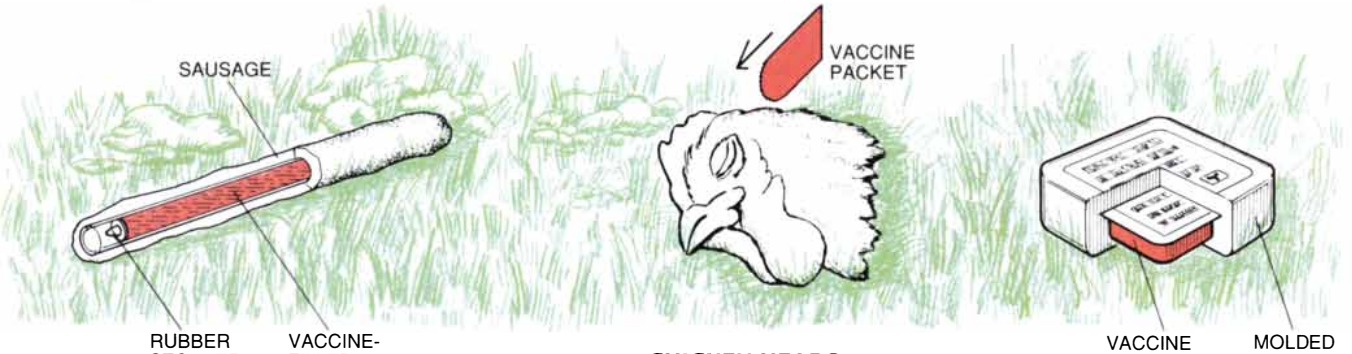
The only reasonable solution was to avoid treacherous machinery by incorporating a vaccine into bait that animals would want to eat. Thus began the CDC's Oral Rabies Vaccine Project. Despite the failure of the Coyote Getter, there was reason to think oral vaccination could be made to work. For instance, mice had sometimes become immunized by feeding on the carcasses of rabid animals.

SAUSAGE BAIT

In the 1970s captive foxes in the U.S. were immunized by eating this bait. As they chewed, their teeth punctured the straw, causing vaccine to leak into the mouth. The U.S. halted funding before the approach could be field-tested.

MASS-PRODUCED BAITS

After 1985 machine-made baits of varied composition came into wide use in Europe and Canada. The type shown here has been dropped from airplanes over Canada. The waxy coating around the vaccine-filled packet incorporates chicken flavor for appeal and tetracycline as a marker of uptake.



CHICKEN HEADS

Swiss researchers turned chicken heads into successful baits in the 1970s by inserting a small packet filled with vaccine into the back. Chicken heads lost popularity in the late 1980s, in part because baits that were easier to manufacture in quantity were introduced.

Yet achieving oral immunization consistently in the field was not going to be easy. The first problem was the vaccine itself: the existing commercial inoculants were ineffective when ingested because they did not readily penetrate the mucous membranes of the mouth and pharynx and because stomach acids tended to degrade them. Such difficulties needed to be solved before serious work on baiting could commence.

Baer and John G. Debbie, a veterinary virologist with the New York State Department of Health, tried stowing an attenuated rabies virus in a time-release capsule, much like those used in long-acting cold medications. Independently, John G. Black and his collaborator Kenneth F. Lawson of Connaught Laboratories in Toronto explored the same idea.

The investigators intended for the capsules to protect the vaccine during passage through the stomach and then release it into the intestines. To their disappointment, neither team achieved adequate antibody production.

Clearly, if oral immunization were going to have a future, a vaccine would have to be absorbed through the membranes lining the mouth and throat, before ever reaching the stomach. Because the rabies virus can pass through the membranes only with difficulty, many viral particles must be present to ensure that enough of them will make the journey. Existing vaccines were too dilute for the task, and so increasing potency became the next aim.

By the late 1960s Baer, in collaboration with virologists from government and industry, had met that goal by growing the virus in cultured cells derived from the kidneys of baby hamsters. Those cells support production of greater quantities of rabies virus than do most other growth systems. He and his co-workers had also improved stability, because the vaccine might sit outside for days before being discovered.

The moment had come for Baer and Winkler to concentrate attention on baits. The ideal bait would enclose the vaccine without reacting to it and lowering its potency; it also would be easy to handle and place in the field and would hold appeal for target species but be odious to other groups. Like the vaccine itself, the bait would be stable, able to resist degradation by heat or rain.

The collaborators evaluated dozens of bait-and-vaccine combinations. For instance, they impregnated all sizes and shapes of dog biscuits with vaccine and coated them with waxes and tallows having different attractant scents.

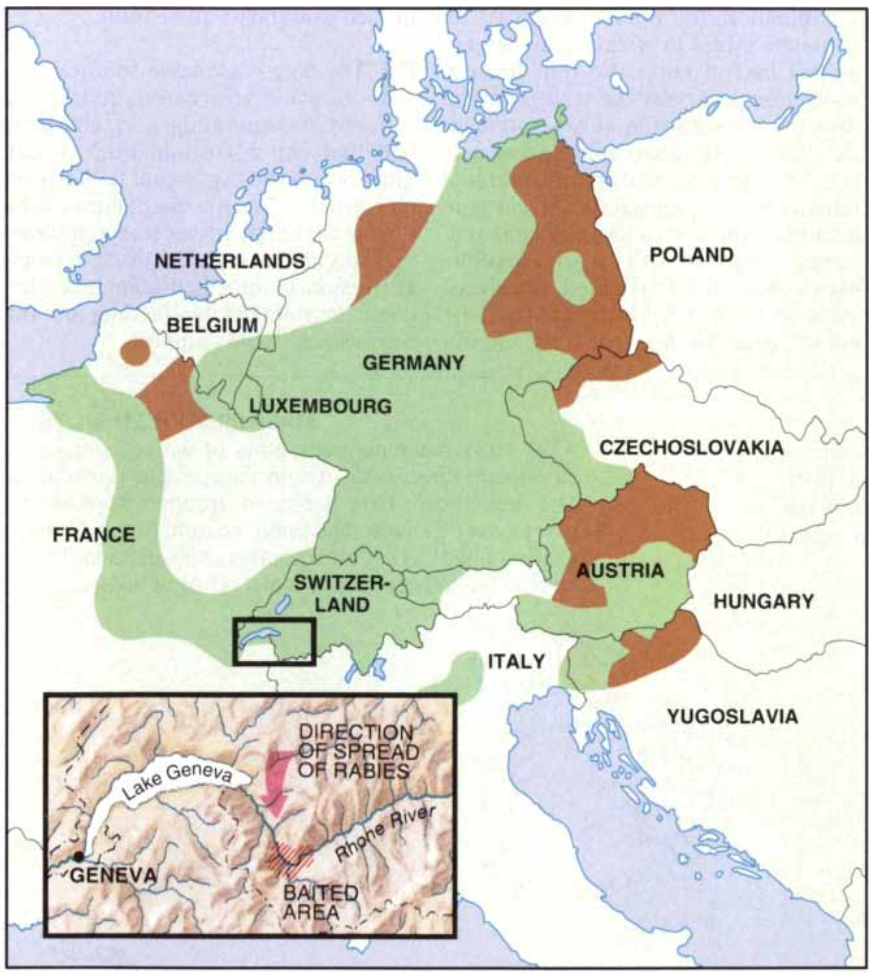
Only those candidates that best withstood extremes of temperature and humidity were fed to laboratory animals. First, foxes, raccoons and mongooses were encouraged to eat the vaccine-laced baits. (Mongooses have been victims of rabies outbreaks on Caribbean islands.) Then, 14 and 30 days later, blood was drawn to determine the levels of rabies antibodies. Raccoons and mongooses invariably failed to develop antibodies, but foxes, which are more sensitive to the rabies virus, had a better response. For that reason, the project ultimately concentrated on foxes.

A visit to a McDonald's restaurant by Winkler helped inspire the earliest success for foxes. Baer had suggested that a commonly available smoked sausage—the Slim Jim—might make a good bait. Looking at the plastic drinking straws at McDonald's, Winkler began to imagine encasing the vaccine in a straw, plugging the ends and fitting the vessel into a cored sausage.

When Winkler and Baer fed sausage baits to caged foxes in the laboratory in 1972, all the animals chewed the baits enthusiastically, swallowing the vaccine as their teeth punched holes in the straws. None fell ill, and all became able to withstand challenge by a lethal dose of rabies virus. (At about the same time, researchers in Germany also succeeded in orally immunizing captive foxes.)

On the strength of their success, Winkler conducted a field study of unarmed, or vaccine-free, baits in 1974. He placed them across Alaska's tiny Amak Island, where red foxes and several kinds of small rodent are the only resident mammals. Sure enough, foxes chewed up the baits almost as quickly as they were placed. Several biologists had been concerned that animals would stockpile baits for later consumption, yet no obvious storing occurred.

This success made an outdoor trial of armed baits seem justified, but it



BROAD REGION OF EUROPE has been dotted with vaccine-loaded baits in an effort to eradicate fox rabies from the continent. Green areas were baited between 1978 and 1990; tan regions were added in 1991. (Baiting is stopped when rabies is eradicated from an area.) The first large-scale field distribution occurred in the Rhône River valley of Switzerland in 1978 (*detail*); there, chicken-head baits prevented a fox epidemic from spreading past the baited territory.

was not to be. By the conclusion of the Amak Island study, fox rabies in the U.S. had declined through natural causes. Health officials in the U.S. therefore halted work on the Oral Rabies Vaccine Project.

Just when fox rabies was waning in the U.S., it was becoming epidemic in Europe, causing public alarm. Consequently, in the early 1970s, one of us (Bögel), a veterinarian with the World Health Organization's Veterinary Public Health Unit, gathered American and European scientists (including Baer and Winkler) to discuss the possibility of orally vaccinating foxes in Europe. In contrast to the U.S., where several species are reservoirs of rabies, foxes are the only serious threat in Europe.

As a result of such meetings, European scientists, supported morally and to some extent financially by the World Health Organization, perpetuated research into oral rabies vaccination after the U.S. government lost interest. Fifteen research teams in nine countries collaborated for many years on studying the composition of baits, vaccine safety, and the physiology and behavior of foxes. The CDC provided the Europeans with virus as seed stock for producing their own slightly varied vaccines; however, the teams opted to develop new baits that would be easier for them to produce.

Swiss veterinarian Franz Steck and biologist Alexander I. Wandeler, then at the University of Bern, were among the first and most enthusiastic European participants in the project. They immediately began comparing different types of baits, ultimately settling on chicken heads (made available by poultry manufacturers) carrying a vaccine-filled packet under the skin.

As part of the effort to evaluate both bait acceptance and vaccine safety, the cooperating teams had established areas for examining the number and types of animals that took up baits. Studies of unarmed chicken heads carrying a tetracycline dye, which was easily detected in animals who ate the baits, indicated that foxes accepted the lures readily. Nontarget species stole relatively few of the heads.

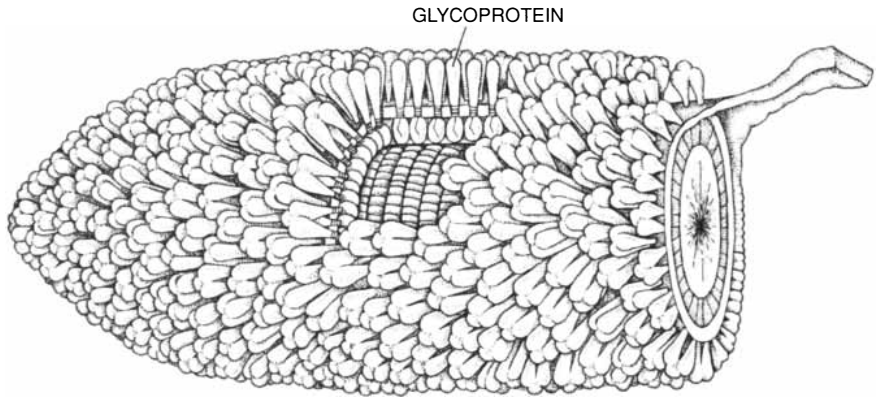
At about the same time, laboratories located in Switzerland, Germany and France independently studied the ability of an attenuated version of the rabies virus to cause disease in rodents and other nontarget species. If such animals were easily infected and transmitted the infection to still other animals, their susceptibility would render release of the vaccine quite dangerous.

Even when the vaccine was delivered so as to optimize the likelihood of infection, very few animals became diseased. In those that did fall ill, the amount of virus in the tissues was so small that transmission of the infection to other animals became highly unlikely. Indeed, the extensive studies, which examined secondary transmission directly, found none. At no point did the vaccine virus increase in virulence. Together these and other studies strongly suggested that the attenuated organisms could be safely administered with minimal risk of causing rabies in nontarget populations.

Despite the wealth of safety data that was accumulating, many German scientists, including Gunther Wachendorfer of the State Veterinary Institute in Frankfurt, remained unconvinced. Yet when Wachendorfer examined the effects of an alternative viral strain, his results supported use of the strain evaluated in the previous studies.

The mounting data, combined with Steck's considerable powers of persuasion, eventually convinced the Swiss government to approve a safety test in the field. Hence, in the mid-1970s, Steck and Wandeler conducted the first field release of a live rabies virus in Europe. They put out armed baits on a rabies-free island in the Aare River and monitored the effect on rodents living there. No epidemic ensued.

Meanwhile analyses of the behavior, movement, eating habits, population turnover and immunization requirements of European foxes provided critical data needed for planning vaccination campaigns. Such information is important for determining the number of baits to spread over an area and the part of the fox life cycle during which delivery would be optimal.



RABIES VIRUS includes a helical core (*cutaway*), where its RNA genome is stored, and a surrounding lipid envelope that is studded with molecules of a glycoprotein. The glycoprotein evokes an immune response in host animals. The gene for the glycoprotein has recently been spliced into a vaccinia virus to form an inoculant that confers immunity but cannot itself cause rabies. The image is based on information supplied by William H. Wunner of the Wistar Institute.

As the late 1970s drew to a close, then, European health officials and researchers were in a good position to test oral live-virus vaccines across large land areas. They found their opportunity in 1978, when an outbreak of rabies in foxes was spreading along the eastern shore of the Lake of Geneva in Switzerland and was threatening to move south into the Rhône River valley. The epidemic seemed destined to extend deep into the valley and to eventually turn east with the river.

In October, Steck and Wandeler set about creating a *cordon sanitaire,* or barrier, to halt the spread before the epidemic turned eastward. Barriers against other animal disorders have been created in the past by removing susceptible individuals from an area at the front of an advancing epidemic. In this case, the barrier was to be formed by immunizing foxes with armed chicken-head baits distributed across a broad band of the Rhône River valley (perpendicular to the river) and high enough up the sides of the bordering mountains to ensure that infected foxes would not climb into the hills and circumvent the barrier.

The Swiss team placed 4,050 baits by hand, covering a 335-square-kilometer area at the riverbend, in the canton of Valais. Then they waited. The rabies outbreak continued up the valley as threatened but, to the workers' joy, stopped within the barrier region.

The success of that trial was later replicated in other Swiss valleys. Naturally, with each success the Swiss government's interest increased, and funding soon became available to conduct programs in areas throughout the country. (Sadly, Steck died during this peri-

od, in 1982, when the helicopter from which he was spreading baits crashed into a mountain.)

In 1983 the Federal Republic of Germany, which had strongly supported research on live-virus vaccines but had been unwilling to consider using them in nature, became the second committed participant in field trials. The Germans reversed their stance after techniques were invented to indicate whether a rabid animal had acquired the disease from a vaccine virus or from a wild strain; they were reassured by knowing they could promptly detect when a vaccine had become virulent.

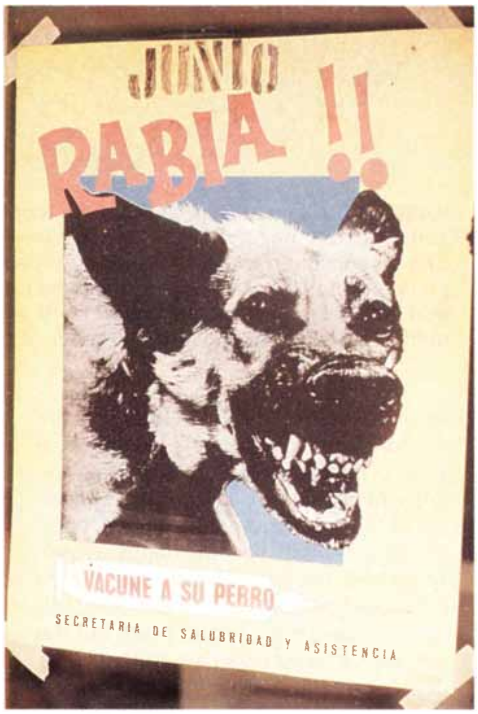
In fact, it was a German veterinarian who developed sophisticated manufacturing equipment for mass-producing vaccine-filled baits: Lothar G. Schneider of the WHO Collaborating Center for Rabies Surveillance and Research in Tübingen. Schneider's method can turn out more than two million cube-shaped baits a year, many more than the few hundred thousand chicken-head baits produced by the Swiss cottage-industry approach. The cubes made by his method package the liquid vaccine in a container that is enveloped by fish meal or other flavoring and a protective fat or other waxy material. Typically, the baits also include tetracycline as a marker of uptake by wild animals.

By 1989 five types of live-virus vaccines were immunizing foxes in Europe. All were closely related to the vaccine originally studied in the U.S. but never field-tested there. Twelve countries on the continent were controlling fox rabies with oral vaccination, coordinating their campaigns through the WHO Collaborating Center. And Canadian teams had begun to examine the value of distributing mass-produced baits over large areas by airplane.

Today Switzerland is essentially rabies free, except for occasional incursions along borders with neighboring countries, and rabies is declining rapidly in other nations where oral vaccination is intensively applied. Fox rabies may well disappear from Europe in the next few years. For the first time in history, a disease of free-ranging animals is being eradicated without severely depleting populations.

Although the work on foxes has demonstrated the feasibility of orally immunizing wildlife against rabies—and presumably against other disorders—alternative vaccines are needed to control rabies in raccoons, skunks and dogs. The early finding that orally delivered live-virus preparations generally are effective only in foxes continues to hold true.

One candidate vaccine has been shown in the laboratory to be safe and effective in several species. It is a genetically engineered product that should be safer than earlier vaccines because it includes only a piece of the rabies virus, not the whole organism. Hence, it cannot cause rabies.



POSTER urges Mexicans to immunize their dogs. Unvaccinated dogs cause most human rabies, particularly in the developing nations. Distribution of vaccine-filled baits for dogs may one day bring canine rabies under control globally. Alan M. Beck of Purdue University photographed the poster in 1975.

Researchers at the Wistar Institute in Philadelphia and at Transgène S.A. in France developed the vaccine in 1984 by inserting a single gene from the rabies virus into a weakened version of vaccinia, which is already a rather innocuous virus. The chosen gene carries instructions for synthesizing a glycoprotein (a molecule including both protein and sugar) that normally projects from the coat of the rabies virus. When vaccinia multiplies in a host's cells, the cells produce the glycoprotein, which in turns elicits production of antibodies against the rabies virus. That recombinant is now used extensively for foxes in several countries, including Belgium and France, and seems to be as effective outdoors as the attenuated rabies virus vaccine.

Field trials are also being carried out in the U.S., where raccoons are the target. Charles E. Rupprecht and his colleagues at Wistar placed armed baits tailored to raccoon tastes on an island off Virginia. The team found that vaccinated raccoons developed rabies antibodies and that nontarget species, which were monitored for a year, were unharmed. The investigators are now completing a similar test on the mainland, in Pennsylvania.

As field trials continue, so does research into other vaccines and baits and into the best combinations for different species. For instance, substitutes for the vaccinia virus may have advantages for immunizing skunks and dogs. In the next several years, oral vaccination could well halt the raccoon rabies epidemic in America and be extended to other species—that is, if research funding, which is already a low priority in the U.S., can be maintained. One day oral recombinant vaccines might also become available for humans.

Oral vaccination programs against other diseases of wild animals could be instituted as well. Indeed, research in Germany suggests foxes might be protected against tapeworm by a vaccine incorporated in a bait.

But from the standpoint of human health, the most exciting prospect is the likelihood that a rabies vaccine will soon be available for distribution to dogs that now go unvaccinated. When those animals in developing nations are protected, the number of people throughout the world who die miserable deaths from rabies will at long last be dramatically reduced.

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Accounting for Environmental Assets

A country can cut down its forests, erode its soils, pollute its aquifers and hunt its wildlife and fisheries to extinction, but its measured income is not affected as these assets disappear. Impoverishment is taken for progress

by Robert Repetto

Natural scientists frequently seem baffled and dismayed when economists display little appreciation of the gravity of environmental degradation. One reason for this seeming indifference is that economists' accounting framework, and the models built on it, assigns no economic value to changes in natural resource stocks. This basic measuring instrument must be recalibrated if policymakers are to recognize and be held accountable for the wholesale disruption of natural systems now under way.

The 50-year-old framework, standardized in the United Nations System of National Accounts (SNA), completely ignores the crucial environmental changes of our times: the marked degradation of natural resources in much of the developing world and the growing pressures on global life-support systems such as climate and biological diversity. These changes may shape the future development of the world economy. But by failing to recognize the asset value of natural resources, the accounting framework that underlies the principal tools of economic analysis misrepresents the policy choices nations face.

Fortunately, at a time when more and more countries are adopting the policies and institutions of the market economy, this methodological model is under revision, for the first time in 20 years. The situation presents an opportunity, not to be missed, to correct a fundamental flaw.

ROBERT REPETTO directs research on the interplay of economics and the environment at the World Resources Institute in Washington, D.C. Before coming to the institute in 1983, he was associate professor of economics in the School of Public Health at Harvard University and a member of the faculty of the university's Center for Population Studies. He received a doctorate in economics from Harvard and a master's degree in mathematical economics and econometrics from the London School of Economics. This is Repetto's second article for *Scientific American*.

Whatever their shortcomings and however little their construction is understood by the general public, the national income accounts are undoubtedly one of the most significant social inventions of the 20th century. It is no coincidence that since these measures have become available governments in all major countries have taken responsibility for the growth and stability of their economies, and enormous investments of talent and energy have been made to understand how economies can be better managed. Their political and economic impact can scarcely be overestimated. In the U.S., should quarterly gross domestic product (GDP, the sum of all goods and services produced in the country) be even marginally lower than in the preceding three months, a recession is declared, the administration's competence is impugned and public debate ensues. Throughout the world the rate of GDP growth is the primary measure of economic progress.

The current system of national accounts reflects the Keynesian macroeconomic model that was dominant when the system was developed. The great aggregates of Keynesian analysis—consumption, savings and investment—are carefully defined and measured. But Keynes and his contemporaries were preoccupied with the Great Depression and the business cycle. Because commodity prices were at an all-time low, natural resource scarcity was the least of their worries. Unfortunately, as Keynesian analysis for the most part ignored the productive role of natural resources, so does the current system of national accounts.

In fact, scarcity of natural resources was of little concern to 19th-century neoclassical economics, from which most contemporary economic theories are derived. In 19th-century Europe, food grains and raw materials were flooding in from America, Australia, Russia and the colonies, while steamships and railroads were lowering transport costs. Forgotten were the dismal predictions of Ricardo, Malthus, Marx and other earlier classical economists that industrial economies would stagnate or collapse because of rising land rents and subsistence wages. What mattered to England and other industrializing nations was the pace of investment and technological change.

The classical economists had regarded income as the return on three kinds of assets: natural resources, human resources and invested capital. Neoclassical economists virtually dropped natural resources from their model and concentrated on labor and invested capital. When these theories were applied after World War II to problems of economic development in the Third World, human resources were also left out on the grounds that labor was always "surplus," and development was seen almost entirely as a matter of savings and investment in physical capital.

As a result, there is a dangerous asymmetry in the way economists measure, and hence the way they think about, the value of natural resources.

TERRACED ORCHARD in Costa Rica still shows the stumps of forest trees that were cut down to clear the land. Agricultural use of steeply sloping hillsides is often unsustainable because the soil quickly erodes.

DEFORESTATION has destroyed more than a quarter of Costa Rica's remaining forest since 1970. The loss of this asset has damaged the nation's earning potential, especially as the value of some tree species has quadrupled in recent decades.

Buildings, equipment and other manufactured assets are valued as income-producing capital, and their depreciation is written off as a charge against the value of production. This practice recognizes that consumption cannot be maintained indefinitely simply by drawing down the stock of capital without replenishing it. Natural resource assets, however, are not so valued. Their loss, even though it may lead to a significant decrease in future production, entails no charge against current income.

Although the model balance sheet in the U.N. SNA (which few countries actually compile) recognizes land, minerals and timber as economic assets to be included in a nation's capital stock, the SNA income and product accounts do not. This approach is fundamentally inconsistent. Logically, if a country's balance sheets at two different times indicate that an asset—say, a forest—has been depleted, then the income and product accounts for the intervening years should show a charge for the depreciation. This follows from perhaps the most fundamental identity of accounting: the difference in stocks between two temporal points equals the net flow in the intervening period. For example, the difference between a person's net worth at the start and end of a year equals his or her net savings (or dissavings) during the year.

The U.N. System of National Accounts violates this basic identity with respect to natural resource assets. Ironically, low-income countries, which are typically most dependent on natural resources for employment, revenues and foreign-exchange earnings, are instructed to use a national accounting system that almost completely ignores their principal assets.

Behind this anomaly is the mistaken assumption that natural resources are so abundant that they have no marginal value. In fact, whether they enter the marketplace directly or not, natural resources make important contributions to long-term economic productivity. Another misunderstanding is that natural resources are "free gifts of nature," so that there are no investment costs to be written off per se. The value of an asset, however, is not its investment cost but the present value of its income potential. Common formulas for calculating depreciation by writing off investment costs are just convenient rules of thumb. The true measure of depreciation is the capitalized present value of the reduction in future income from an asset because of its decay or obsolescence. In the same way that a machine depreciates as it wears out, soils depreciate as their fertility is diminished, since they can produce the same crop yield only at higher cost.

Codified in the U.N. SNA, the bias against natural resource assets gives false signals to policymakers. It reinforces the illusion that a dichotomy exists between the economy and the environment and so leads policymakers to ignore or destroy the latter in the name of economic growth. It confuses the depletion of valuable assets with the generation of income. The result can be illusory gains in income and permanent losses in wealth.

There is nothing wrong with drawing on natural resources to finance economic growth, especially in resource-dependent countries. The revenues derived from resource extraction can finance productive investments in industrial capacity, infrastructure and education. A reasonable accounting representation of the process, however, should recognize that one kind of asset has been exchanged for another. Should a farmer cut and sell the timber in his woods to raise money for a new barn, his private accounts would reflect the acquisition of a new income-producing asset, the barn, and the loss of an old one, the woodlot. He thinks himself better off because the barn is worth more to him than the timber. In the national accounts, however, income and investment rise as the barn is built, and income also rises as the wood is cut. Nowhere is the loss of a valuable asset reflected. Even worse, if the farmer used the proceeds from his timber sale to finance a winter vacation, he would be poorer on his return and unable to afford the barn. But national income would still register a gain.

The true definition of income encompasses the notion of sustainability. It is similar to the definition of sustainable development given by the World Commission on Environment and Development (the Brundtland Commission): that which meets the needs of the present generation without sacrificing the welfare of the future. This income concept encompasses not only current earnings but also changes in asset positions: capital gains are equivalent to an increase in income, and capital losses are a reduction in income.

The experience of Costa Rica shows how failure to account for natural resource assets can lead to economic disaster. To many naturalists, the country is renowned as the Western Hemisphere's conservation leader. It has set aside a fifth of its land for national parks and is the site of pioneering programs in nature tourism and restoration ecology. Yet during the past 20 years, Costa Rica has suffered devastating deterioration of its natural resources.

One of the hemisphere's highest rates of deforestation has led to the loss of 30 percent of the country's forests. Furthermore, most of the forest was simply burned to clear land for relatively unproductive pastures and hill

farms, sacrificing both valuable tropical timber and myriad plant, animal and insect species. Because most of the area converted from forest was unsuitable for agriculture, its soil eroded in torrents. Losses averaged more than 300 tons per hectare from land used to grow annual crops and nearly 50 tons per hectare from pastures. Between 1970 and 1989 an estimated 2.2 billion tons of soil washed away, enough to bury the capital city of San Jose to a depth of 12 meters. Meanwhile water pollution and overexploitation devastated coral reefs and coastal fisheries.

Because forests, fisheries, farming and mining directly account for 17 percent of Costa Rica's national income, 25 percent of its employment and 55 percent of export earnings, this destruction caused severe economic losses. The year 1989 saw the destruction of 3.2 million cubic meters of commercial timber worth more than $400 million. This amount, $69 for each person in Costa Rica, exceeded payments on the foreign debt by 36 percent. Erosion from farmland and pastures washed away nutrients worth 17 percent of the value of the annual crops and 14 percent of the value of livestock products. The deterioration of stocks in the main fishing ground was so severe that fishermen's earnings fell beneath the level of welfare payments to the destitute. Yet nothing in Costa Rica's national economic accounts records these asset losses.

When Costa Rica ran into economic difficulties in the early 1980s, economists diagnosed the problem as a debt crisis. Foreign liabilities had increased, and servicing that debt became ever more burdensome. The International Monetary Fund rushed south with programs to stabilize the monetary base. No one spoke of stabilizing the natural resource base, even though the loss in domestic assets—forests, soils and fisheries—had been much greater than the increase in external liabilities and had deprived the country of export income from which debt-servicing payments could have been made. The difference is that the buildup in foreign liabilities had been recorded and scrutinized; the depreciation in natural resource assets had been obscured and ignored.

To derive an accurate picture of what had happened, the Tropical Sciences Center in Costa Rica and the World Resources Institute collaborated to compile natural resource accounts for the country's soils, forests and fisheries for the period from 1970 to 1989. Estimates of changes in forest cover, mangrove area and other land uses were based on periodic surveys using remote sensing and satellite imaging. Data on forest type, volume, growth and composition were derived from detailed field studies, and estimates of soil erosion were generated using maps of topography, rainfall, soil types and land uses. The fishery accounts were based on sampling studies of fish populations.

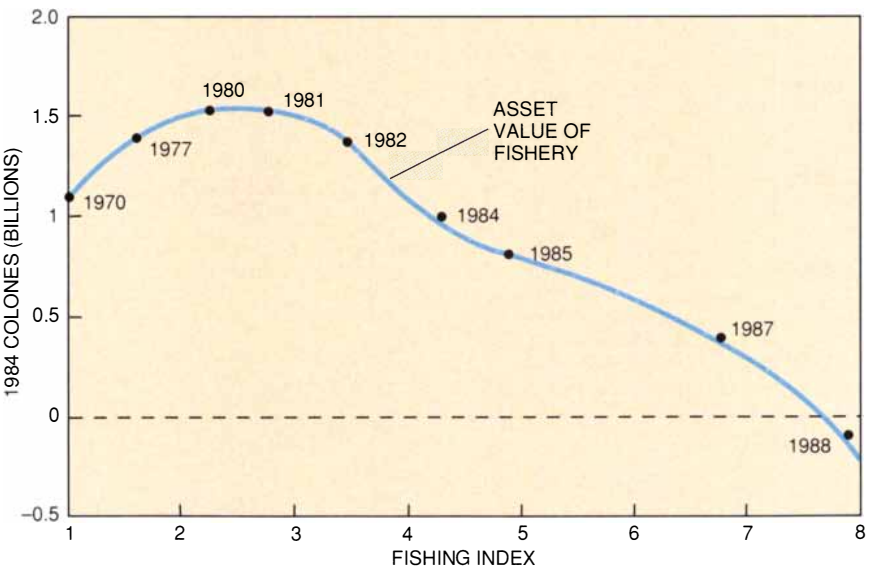
The most visible loss of natural resource assets in Costa Rica has been the destruction of its forests. Researchers constructed forestry accounts based on detailed maps of bioclimate, soil type, geology and topography, which were overlaid with land-use maps spanning the period under study. They estimated the proportions of various tree species in each forested area, along with age distributions, timber volumes and growth rates. The results are considerably more detailed and accurate than conventional forest inventories carried out for purposes of commercial logging.

The analysts then examined changes in land use to estimate the extent of deforestation. Between 1966 (the year closest to 1970 for which land-use data are available) and 1989, 847,000 hectares (2.1 million acres), or 28 percent of Costa Rica's forests, were lost. The largest losses were suffered in upland and tropical wet forests and tropical moist forests, precisely those sheltering the highest biological diversity. Two thirds of the deforestation affected ecological zones in which forest uses represented the most intensive sustainable use of the land. Despite the dominant role of the livestock industry in deforestation, only 14 percent of the area cleared was suitable for pasture.

The complete physical accounts related changes in standing volumes to annual harvesting and deforestation, as well as to growth and regeneration on remaining forest areas. The value accounts were derived from estimates of stumpage value (the market value of standing trees), which varied by species, maturity and distance from sawmills. Over time, the fraction of the forest stock that could be marketed increased substantially. Stumpage values in constant prices have risen between fourfold and 10-fold since 1970, depending on the timber variety, demonstrating how shortsighted the wanton destruction of forests has been.

Indeed, despite a declining rate of deforestation in recent years, asset depreciation has increased dramatically because the hardwoods being destroyed have become more valuable. The forestry sector generated substantially negative levels of net national income throughout the 1980s: the value of forest capital destroyed greatly outweighed the value of forest products generated.

Much of Costa Rica's terrain is steeply sloping and subject to heavy rainfall; the loss of forest cover leads to rapid erosion. Estimates of soil erosion rates were based on much the same empirical base as the forestry accounts: detailed mappings of topography, geology and soil type, rainfall and land use. From these figures, analysts subtracted estimates of the erosion rates that would occur under the highest sustainable land use for each land unit. Total erosion averaged 92 tons per hectare across all land uses, and nonsustainable erosion



TRAJECTORY OF EXPLOITATION shows how the effort expended on fishing in Costa Rica increased (as measured by an index developed at the Tropical Sciences Center), but the industry's profits decreased and eventually disappeared.

averaged nearly 300 tons per hectare on land under annual crops. Because of the decline in the area under forest cover, total erosion increased from 122 million tons per year to 189 million tons between 1970 and 1984.

The resulting monetary loss comprises both declines in farm productivity and off-site damage caused by the runoff of such enormous quantities of soil. Only partial estimates—based on sedimentation effects on hydroelectric systems—could be made of off-site damage. The overall estimate of the cost of soil erosion to agricultural productivity was based on the cost of replacing principal plant nutrients lost from the vanished topsoil. This approach is only a first approximation, since erosion also harms soil structure and biological activity and removes micronutrients.

The resulting accounts show losses increasing roughly in proportion to the acreage under agricultural uses. Annual cropping, especially on sloping land subject to heavy rainfall, contributes the largest amount to estimated depreciation, but pastures, because of their predominance among land uses, also contribute about a third of the total. Soil depreciation charges an average 13 percent of the value added for livestock production, 17 percent for annual crops, and between 8 and 9 percent for all agricultural production.

During the same period that forest and soil assets suffered serious damage, the value of the nation's principal fishery has essentially been wiped out. The Costa Rican fishing industry is mostly artisanal; it is unregulated and also subsidized through diesel fuel prices and tax benefits. The influx of small boats accelerated sharply in the 1980s as alternative employment opportunities in rural and urban areas stagnated. Meanwhile evidence of overexploitation has multiplied: fewer fish of highly valued species are caught, and the ratio of catch to fishing effort has declined steadily. Because fish stocks cannot be measured directly, changes in the value of the principal fishery in the Gulf of Nicoya were estimated by constructing a bioeconomic model relating sustainable yield to fishing effort. Researchers created an index of fishing activity by boats of differing power classes and capacities, reflecting the relative daily harvests by each type of boat.

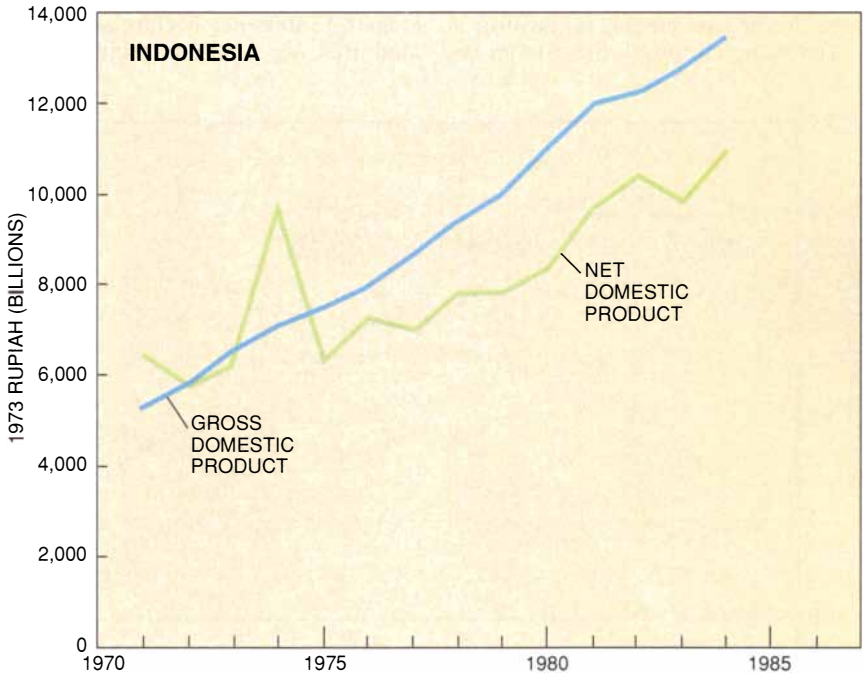
In this framework the value of the fishery can be estimated as the capitalized value of the annual sustainable profit that it can generate. As fishing effort increased throughout the 1980s, profits declined. By 1988 fishermen were scarcely recovering their direct costs, even assuming that their time was worth no more than the subsistence allowance provided to the unemployed, only a fraction of the agricultural wage. In other words, the asset value of the fishery was zero.

These three sets of accounts demonstrate that Costa Rica has been using up its natural capital at a rapid rate. From 1970 to 1989, the accumulated depreciation in the value of its forests, soils and fisheries exceeded $4.1 billion in 1984 prices—more than the average value of one year's GDP. Relative to the size of the economy, the annual loss is huge. It is as if in the U.S. the entire defense budget disappeared every year without a trace.

Yet this is only part of the loss that actually occurred. For forests, the numbers include only the loss of immediate and future timber value. Costa Rican forests provide other important services—as wildlife habitat, tourist attraction, ecosystem regulator and supplier of nontimber commodities—but their value has yet to be estimated. For soils, depreciation counted only the loss of principal nutrients for plant growth because of erosion. Other deleterious changes caused by erosion, such as the loss of micronutrients, microbiological activity and desirable soil structure, which also reduce soil fertility, were not captured. And for fisheries, only the value of the principal species in one important fishing area lost through overfishing enters the accounts.

Even the conservative methods used here show that the performance and prospects of the Costa Rican economy have been substantially overstated. The rate of net capital formation, a critical variable in economic growth, was much less than estimated. Natural resource depreciation rose from 26 percent of gross capital formation in 1970 to 37 percent in 1989. The conventional accounting framework overstated actual net capital formation (which subtracts depreciation of man-made and natural capital from gross capital formation) by more than 70 percent in 1989. An accounting system so misleading about an economic process as important as capital formation can be of no use for economic analysis, planning or evaluation.

The experience of other developing countries for which natural resource accounts have been compiled parallels that of Costa Rica. In the Philippines, for example, annual losses resulting from deforestation averaged 3.3 percent of GDP between 1970 and 1987. In 1988 dryland farming losses attributable to erosion totaled roughly 2.5 percent of GDP. More important, the lost topsoil degraded the nation's watersheds, reducing the output of hydroelectric projects and interrupting the irrigation of lowland rice paddies. These identifiable effects totaled nearly 5 percent of GDP. Once washed out to sea, topsoil damaged the coral reefs that support the small-scale fisheries. This pollution, together with overfishing, wiped out all profits by 1984. Although the na-



ECONOMIC GROWTH is overstated by measures that ignore the value of natural resource assets. Adjusting for depreciation of those assets (*green line*) presents a different picture in Indonesia and other nations.

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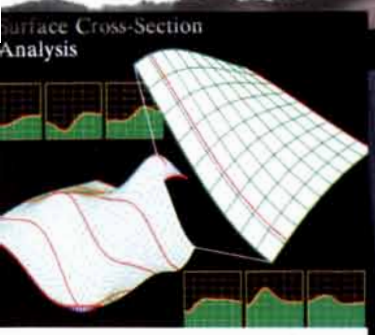

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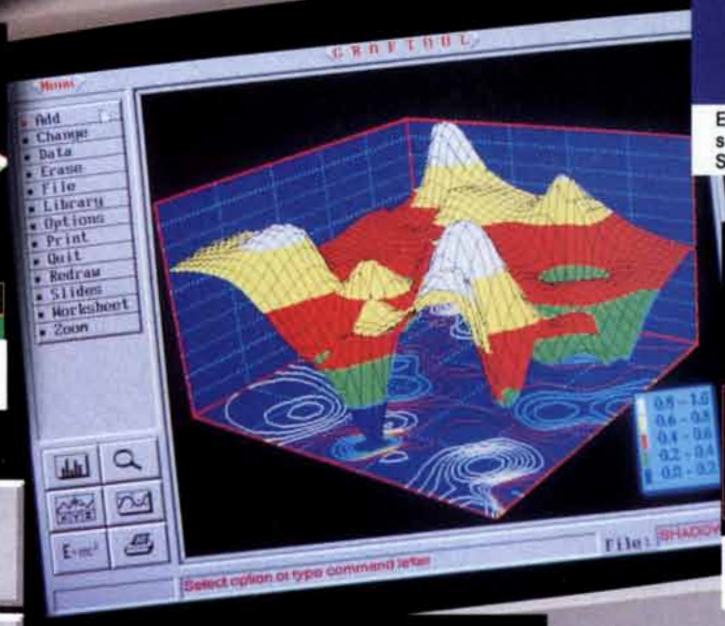

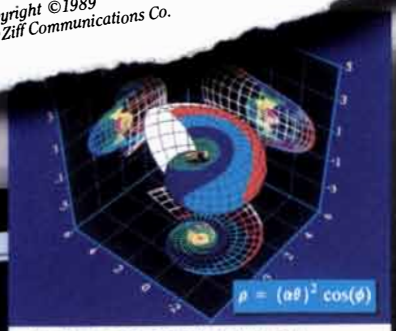

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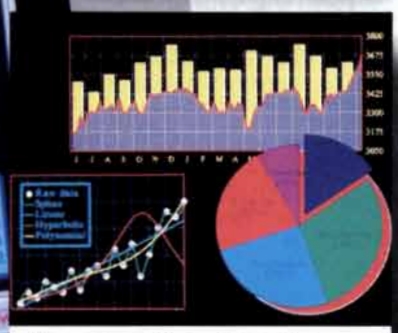

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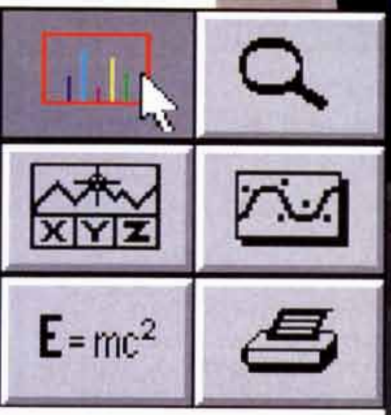

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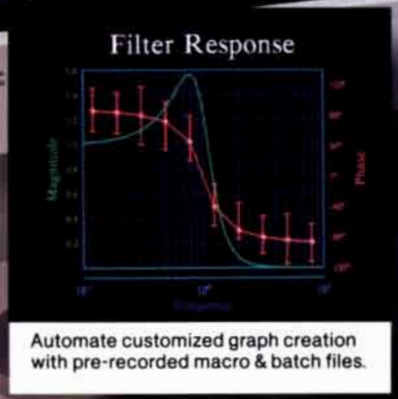

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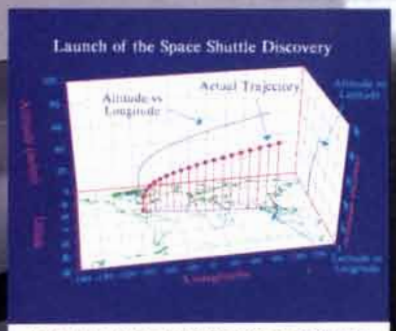

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tion's accounts showed a mounting external debt, they gave no sign of the destruction in productive capacity that made paying back that debt more and more unlikely.

Indonesia's natural resource accounts show that between 1977 and 1984 the depletion of natural resources totaled 19 percent of GDP. The 4 percent annual depreciation of soil fertility, for example, is roughly the same as the annual increase in farm production, suggesting that current increases in the yield of the nation's upland farms are being achieved almost entirely at the cost of future production. Once again, conventional accounting methods show no sign of this impending danger.

A growing number of resource-dependent countries are coming to realize the inadequacy of the current system of national accounts. Analysts have begun compiling natural resource accounts along the same lines as Costa Rica's in Mexico, El Salvador, Bolivia, Brazil, Chile, the Philippines, Indonesia, China, Malaysia, India and possibly other developing countries. In some countries the official statistical or environmental agencies are closely involved in these efforts. Economists are also constructing such accounts in Norway, Canada, Australia, France, Germany, the Netherlands and the U.S.

The importance of providing an accounting system that accurately and effectively integrates economic and environmental values has been repeatedly emphasized by world leaders. In addition, the U.S. Congress has instructed U.S. representatives to the United Nations and the multilateral development banks to urge that such changes be made in the standard system of national accounts and instructed the U.S. Agency for International Development to support the efforts of countries to compile natural resource accounts.

At the focal point of these efforts are the U.N. Statistical Commission and the U.N. Statistical Office, which are in the process of revising the standard U.N. System of National Accounts. In addition, formerly socialist countries and others, including the U.S., are now reconciling their national accounting systems with the SNA.

At present, however, the U.N. statistical authorities are adopting an equivocal stance toward the problem of natural resource accounting. They have refused to correct the basic inconsistency in the SNA's treatment of natural resources. Instead they are merely developing guidelines that countries may use to compile natural resource accounts as an adjunct to the official definitions.

NATURAL RESOURCE ASSETS are capable of generating considerable income if properly managed. Their loss (as seen in the now destroyed section of the Brazilian rain forest above) must be recognized on national balance sheets.

This straddle is unlikely to be helpful. Such adjunct accounts, even if compiled, will not command the attention of the public and policymakers as do the well-known measures of GDP, national income and investment. These, with all their distortions and inconsistencies, will continue to be the main yardsticks by which economic performance is evaluated and analyzed. Moreover, since statistical offices around the world are chronically underfunded, they are not likely to take on the task of constructing natural resource accounts on a regular basis until they are made part of the core system.

The U.N. statistical authorities should not lose the opportunity now at hand to make changes that are already long overdue. Indeed, the U.N. Conference on Environment and Development (UNCED) which will take place in Rio de Janeiro this month, would be the ideal occasion for announcing a definite timetable for change. The work done in Costa Rica and other nations has shown that realistic accounts covering a country's principal resources can be constructed at modest cost, using only data already available. These countries have also demonstrated that such accounts drastically alter the evaluation of economic performance in resource-dependent countries, providing a direly needed early warning of ecological as well as economic losses.

Three years would seem to be ample time to complete the change. It is hard to believe that countries that have labored under Marxist-Leninist economic systems for 50 years or more can convert their economies to capitalism in less time than the U.N. can change the definition of capital depreciation. The UNCED conference faces a serious challenge in achieving tangible results that will benefit the global environment. The correction of the system of national accounts is one that is within reach and that in the long run will have enormous significance.

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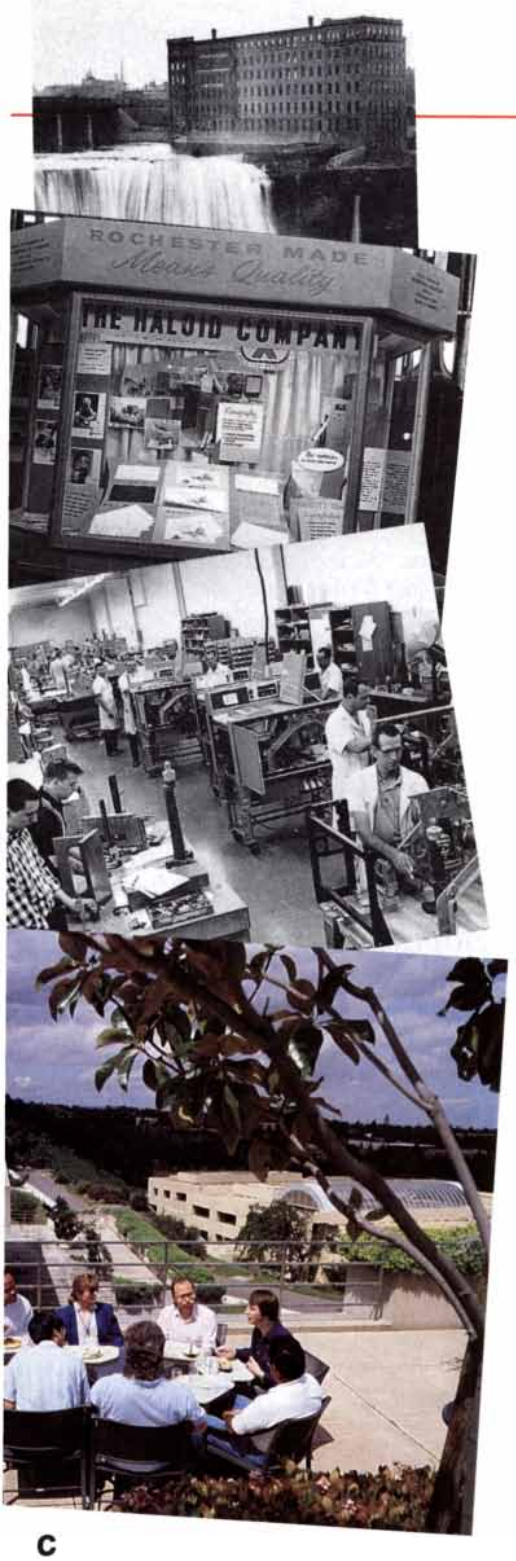

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R&D THEN AND NOW. (a) *IBM team that developed recent graphics supercomputer; Watson research center in 1960 under construction; 1933 IBM tabulator; Thomas J. Watson, Sr.* (b) *Bellcore researcher analyzing materials; wiring and back of television, Bell Labs 1927; 1884 experimental workshop; 1922 transmitter laboratory.* (c) *Xerox PARC and business division share site; 1964 copier production; 1957 display of products; 1904 first offices.*

As U.S. spending on industrial research and development flags, a few companies are trying to invent new rules.

In the industrial heyday of the 1950s, companies boasted about their scientific prowess. A flip through the June 1952 issue of *Scientific American* turns up dozens of advertisements parading the triumphs of industrial research. The Radio Corporation of America reported that its "years of research and engineering" were opening the doors for television service throughout the U.S. Westinghouse extolled the work of one researcher who had churned out 225 patentable ideas. Bell Telephone Laboratories bragged that its "tiny amplifying device" (the transistor) was about to find its way into telephony.

These days the refrain is muted. Even prominent laboratories have been sold or shuttered; RCA's research center, where liquid-crystal displays were invented, was simply given away. Where research efforts persist, funding has dried up. According to data compiled by the National Science Foundation, annual real growth in industrial R&D spending, which had averaged almost 7 percent between 1975 and 1985, slid to 1.5 percent between 1985 and 1990.

Although product development and engineering departments have suffered from the R&D cutbacks, in many companies central research has been the most visible target. Projects aimed at developing future technologies—once the crown jewel of corporate R&D—have been whittled down. Many of those that survive are under enormous pressure to justify their keep by producing commercially valuable results.

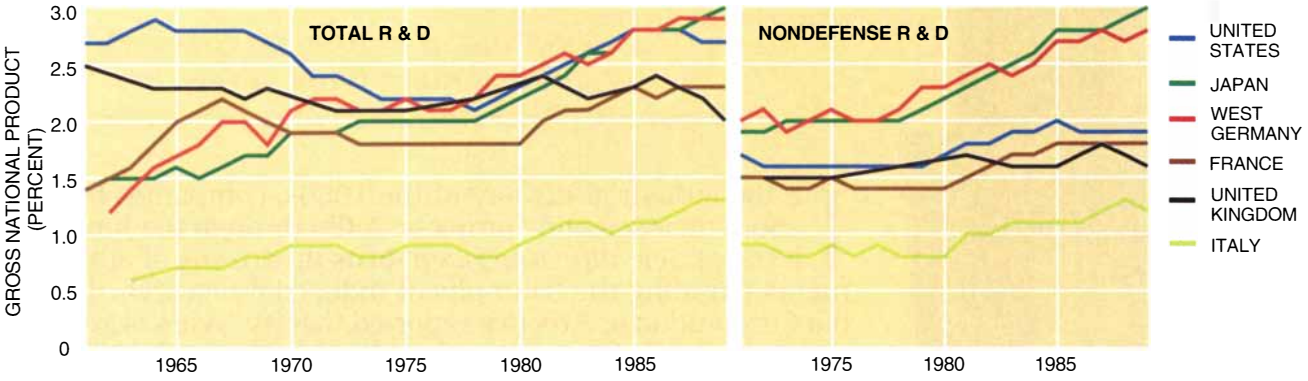
Managers point to several reasons for the cutbacks. In many ways, the large research laboratories seem to have become disengaged from the business of the company. From the windows of the corporate finance office, the research center has looked more like a resort for misplaced academics than a business division. Scientists often seem motivated by obscure, intensely personal goals rather than by company goals. Production and marketing staffs have had more than their fill of assimilating inventions "thrown over the wall" by research.

Even worse, R&D has not always galvanized corporate growth. Fewer than half the companies that have spawned an important invention in the past few decades have made much money from it, notes Charles H. Ferguson, an industry analyst at the Massachusetts Institute of Technology. The problems are greatest at America's largest companies.

Why? At a few U.S. corporations, leaders have come to the realization that the problem lies not with "research" but with how research, or more precisely, innovation, is managed. If an invention is too far outside the company's agenda to exploit, both research and management must ask themselves why research wandered so far afield. When relevant inventions are not translated into commercial innovations, management must bear much of the blame.

Some of the difficulties are not industry's fault. Sometimes the existing infrastructure has not been ready to support a promising idea. Economic conditions have also changed.

International Spending on Research and Development



SOURCE: National Science Foundation

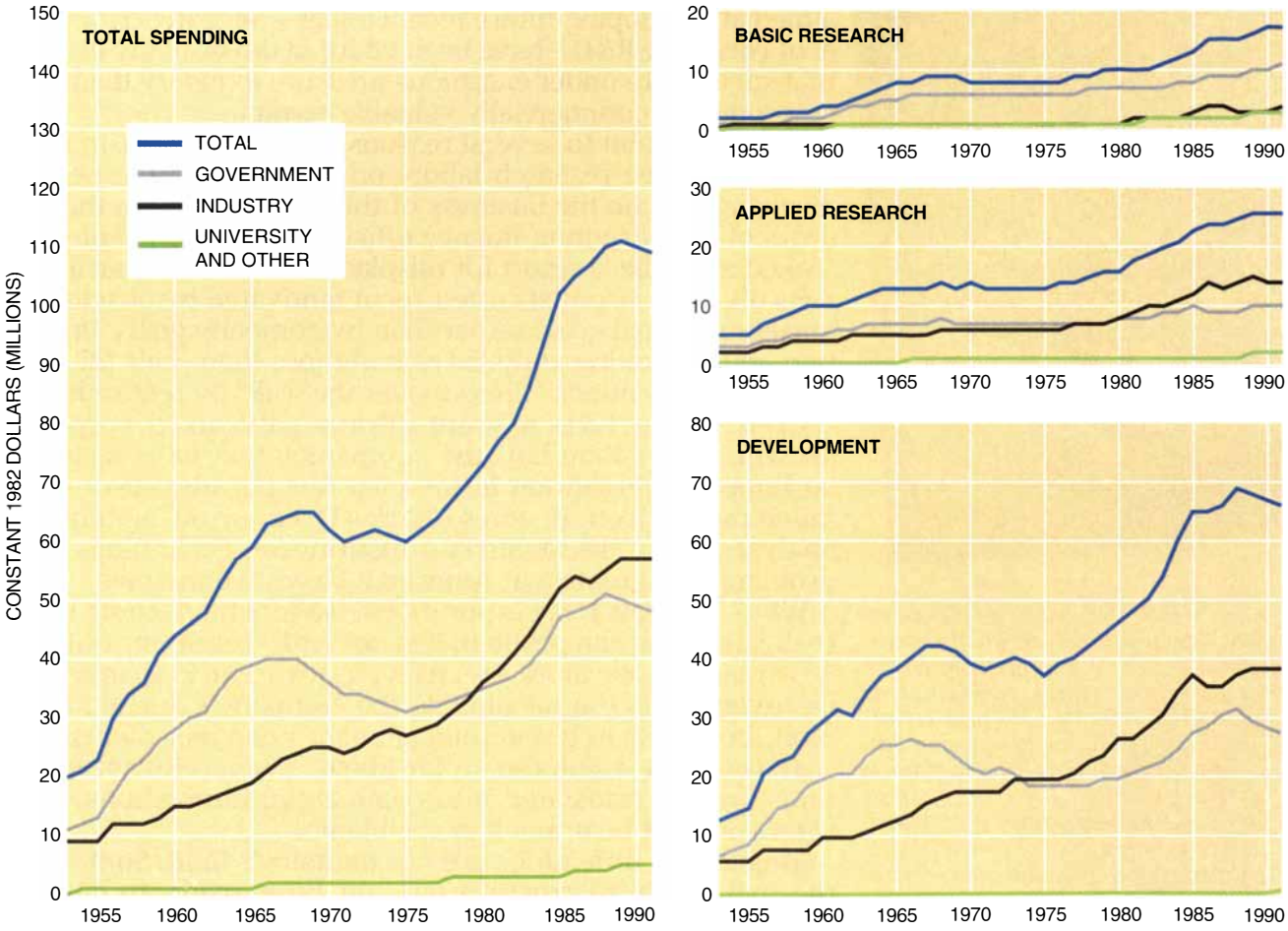
Whereas success once meant stoking the consumer's appetite, now a bevy of producers compete to churn out more goods than consumers either want or can afford. Tax policies, demands for quick financial returns and takeover threats have discouraged long-term strategies based on investing in research.

To break fresh ground, innovators must gauge the current and future needs of consumers. Producers must work more intimately with their customers, helping them use the technology to shape their own businesses. In this way, "the role of R&D is more important than ever before in making a viable business," asserts Jack D. Kuehler, president of IBM.

These demands portend cultural changes—sometimes wrenching ones—for corporate research. As firms tighten their ties to the customer, research must do more than invent technology, asserts John Seely Brown, chief scientist for Xerox. "Less and less of the value-added chain turns on technology," he says. "We are an endangered species if we just focus on technology."

Brown and others believe research must become involved in every facet of the corporation, from evolving the enterprise's strategy to improving internal work practices, including tuning manufacturing and spurring collaboration with co-workers and customers. Research must also intuitively understand the business of the company. When a research insight suits a company's customers and fits its agenda, the company

U.S. Spending on Research and Development



SOURCE: National Science Foundation

must then be able to accelerate its internal "clock speed," the time it takes to transform that idea into a product that can be refined in the marketplace. And throughout the process, managers must nurture research's key strength: the ability to step back and ask critical questions that can shape the company's future.

This is hardly the first time companies have tried to redesign research programs. There have been notable successes, notes Margaret B. W. Graham, formerly at Boston University's School of Management and now a manager with Xerox. But where managers failed to leaven the relationship between research and customers with longer-term thinking, she says, research became routine and, ultimately, inconsequential.

A handful of companies are now boldly grappling with how to formulate research into a more potent catalyst for growth while preserving its vitality. Among them are Bellcore (the research arm for the regional Bell operating companies), IBM and Xerox. The programs are very different, even in size: IBM annually spends about $500 million on research alone, Bellcore about $150 million (for "applied research") and Xerox about $120 million.

All draw from rich pools of scientific talent. As these companies try to change the chemistry of these resources, they face tough challenges that reflect their own histories. Because Bellcore serves a family of seven owners, it must work harder than most organizations to understand how research can support customers' needs and lay the groundwork for the future. As one of the world's largest corporations, IBM must unwrap the swaddling of bureaucracy that has constricted research from swiftly reaching the market. And Xerox, which paid little heed to the promises offered by past research inventions, must recognize and harness ideas that can transform the company.

Mark B. Myers, senior vice president for corporate research and technology at Xerox, sums up the problems facing all three. "We see extraordinary things in research," he says. But if a company cannot design, manufacture and service the idea-turned-product, as well as relate it to customers' needs, "it may be a very interesting and exciting scientific artifact—but nothing more."

Eventually the progress of these companies will be measured in the stark numerology of corporate life: profits, dividends and growth in asset value. What follows are portraits of how Bellcore, IBM and Xerox are trying to balance the tensions between aligning research with the corporation without crushing the spirit of inquiry.

Bellcore: Seeking the Customer

When Robert E. Nahory quit Bell Labs on December 31, 1983, to help establish Bellcore, or Bell Communications Research, he thought he had a good idea of who the customers were. Bellcore would serve the technological goals of the seven regional Bell operating companies, after AT&T divested them. And Nahory thought he knew what they needed. He had pioneered such specialty optoelectronics elements as semiconductor lasers; the devices seemed likely to become key to establishing high-speed optical communications networks. At a newer organization, Nahory says, "we all thought our work could make a difference."

But by the early 1990s the operating companies and Bellcore seemed headed in different directions. Bellcore was indeed winning acclaim for its research in solid state physics and apparently meeting needs by laying the foundation for future generations of hardware. "We tried to establish a patent portfolio that we could keep for ourselves and our owners," says Vassillis G. Keramidas, an executive director in applied research. Yet the impressive results met with lukewarm enthusiasm from the local telephone companies.

One reason for the response was that existing communications hardware had already leaped several generations ahead of much network software. The customers needed better software to utilize the existing equipment, not improvements in the gear itself. "There are people maintaining software systems who are younger than the systems themselves," points out Alfred V. Aho, assistant vice president for information sciences and technologies research. Moreover, many of Bellcore's projects did not satisfy all seven owners. "I think for a while Bellcore forgot to ask how

AT BELLCORE, Robert E. Nahory is using his understanding of optoelectronics to help solve hardware problems in existing telephone networks.

BELLCORE CATECHISM

- What are you trying to do?
- How is it done now and what are the limitations of the current practice?
- What's new about your approach and why do you think it will work?
- If you're successful, what difference does it make?
- How do our customers get paid?
- What are the risks?
- How much will it cost?
- How long will it take?
- What are the mid-term and final exams?

its work was serving its owners," says Edmond J. Thomas, a vice president at NYNEX Science and Technology, Inc.

Thomas's observation took on a sharp edge at the end of last year, as George H. Heilmeier, who joined Bellcore in March 1991 as chief executive officer, began restructuring Bellcore's programs. Heilmeier acknowledges that the changes are taking place more swiftly than even he had anticipated a year ago. "The books say it takes five to seven years to make a cultural change," Heilmeier points out. "We don't have that much time, because the regional companies have made theirs." Nevertheless, Heilmeier is determined to drive home the importance of working with the regional Bell companies. "Customer satisfaction has got to become a religion around here," he declares. To that end, he preaches a "catechism" of questions. Among them: Who will care if you are successful?

The ways in which researchers are learning to ask that question differ. In some cases, managers are sending staff on "internships" to groups within Bellcore that work directly with the regional phone companies. For instance, Richard S. Wolff, who now directs Bellcore's research in personal communications applications, spent three months helping a department write technical requirements for nascent portable communications services.

In previous research projects, Wolff had explored the ways that customers might one day plug into very high speed networks. Because such networks did not yet exist, "we could continually refine and modify our project as we saw fit," Wolff recalls. During his internship, he realized that the operating companies felt such changes meant the work was too preliminary to pursue. "There was a pretty big culture difference" between research and engineering, Wolff concedes. In the latter, "timely delivery of commitments is the number one metric."

Wolff also began asking questions about the possibilities for wireless data (as opposed to voice) networks. Because the engineering group lacked the resources and time to pursue such work, Wolff took the idea back to applied research. The effort is still long term, he emphasizes, but now he feels he has a more refined sense of how to adapt the project to the demands of the operating companies.

Other researchers have had a more abrupt introduction to customer needs: Bellcore stopped supporting their work. The changes have exacerbated tensions and provoked critics to accuse Bellcore of dropping long-term research. "We continue to want to research new physical phenomena," Heilmeier insists, "but once we determine that a phenomenon isn't going to have a first-order impact on our business, we have to go on to the next one, even though interesting questions still remain."

High-temperature superconductivity is a case in point. Over the past few years, Bellcore became one of the leading groups exploiting a result that originally emerged in IBM's laboratory in Zurich. When Bellcore researcher Arun Inam began work on high-temperature superconductivity four years ago, he was "genuinely convinced" that one day it would be important. But just how the new class of ceramic materials would solve telecommunications bottlenecks was less clear to him, he concedes. "Those questions fell to the side because we became famous very, very fast," he says.

Famous was not good enough for the operating companies. "There's got to be a clear way for us to directly benefit from research," Thomas declares. Work on high-temperature superconductivity was dropped. Inam switched to exploring very high capacity data-storage devices that rely on holography. This project may also take a decade or two to bear fruit, he says. But as the phone companies begin to offer such services as multimedia and personal information networks, Inam believes holographic memories will evolve into a powerful solution for data-storage problems. And to try to better understand the operating companies' needs, Inam is also spending hours reading about their businesses.

Since the beginning of the year, Nahory has found an even more direct way to move closer to Bellcore's customers. He has been seeking out engineering departments stumped by problems and then helping them find solutions. "In research, you solve problems every day—that's one of the skills we're selling," he says. For instance, one group has been wrestling with the reliability of existing optoelectronic components. Nahory could help: "We've been measuring these characteristics for years," he notes.

Nahory set on this direction somewhat by chance, but he may nonetheless be pioneering a way to use the synergies of research and engineering to strengthen a building-block technology for the phone companies. In the course of testing the reliability of an off-the-shelf laser, his research team found a way to narrow its spectrum dramatically, increasing the efficiency of the device. The engineers did not have the equipment or the inclination to redesign the component; Nahory and his colleagues, on the other hand, would not have previously had reason to work with such a standard component.

Still, Nahory worries about the future

of Bellcore's research skills. "The question is, how do you stay on the forefront of science while you're applying it?" he asks. "You don't want to lose the skill of asking further questions as you answer existing ones."

As his researchers seek customers for their work, Heilmeier hopes to clarify Bellcore's mission by espousing a vision of the future that all seven operating companies can share. As much as AT&T was once committed to "equal access" telephone service for all, Heilmeier talks about building a national knowledge and information infrastructure that would reach consumers and businesses nationwide. Already Bellcore has highlighted seven of its broad projects, which could serve as stepping-stones to that vision—and give the regional phone companies new services for their customers within a short time.

"You've got to be willing to do near-term work because it helps build credibility," Heilmeier says. "Then, when you have something longer range, they're willing to listen."

IBM: Multiple Paths to the Market

In the early 1960s IBM managers bet the fate of the company on a single idea. It was the System/360 computer line, which like its geometric namesake, was intended to encompass all the needs of IBM customers. The strategy was a smashing success: IBM achieved dominance of the computer industry. But later, as its research laboratories made fundamental advances in science and eventually won two Nobel Prizes, success took a toll. IBM introduced products only on "a worldwide, homogeneous basis," recalls James C. McGroddy, vice president and director of research. Promising ideas lumbered slowly through the corporate hierarchy, often perishing along the way.

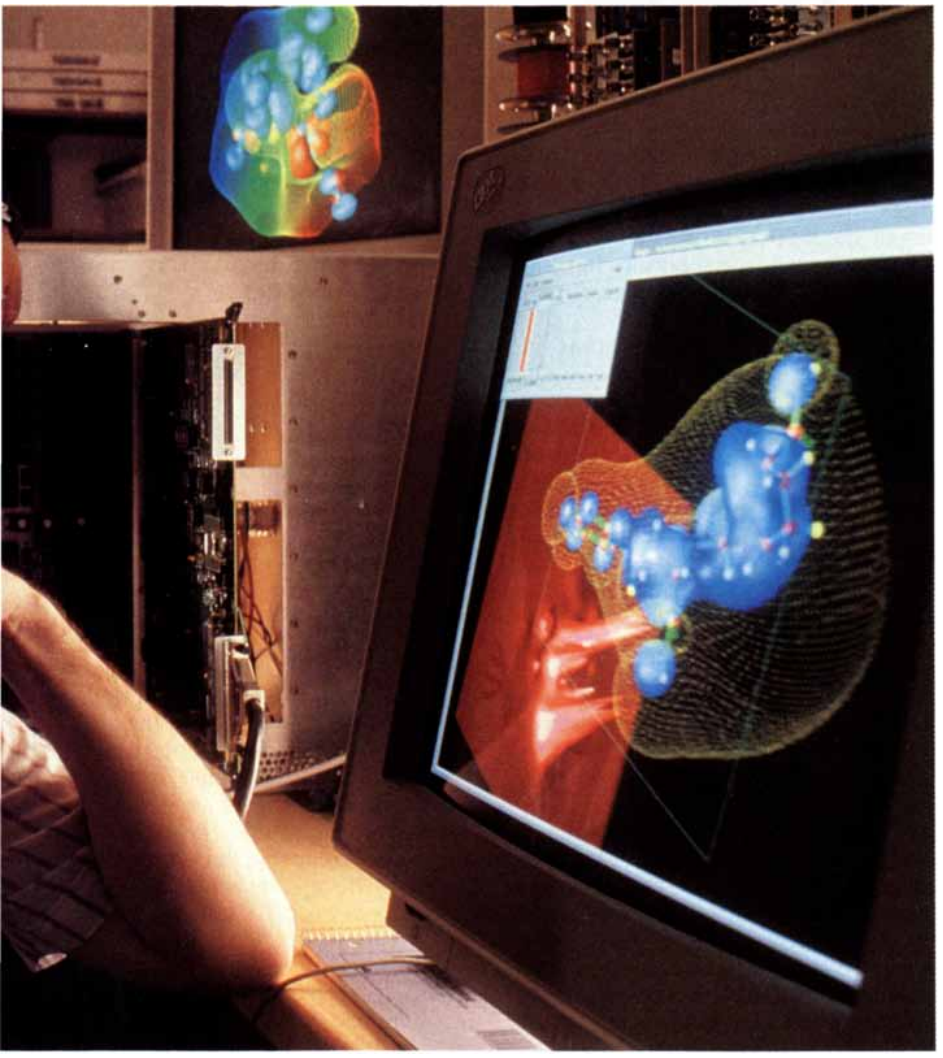
Among the most painful examples was IBM's decision to put off exploiting the Reduced Instruction Set Computer (RISC) processor design pioneered by John Cocke at the company's Thomas J. Watson Research Center. A major factor in the decision, according to former IBM employees, was the concern that RISC-based systems would compete against IBM's installed base. "We had good reasons for not doing it," says John A. Armstrong, now vice president for science and technology at IBM. "They just happened to be wrong."

These days IBM managers are encouraging competition throughout the company. Late last year IBM announced it was giving more autonomy to its nine manufacturing and development businesses eventually judging each on its own bottom line. These units, which are assessed a fee for corporate research expenses, are also free to draw on IBM resources, pay for additional in-house research projects or look outside the company for technology.

Managers are keenly aware of the pitfalls of relying on outside technology, however. IBM's personal computer quickly became a commercial success, in large part because of smart decisions to use outside vendors for such critical elements as processors and operating system software. But that reliance eventually impeded IBM's efforts to direct future PC developments. "Which is why we've started a number of alliances," says Jack D. Kuehler, IBM's president, ticking off some of the current 300 or so joint projects.

Those alliances run from chip development with Intel and object-oriented programming with Apple to multimedia applications with a small company called Kaleida. Kuehler hopes such ventures will enable IBM "to position for growth and add value and differentiation." At the same time, IBM is encouraging its researchers to push ideas more quickly into a large number of diverse markets. "We have 100,000 competitors creating the solution for this niche and that niche and the other," McGroddy says. "Some of the niches get to be very big, so our strategy is to pick those niches that we think will evolve into larger things."

About 30 percent of the company's research force is now involved in experiments that McGroddy hopes will blossom. One way IBM plans to fill those niches is with tiny "intrapreneurial" companies. The first such offering: a visualization supercomputer created by a team of about 50 IBM researchers,



IBM'S Armando Garcia (*left*) and Bruce Lucas (*right*) felt like they were working for a start-up as they helped build IBM's first visualization supercomputer.

engineers and marketing managers, who labored for two years in a rented, suburban office about 15 minutes from IBM's Watson center.

The pilot project grew out of the frustration of Abraham Peled, vice president of systems and software in IBM's research division, who was distressed that the company was not jumping more quickly into new areas. At the time, IBM had no significant products in the burgeoning market for computer graphics. Because a graphics system would not have to be compatible with any other IBM products, Peled, along with Ralph Gomory (then senior vice president for science and technology), persuaded IBM to play the role of a venture capitalist and put up $25 million.

Like the employees of any high-tech start-up, the group put in long hours, straining to meet its self-imposed deadline of unveiling a machine at a key industry trade show in 1991. "You talk to those kids, and they don't know what company they're in," Kuehler says. "They're just having a good time getting a product into the marketplace without all the bureaucracy that gets in the way of speed."

Although the workers knew they could return to Watson, they felt their reputations were on the line. "We took a lot of risks," says Armando Garcia, who headed hardware development. To reach the target processing power, he based his design on unusually large processor boards packed with multiple RISC chips made by Intel.

The gambles seem to be paying off. IBM began shipping its Power Visualization System late last year and has won warm technical reviews. Now they are looking for revenues. Garcia expects to continue working with the project for at least another year. "It may be that dotting *i*'s and crossing *t*'s can be painful and hard work," he says, "but it's worse to see your ideas languish."

McGroddy also has high hopes that a tiny start-up company in Sacramento, Calif., will move IBM into the lucrative area of medical equipment. Integrated Surgical Systems (ISS), with IBM, has been developing a robotic system to assist in such surgical procedures as hip replacements. "It began in 1985 when we went to IBM with a problem—how to cut the shape of an implant into bone," recalls Howard Paul, chairman of ISS. "We couldn't get anybody else to do it."

Paul and his colleague William L. Bargar at the School of Medicine of the University of California at Davis were among the first to use replacement implants with porous surfaces that can bind with new bone. The more snugly the implant fits the cavity in a patient's bone, the more successful the replacement should be. The doctors reasoned that they could dramatically improve such procedures by relying on a robot to sculpt the cavity.

Over the next few years, IBM provided the researchers with funding, equipment and technical assistance; eventually the corporation gave the start-up venture seed money and management advice from its upper echelon. "They've been great to work with," Paul says. "When we have a technological problem, we just put in a call to McGroddy, and he gets it done." Since late 1990, Paul has used RoboDoc to replace defective hips in more than two dozen dogs. The company's first trial operation on a human is scheduled for this summer.

Still, the most successful collection of such skunkworks cannot alone propel the growth of a company the size of IBM. And even IBM could not support more than 10 projects like the visualization start-up at a time, McGroddy says. As a result, he has a number of other experiments under way. To get into the business of flat-panel, liquid-crystal display screens, IBM undertook a joint venture with Toshiba in Japan. "We created an entity that's a lot more lightweight in its demands on the management team and on the resources of IBM," he says.

In its familiar domains, IBM continues to try to erode the classic bureaucratic and cultural barriers isolating researchers from their peers in product development. In 1981 the company began nudging Watson researchers and development engineers together under the auspices of its first "joint program"—the Advanced Silicon Technology Laboratory.

Under that umbrella, researchers designed pivotal elements of dynamic random-access memory (DRAM) chips that could store millions of bytes of data. But as the preliminary designs were finished and engineers became increasingly involved, the scientists bowed out, turning instead to an even more advanced generation of chips. By the time the development team began constructing prototypes, knowledge about why certain design choices were made often fell between the cracks, and the project slowed. "There was no continuity of vision, and the program tended to veer off," says Gary B. Bronner, who manages DRAM technology at the Watson center.

As a result, IBM is now trying to keep its development teams tied tighter together. Last fall Bronner and his colleague James H. Comfort were offered a chance to help lead separate chip projects that over the next few years will take them out of research altogether and into manufacturing. "We've got both research and development people in one place," Comfort says. "There's a lot more pressure. You don't get to walk away."

Such intimate teamwork can be unsettling to scientists who have spent most of their careers working independently. "Some people are nervous because change makes people nervous," Comfort points out. Others worry that the demands of such projects will come at the expense of basic research.

Paul M. Horn, who directs the silicon technology laboratory at Watson, contends that IBM can balance those demands. "We're supposed to be famous and vital," he says, repeating a phrase that was coined by Gomory in the mid-1980s and is embedded in acrylic paperweights that are handed out to all research managers. "Ultimately, IBM research has to be measured by its vitality to the company. But we can't do it without being famous," he insists. "There needs to be the kind of basic research that leads to Nobel Prizes."

As for vitality, IBM is determined not to let its technology languish in the laboratory. After years of exploring the idea, Watson researchers are now

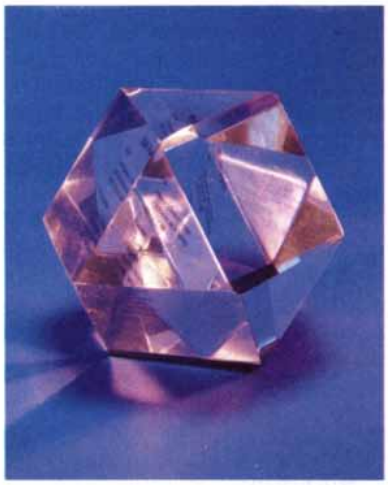
IBM RESEARCH

GOAL

A research division famous for its science and technology and vital to IBM

PRINCIPLES

- Excel technically
- Know IBM
- Know the technical world
- Provide technical leadership



PAPERWEIGHT given to IBM research managers lays out objectives.

cooperating with a business unit to build a scalable, multiprocessor supercomputer, a design that offers a wide range of performances. Alliances with Thinking Machines Corporation and Supercomputing Systems, Inc., which are also aimed at scalable architectures, continue independently.

IBM's experiments, McGroddy contends, will give research more paths to the market. "Our vision as a company is in a sense hierarchical," he says. IBM wants its traditional customers to continue to look to the company for technological solutions to their problems. Those "answers," McGroddy emphasizes, will probably include non-IBM elements. At the same time, research will lend a hand. "Never in the past has research gone directly to a big customer and said, 'This is part of how we can help you.' We do that now," he says.

But how can IBM ensure that the entire ensemble of technology efforts will indeed be stronger than a collection of companies strung together? The information technology business is too competitive for a company to make much headway as a holding company. "Our systems will compete with one another," McGroddy predicts. Still, the key to the future, he believes, will be getting IBM into promising niches "in a lightweight way"—then growing from there.

Xerox: Picking Up the Pace

In the late 1980s employees at Xerox encountered a new phrase that seemed to carry the weight of an advertising jingle. Xerox was preparing to rechristen itself "the Document Company," and researchers were frankly skeptical. "We thought, 'This is absolutely ludicrous!' " recalls Per-Kristian Halvorsen, a linguist at the company's Palo Alto Research Center (PARC). "It was prestigious to be a computer science laboratory," he says. Being a "document lab" sounded odd.

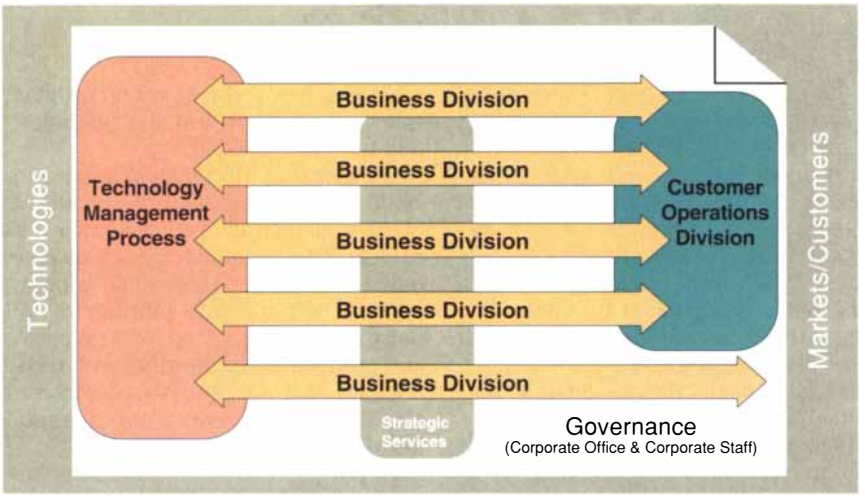
Behind that slogan, however, was 18 months of soul-searching by senior managers. Xerox bore the scars of missed opportunities; others profited more from PARC's inventions in personal computing. And although Xerox's Webster Research Center near Rochester, N.Y., had built the first color printer, competitors proved more successful at exploiting such technology. Moving ideas from research through the company was like running a gauntlet, recalls Steven B. Bolte, who heads Webster.

But by the end of the 1980s, Xerox was stronger. It was recapturing market share in its copier business and won a Malcolm Baldrige National Quality Award. Xerox began turning to research for new technology and insights into how to transform the "gauntlet" into a smooth passage.

The theme of "documents" seemed to capture the spirit of those 18 months of discussion. Instead of considering itself principally a manufacturer of diverse office equipment, Xerox would concentrate on the ultimate purpose of all those devices: improving work practices and productivity in the office with technologies that change how people create, transmit, reproduce and manipulate documents in any form.

To put those ideas into practice, Xerox "is changing the clock speed of the organization," asserts Mark B. Myers, a senior vice president. As a result, Chairman Paul A. Allaire is overhauling what he calls the hardware and software of the company—the formal ways the organization works as well as its values and goals. "We have to change our culture, our organization, the way we manage, our systems, our processes and

XEROX'S ROADRUNNER project, led by Richard J. Beach, uses novel hardware and software to build a family of fast printers that produce documents ranging from black-and-white to color.



XEROX REORGANIZATION emphasizes that the company is built of small teams that use Xerox technology to improve customers' productivity.

how we behave as individuals," he recently told Xerox employees.

As of this month, the company is to undergo a metamorphosis from a classically structured monolith into a group of nine business divisions. The mandate of those divisions is to work hand in hand with Xerox's technology groups and its customers. Webster, for instance, has always had close links to manufacturing, mainly because the groups share one site. To draw customers into the loop, Webster opened a color research studio where clients can experiment with—and critique—Xerox technology still in development. Some social engineering is also moving PARC closer to the market. Last summer the company's fledgling software division, XSoft, moved into a home on PARC grounds. Because XSoft has no separate cafeteria, engineers and PARC researchers regularly dine together.

The emphasis on documents is also transforming research perspectives and projects. For instance, rather than focusing on designing color copiers, Webster researchers are devoting thought to how color adds value to documents. The result: an early emphasis on "highlight" copiers that focus readers' attention by adding a single color.

As Halvorsen and his colleagues at PARC talked in workshops about documents as representations of thought and work practices, they began to see the limits of some traditional linguistic investigations. Simply parsing, or dissecting, sentences seemed "unnatural" in the context of managing information, Halvorsen says. The linguists consequently began developing novel algorithms that could find what Halvorsen describes as the "natural joints" or connections in a collection of text documents by identifying key shared phrases, words and other lexical content.

From such broad insights, PARC and XSoft workers are together building tools for accessing information. Their first application is modest: a new way of retrieving phrases. But they aim to use that work as the cornerstone of more sophisticated products that can automatically cluster or categorize a collection of documents. Another application will "visualize," or render into three-dimensional displays, such information as a troubleshooting manual.

Elsewhere at PARC, researchers began wondering how to meld various document technologies. XSoft has already produced the first of a new line of Xerox offerings. Called PaperWorks, it enables people to tap directly into their computers via a facsimile machine by using a specially marked form. Soon to follow will be a family of very fast printers, developed in a project codenamed Roadrunner, that will allow customers to choose the quality, color and speed that they need.

Roadrunner grew out of radical questions posed by PARC researcher, Richard J. Beach. Why, for instance, can't bookstores or publishers serve up the literature a customer wants on demand? The short answer is that no printers have the combination of speed, flexibility and resolution to churn out quality books.

Beach became committed to finding a way to unify the printing and the copying of documents, whether they are in printed or digital form. The technological solution lay with hardware and software inventions that could link various printing engines (which determine print quality and color) with the computers that control them.

Because Beach's approach marked a dramatic departure from the way Xerox traditionally developed products, the proposals initially met with more questions than enthusiasm. He enlisted the help of people throughout Xerox. The turning point came when a major Xerox customer called with a problem; Roadrunner held the most promising answer. The project "absolutely caused us to see the world differently," says John Seely Brown, who directs PARC. "It's shown how one architecture can cut across many things that we thought were very different."

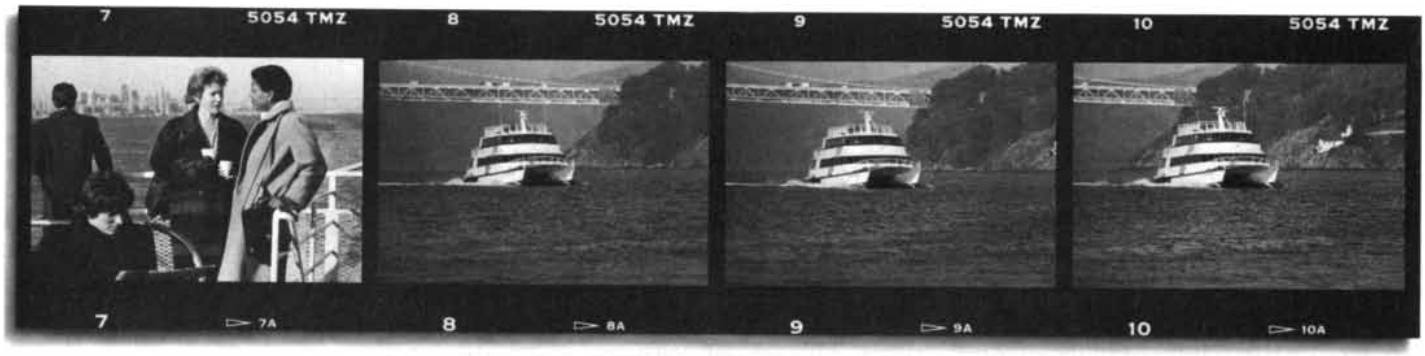
Xerox's focus on documents has also pushed the company away from trying to commercialize some ideas on its own. For several years, a handful of PARC researchers had been toying with a design for a scalable multiprocessor computer. With a few nudges, the research team found an established computer vendor willing to help them build the machine. Xerox's partner will soon unveil a new computer line. Xerox, in turn, will use that computing power to push its Roadrunner fleet closer to Beach's goal of uniting document printing and copying.

In many ways, Xerox's emphasis on technology that evolves echoes the Japanese principle of *kaizen,* or gradual, unending improvement. Xerox managers add a twist to that approach, however: they are aggressively searching for revolutionary ideas that challenge the status quo. "I call it 'radical incrementalism,'" says Myers, who adds that he is seeking "not just a good idea, but a paradigm shift." Such shifts—like Roadrunner—inevitably jar the company. But if Xerox can understand how its technology can help its customers it might similarly learn how to fuse its own diverse groups of research, manufacturing, marketing and service into teams resilient enough to grow by exploiting radical change.

American companies have long shown they can be wellsprings of fundamental science and technology. Now they aim to prove equally adept at transforming such findings into profits. Most researchers want to make a difference. Still, many worry about the future of traditional research skills.

Remolding research into an adjunct of engineering is not the answer. But if closer contact with customers becomes an inspiration for new research directions, which then help to build a vision of the future corporation, then both research and business will benefit. These companies believe they can use research this way. Now they have to prove it.

"Steve called from DC." *"And?"* "The presentation went better than we could have hoped."



"Great!" "He made some last-minute changes, though. Turned up some better data."

"What did he do, hire an expert?" "Said he did it himself." *"Himself? How?"*

Genes to Order

Companies queue up to realize the promise of gene therapy

Less than two years ago a medical research team at the National Institutes of Health was granted the first permission to treat a patient with genetically modified cells. A functional gene for adenosine deaminase (ADA) was inserted into white blood cells removed from a young girl whose own body did not produce enough of that essential enzyme. Then the altered cells were returned to her bloodstream.

That landmark experiment in gene therapy was a success. The transformed cells produced enough ADA to relieve her severe immune deficiency even better than daily injections of the enzyme. Today two ADA-deficient girls are given transfusions of their altered cells every two to three months. The pioneering researchers—R. Michael Blaese and Kenneth W. Culver of the National Cancer Institute and W. French Anderson of the National Heart, Lung and Blood Institute (NHLBI)—continue to seek ways to improve the therapy.

The continued good health of the ADA patients has ushered in further approvals for experiments. So far the NIH's Recombinant DNA Advisory Committee (RAC), which oversees the scientific and safety review of biotechnology experiments, has recommended approval of 17 clinical trials. All such protocols must also be approved by the Food and Drug Administration. Like the first experiment, some of the trials will replace missing genes that cause diseases such as cystic fibrosis. Others are intended to give new therapeutic abilities to a specific cell type, to treat AIDS and some cancers, for instance. Additional tests will track inserted markers, to learn more about basic biology.

Lured by the potential of gene therapy, a number of companies, including Genetic Therapy, Inc. (GTI), Somatix Therapy, Targeted Genetics, TargeTech, Transkaryotic Therapies, Viagene and Vical, are intent on commercializing the process. Some larger corporations, such as Sandoz and Merck & Company, are also becoming involved, mostly through agreements with smaller firms. Their immediate goal is to develop better, off-the-shelf materials for clinicians, especially the vehicles for inserting new genetic material into target cells. "We believe the first products will be vectors in a bottle," says Paul Tolstoshev, vice president and director of research for GTI in Gaithersburg, Md. The firm has supplied vectors for most of the gene therapy trials initiated thus far.

***MICHELANGELO TURTLE** celebrates the benefits of gene therapy, in this drawing by one of the little girls being treated for ADA deficiency.*

As yet, only academic scientists have been named as primary investigators on experimental protocols submitted to the RAC. But many researchers are teaming up with biotechnology companies. For example, Targeted Genetics, a spinoff of the Seattle-based Immunex, and researchers at the Fred Hutchinson Cancer Research Center got the go-ahead in February for a trial of an AIDS treatment. The company will supply the clinicians with a vector meant to enhance the ability of certain *T* cells to recognize the AIDS virus. Patients already slated to receive marrow transplants to treat advanced lymphomas will be infused with the boosted cells.

In most of the experiments approved so far, the vectors have been modified retroviruses that naturally insert their own DNA into the genomes of invaded cells. After the viruses are stripped down to their bare essentials, the human gene and regulatory sequences such as promoters and enhancers are added. The altered retroviruses are more effective than other physical and chemical methods at carrying genetic material into cells.

Although these delivery vehicles have been well behaved in trials, concern persists that somehow they could turn against the body to cause infection or stimulate a latent virus or cancer. The risk is slight, researchers say, and worth tolerating for now. "The field is in its infancy, so people are taking approaches that aren't what they ultimately want to do," observes Stanley R. Riddell, an assistant member at the Fred Hutchinson Center and co-director of the study involving Targeted Genetics.

To track modified cells released into patients' bodies and to control their fate, Targeted Genetics inserts a "suicide gene" into its vectors. Company scientists add a gene for a telltale protein, called thymidine kinase, which is the target of antiherpes drugs such as ganciclovir. If the altered cells need to be stopped, the drug will kill them. Riddell believes the safety mechanism "establishes a precedent for gene therapy in general."

Scientists are also devising experiments utilizing other types of viral vectors that home in on specific types of tissues. For instance, Ronald G. Crystal of the pulmonary branch of the NHLBI hopes to modify an airborne virus that normally causes colds to deliver genes to patients via an aerosol. This adenovirus will carry the gene for a cell membrane protein missing in individuals with cystic fibrosis. The protein helps cells break down mucus in the

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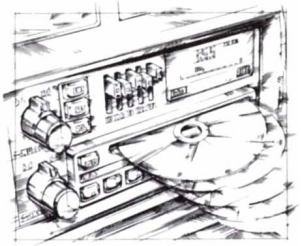

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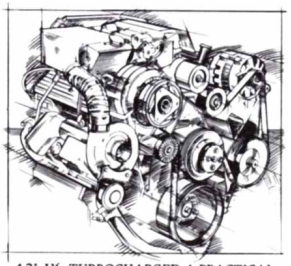

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THE STRENGTH OF EXPERIENCE

Targets for Gene Therapy

FAMILIAL HYPERCHOLESTEROLEMIA Liver cells taken from patients unable to process dietary fats are given the missing gene for a receptor molecule that ushers the substances into the organ for breakdown. The cells are returned to a hepatic vein.

Principal investigator: James M. Wilson, University of Michigan
Approval: October 1991

SKIN CANCER Metastatic melanoma tumors will be directly injected with a gene that produces an antigen intended to stimulate the immune system to attack the tumors. Experiment is the first in which cells are not removed from the body for treatment.

Principal investigator: Gary J. Nabel, University of Michigan
Approval: April 1992

BREAST AND OVARIAN CANCER A gene that confers resistance to multiple cancer drugs is implanted into bone marrow cells. Reimplanting these cells may enable patients to tolerate high doses of chemotherapy.

Principal investigator: Arthur Bank, Columbia University
*Approval: Pending **

AIDS Genes encoding short antisense RNA sequences are inserted into CD4 lymphocytes, the targets of HIV infection, to interfere with viral replication.

Principal investigators: Clay Smith and Eli Gilboa, Memorial Sloan-Kettering
*Approval: Pending **

BRAIN CANCER Genes that produce thymidine kinase, an enzyme made by herpes simplex virus, will be introduced into brain tumors. Then intravenous administration of the antiherpes drug ganciclovir should kill the cancerous cells.

Principal investigators: Edward Oldfield, National Institute of Neurological Disorders and Stroke, and Kenneth Culver, National Cancer Institute
*Approval: Pending **

** To be reviewed by the National Institutes of Health Recombinant DNA Advisory Committee in June.*

lungs. Researchers acknowledge that the body may become immune to the airborne virus and eventually render the therapy ineffective.

Other kinds of viruses that travel to specific parts of the body, such as herpes, which targets nerves, are also being explored as delivery vehicles. The ability of herpesvirus to sit quietly latent in the genome until it is switched on, by ultraviolet light or other means, might be used to advantage some day. The adeno-associated virus, already present in many people, is another possibility. It has a unique ability to integrate at a particular site in one chromosome, but it does not seem to be associated with any disease. The system is not yet ready for clinical trials. Some scientists anticipate that vectors for gene therapy ultimately will share features and properties from an assortment of viruses.

Several companies intend to avoid the issue of viruses completely. Although cells are notoriously poor at picking up naked genetic material, Vical in San Diego says it has gotten surprising results when it injects DNA directly into muscle tissue. Admitting that the firm made the observation quite by accident, Dannie H. King, president and chief executive officer, says his approach "reduces the paranoia about retroviral vectors." Vical plans to approach regulatory committees by the end of the year for permission to test vaccines for AIDS and influenza. "If it's not the way to go, it's certainly a way to go," King says. TargeTech in Meriden, Conn., also eschews viruses as guides for genes. Instead it makes a carrier of glycoproteins that bind tightly to receptors in the liver.

After deciding how to transport genes, companies can be very particular about the kinds of cells they choose to transform. "Our favorite cell type is a lymphocyte," GTI's Tolstoshev offers. "It's easy to get and easy to give back." Other cells are prized for attributes such as longevity or location or mobility. "There is something very special about putting a gene in the cell where it normally belongs," observes Culver of the NCI. "I think we'll see more of that."

But it is not always necessary to match genes to their usual types of cells, if all that is needed is a factory to synthesize a product. "We think fibroblasts are a great cell type for gene therapy," asserts Richard Selden, founder of Transkaryotic Therapies in Cambridge, Mass. Because these connective tissue cells cling together, Selden envisions subdermal implants that churn out such proteins as the clotting factors to control hemophilia or growth hormone to treat short stature. The clumps could be retrieved if something went amiss.

Eventually scientists would like gene therapy to progress beyond the periodic infusion of modified cells and become a once-and-for-all cure. Altering a human's genome so that changes are transmitted to offspring is ethically out of bounds at present, but lasting repair might be accomplished by transforming the stem cells in the bone marrow, which differentiate into all the types of immune system and blood cells. The door to this therapeutic approach opened in February, when the NCI team received permission to modify the stem cells of the children currently receiving gene therapy for ADA deficiency. "This could really be it," Culver exults. "We could have a one-shot cure as opposed to chronic therapy."

Although GTI provides the vectors for the ADA experiment and others, profits from gene therapy are still a long way off. Many of the diseases being explored in early experiments are extremely rare. For example, fewer than 30 people worldwide are afflicted with ADA deficiency. But some experiments are beginning to show a glimmer of commercial potential. James M. Wilson of the University of Michigan, for example, plans to treat severe hypercholesterolemia, a hereditary blood disease that renders the body incapable of metabolizing dietary fats. Patients have cholesterol levels as high as 1,000 milligrams per deciliter.

Wilson will transfer into liver cells the gene for a complex molecule called the LDL receptor, which is in charge of admitting low-density lipoproteins—the so-called bad cholesterol—into the liver for destruction. Only one person in a million suffers the familial disease, but one in 500 Americans has a less severe gene defect that results in high cholesterol levels and invites heart attacks.

"We want to push it faster," Wilson declares. "When we get beyond transplanting cells, to direct injection of genes, that kind of therapy begins to resemble things the pharmaceutical industry is comfortable with," he observes. Wilson's current laboratory research into nonviral molecular conjugates that carry genes to receptor-loaded tissue, such as the liver, typifies the kind of approach he thinks will stand the test of time.

As in other areas of biotechnology, the companies pursuing gene therapy are likely to squabble over rights to genetic sequences. Some firms are looking to the Human Genome Project as a font of disease-curing genes; others are developing gene-seeking technology of their own or instituting aggressive licensing programs to process the fruits of academic research. The rate of progress indicates that if you weren't born with the proper genes, you may one day be able to buy them. —*Deborah Erickson*

Tap Dance

Keeping communications networks safe for bugging

The Federal Bureau of Investigation was once fond of pointing out that "it always gets its man." One of its most heavily used techniques—as in the recent murder trial of mob boss John Gotti—is the trusty wiretap. But the bureau fears that new digital communications systems could leave its agents listening to an uninformative cacophony. So this spring the U.S. Department of Justice proposed legislation requiring makers of electronic communications equipment to ensure that their equipment could be tapped.

While civil libertarians rose up in outrage, many communications engineers scratched their heads in puzzlement. The idea that digital technology could make it impossible to intercept communications appeared to be somewhere between incomprehensible and flat wrong. Soon after, participants in the Telecom Digest, an international on-line discussion of communications-related issues, outlined how existing digital switching technology could be used to perform completely undetectable taps.

One technique is simply to turn every call to or from a tapped phone into a conference call with law enforcement on the third line. Another way would be to allow officers access to "maintenance ports" normally used to monitor phone line quality. "Maybe the FBI doesn't know how to do it yet," asserts Michael A. Schwartz, an engineer at Bellcore, but "hundreds of thousands of people" outside the bureau know how to tap digital phone lines. It's a question of getting the right equipment, he says. Special electronics capable of tapping fax transmissions have been commercially available for years, for example.

The bureau is not pleased at having its technical prowess impugned. William A. Bayse, the FBI's assistant director for technical services, snaps, "It's not worth having this conversation" at a reporter who asks him about the claims made by communications engineers. Bayse contends that few facilities are available for tapping digital conversations, and, furthermore, he declares, digital phone standards are still in flux—not only must would-be listeners get their taps in place, they must also figure out in just what form their information is being transmitted.

Bayse has a point. Tapping digits is not as easy as hooking up the time-honored "alligator clips"—those tiny spring-loaded connectors that clamp onto a piece of copper wire and let anyone with earphones or a tape recorder listen in. These days it is as likely to be the singularly uninteresting sound of bits as an analog human voice. Not only must a digital wiretap convert bits to sound, it must also cope with the

Getting Agricultural Biotech off the RAC

Like a coat that remains in a closet, unworn year after year, the Recombinant DNA Advisory Committee's responsibility for overseeing environmental release of genetically engineered organisms is there just in case. "A court of last resort for scientific expertise is a comforting thought," says Nelson A. Wivel, director of the RAC.

But it truly is time to remove this official burden, Wivel asserts. The committee was set up at the National Institutes of Health in 1976, when concerns about releasing genetically altered forms of life into the environment were at their height. Those fears have mostly been put to rest, and today the RAC spends much of its time advising scientists about experimental protocols for gene therapy. The passage should be officially recognized, Wivel says, because there is no point in having responsibility without the authority and tools to carry it out.

"We think environmental release is more properly in the purview of regulatory agencies," Wivel declares. "We're simply in the business of augmenting research." Indeed, the only environmental release of a modified organism approved by the RAC was the first spraying of "ice-minus" bacteria, which were expected to prevent frost damage to crops, on a California strawberry field in 1986. A provision written the following year allowed applicants to avoid review by the RAC or the NIH if they could get another agency to issue a permit.

Ever since, oversight has devolved on three agencies. The U.S. Department of Agriculture has shouldered most of the burden for genetically altered plants and animals, granting permits to over 200 field tests through the Animal and Plant Health Inspection Service (APHIS). Meanwhile genetically engineered pesticides have been shepherded, some would say slowly, through the Environmental Protection Agency. The Food and Drug Administration has been considering whether genetically engineered foods are safe to eat.

The Bush administration seems to have given the RAC a perfect opportunity to bow out formally. In late February the president's Council on Competitiveness called for federal agencies to streamline the regulation of biotechnology products by creating a risk-based oversight policy. In addition, the group's so-called Scope document asks that the agencies publish the rules they will observe in making decisions about environmental releases and develop detailed "road-maps" that companies will be expected to follow in bringing biotechnology products to market. "Were federal agencies to regulate products simply because an innovative process such as recombinant DNA technology had been used, we would be unable to reap the benefit of our own research investments," said the president's science adviser, D. Allan Bromley.

If the new document accelerates the approval process, it may shorten the time to market and allay the frustrations of agricultural biotechnology companies. "Delay is the worst form of denial," says John L. Callahan, vice president of marketing and product development for Calgene. The Davis, Calif., firm admits that it has been concerned about the fate of the rot-resistant tomato it has developed. Last year Calgene employed a bit of public policy in a new way, petitioning the FDA to issue an advisory opinion on the safety of the tomato. Other companies are rumored to have done the same.

"When some of the food safety issues are solved, a lot of other things will fall into place," asserts John H. Payne, associate director of APHIS. "You can't come to significant findings of environmental impact if you have open questions as basic as, 'Is it safe to eat?'"

The agencies expect to resolve such questions, or at least establish a procedural approach to answering them, within the next few months. "There's quite a bit of concurrence about the safety of genetically engineered organisms," observes Sue A. Tolin, professor of plant pathology at the Virginia Polytechnic Institute and State University and longtime USDA representative to the RAC. When regulators finally begin to feel comfortable about assigning certain products to "low-risk" categories, new agricultural products may begin sprouting with vigor. —*Deborah Erickson*

possibility that a digital line is carrying anywhere from two to dozens of conversations and strip out only the information authorized by warrant. At some point when optical fibers replace copper phone wires, tappers could be forced to invest in the extraordinarily finicky gadgetry required to siphon off photons without being detected.

Faced with such an uncertain future, law enforcement officials might well prefer to get their taps directly from the telephone switching system, but engineers will guard their system jealously. Schwartz contends that adding convenient wiretapping to the long list of other features for call routing and tracing on a digital switch at best would be expensive and at worst could make the phone system unreliable.

Cost is also a sensitive issue. Under the proposed legislation, telephone companies and equipment makers would be allowed to charge customers for the privilege of being tappable. FBI director William Sessions has estimated the cost at a mere $250 million to $300 million.

And the U.S. telephone system is only the beginning of the problem. The FBI's proposal applies equally to private branch exchanges (internal corporate telephone systems), local-area networks, computer bulletin boards and even the Internet, which links computers across the U.S. and throughout the world. All these systems, according to the FBI's bill, would have to conform to (potentially unpublished) ease-of-tapping standards promulgated by the Federal Communications Commission. Violators would face fines up to $10,000 a day.

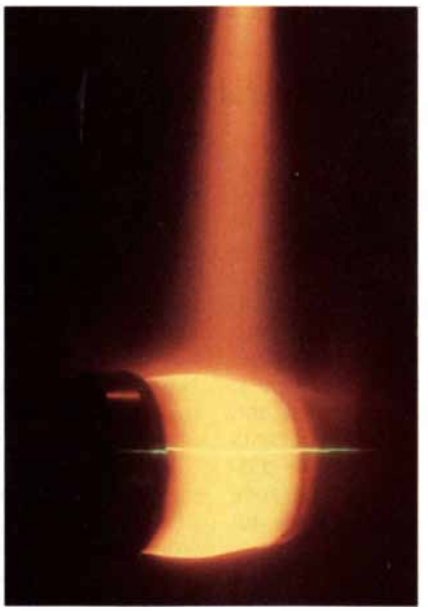
Computer manufacturers have been working hard to make their hardware and software more secure and to build in encryption and other techniques that will safeguard information from prying eyes, says John Podesta, a former congressional staffer who helped to draft the Electronic Communications Privacy Act of 1986. Consequently, computer makers are not welcoming the idea of increased "porousness."

After first discussing the issue only with telephone companies, the FBI met privately with some computer companies in mid-April. On Capitol Hill, public discussions were scheduled for the end of the month, amid a growing sense that legislation bending all the nation's communications systems to the current needs of the FBI is a wrongheaded way of attacking the problem. Mitchell Kapor of the Electronic Frontier Foundation suggests, "Give the FBI the funding they need" to develop better taps and leave the telephone and computer networks alone. —*Paul Wallich*

Joy of Cooking

A better way to bake high-tech materials

Materials scientists keep hinting at a day when a mere technician will be able to cook up a new supermaterial by simply adjusting the dials for strength, elasticity and other properties. But before that day comes, they have to figure out how to fabricate such designer materials without having to throw away half of every lot that is made. "I still go to meetings where somebody holds up an I beam and boasts that the cost has come down to $5,000 a pound," says Dawn R. White, an advanced technology manager for MTS Systems, a manufacturer of computerized-control equipment.



***SMART PROCESSING** is used at the Naval Surface Warfare Center in spraying a nickel superalloy to make piping.*

Prices like that cause even the Pentagon to quail. So in the mid-1980s the Defense Department became worried that metal matrix composites and other exotic materials needed for advanced aircraft and submarines would remain stuck forever on a remote laboratory workbench. To get uniform quality and to bring prices down from the stratosphere, the Defense Advanced Research Projects Agency launched a program called intelligent processing of materials (IPM).

The idea behind IPM is to develop a new generation of sensors and computer controls that can make instantaneous changes in processing conditions. Instead of the standard point readings of temperature and pressure, IPM would include more sophisticated measures, such as the surface roughness of a molten part. That information can then be compared with a physical model—or perhaps a computerized expert system—and if the process is not proceeding as it should, controls would adjust parameters ranging from gas pressure to the rate at which the metal flows through a spray nozzle.

Interest in IPM broadened quickly beyond the type of company that produces parts for Stealth bombers. Today even the staid steel industry wants to get involved. A leader in IPM for the past six years has been the National Institute of Standards and Technology (NIST), which in 1991 formally established an Office of Intelligent Processing of Materials. NIST is organizing five consortia of industrial companies to work on problems ranging from sensing techniques for polymer manufacturing to controlling the paint-finishing of automobiles.

Some intensive programs are already under way. General Electric is developing an IPM system for manufacturing expensive metal matrix composites for jet engines. These difficult-to-fabricate structural materials offer designers the benefits of lower weight and higher operating temperatures. Using fluid-dynamics modeling, GE can simulate the process by which titanium particles heated in a plasma of helium and other gases are deposited onto fibers of a material such as sapphire.

GE hopes it will be able to convert these complex simulations into pared-down models that can work as fast as a material can be processed. The simulation software could predict from the temperature and velocity of the plasma jet what the porosity of the finished materials will be. That information can then be immediately incorporated to control the process.

The software that does the initial fluid-dynamics modeling can still be maddeningly slow. In addition, new sensors, such as those that provide a picture of the crystal structure of the composite, are needed. Getting the control software to cope with the flood of inputs from the sensors is another challenge. "Even the simplest process has 50 to 100 pieces of sensor information," says Daniel G. Backman, a GE materials engineer, who is head of the company's IPM program.

Instead of trying to simulate the dynamics of the process, some researchers are turning to expert systems and other techniques of artificial intelligence

that are capable of embodying the intuition of skilled technicians. The Naval Surface Warfare Center in Annapolis, Md., employs a series of artificial-intelligence methods to control a spray of molten metal droplets that are formed into a finished part.

An expert system there is based on the observation of project leader Angela L. Moran that technicians relate the degree of surface roughness during manufacture to the quality of the final part. A video camera digitizes the image while molten metal is sprayed onto a disposable substrate. Data on surface roughness, rate of growth and shape of the object help to predict porosity, cracking and other qualities of the finished part. The expert system then decides how to adjust the process.

To control gas pressure and other parameters, Moran chose fuzzy logic, an artificial-intelligence technique that can quantify vague descriptions such as "big" and "small." Fuzzy logic allows pressure, metal flow and other values to be adjusted slightly up or down until the desired properties are attained, an action that is intended to replicate the subtle adjustments are made by an operator.

The U.S. Navy's sophisticated spray-forming process was developed to produce parts for submarines, ships and aircraft. With the end of the cold war, the military is considering how to apply its technology to industry. Researchers at Wright-Patterson Air Force Base are trying to adapt algorithms for maintaining aircraft stability in flight to the more mundane task of adjusting a manufacturing process. "Instead of adjusting for yaw, pitch and roll, the outputs are temperature, strain rate and time," says James C. Malas, a materials research engineer at Wright-Patterson.

The steel industry also hopes to benefit from IPM. The American Iron and Steel Institute, a trade group that represents the steelmakers, recently applied to the U.S. Department of Energy to develop sensors, models and control software through a nearly $23-million program that is proposed to begin in October and last for five years. "These are the things at the boundary of science that industry doesn't have the resources to do itself," says Ian F. Hughes, vice president of technology for Inland Steel Flat Products Company.

Incorporating IPM into the manufacture of steel and other materials will not cost a pittance. But intelligent processing may be the only way to move beyond a set of manufacturing skills that has little more sophistication than sticking a toothpick in a cake to test whether it is done. *—Gary Stix*

Fuelish Study?

The crystal ball the National Research Council used in a study that estimates achievable fuel economy for automobiles bears a suspicious resemblance to a mirror. Or that is what critics allege. The council's handiwork had barely rolled off the end of the line when critics charged that the study's most optimistic estimate of "technically achievable" test-rated fuel economy for subcompact cars in the year 2006 is 25 percent below the test-rated fuel economy of production vehicles on the road today. Estimates for larger vehicles, the critics said, were equally unambitious and reflective of the status quo.

The work was commissioned by the Department of Transportation and carried out by a panel chaired by Richard A. Meserve, a policy analyst and Washington lawyer. The committee estimated with "higher confidence" that subcompact cars could reach 39 miles per gallon by 2006, and it judges with "lower confidence" that they might reach 44 miles per gallon by the same date. Large cars, the group concluded, could achieve 30 to 33 miles per gallon in that year. The NRC committee emphasized that its estimates of achievable fuel economy should not be understood as goals.

John M. DeCicco of the American Council for an Energy-Efficient Economy, a Washington-based environmental group, notes that the Honda Civic VX, a subcompact car now commercially available, has a laboratory-rated fuel economy of 59 miles per gallon. Meserve replies that his committee's estimates are averages across entire car size classes. The Honda model, he counters, is a "specialty car" whose fuel economy probably does not pay for itself at today's low gasoline prices. And Meserve doubts whether the Honda Civic VX with automatic transmission and air conditioning can reach 59 miles per gallon.

The NRC study, Meserve says, "shows that you get what you pay for" in fuel economy. Many improvements may be too expensive or too unappealing for consumers, he says. And tightening vehicle emissions regulations could make improving fuel economy even harder. "There are," he notes, "trade-offs between national security interests and the economic effects on industry and consumers." The improvements whose effects the committee considered would add from $500 to $2,500 to the cost of a car.

DeCicco maintains that the committee "perverted the common meaning of what is 'technically achievable'" by relying on industry-derived assumptions of what the market can bear, not on what engineering can achieve now or in the near future. Furthermore, the study group accepted the standard 10- to 15-year lead time for new products.

The group also underestimated the savings that could be achieved through several technologies, DeCicco contends. For example, it estimated that variable valve timing—a key innovation in the Honda Civic—would produce a gain in fuel economy of 6 percent. DeCicco puts the figure at 10 percent, but Meserve retorts that he is "just wrong." DeCicco also objects to the committee's excluding from its estimates the energy-sparing potential of cleaned-up two-stroke engines, direct-injection diesels, electronic throttle control, "idle-off," "tall gearing" and heated batteries.

The NRC committee does some fender denting of its own. It attacks the corporate average fuel economy (CAFE) system for stipulating that manufacturers must achieve an average fuel consumption of 27.5 miles per gallon across all model sizes. That penalizes manufacturers of large cars and has benefited Japanese makers of small models, the report says.

The study does concede that CAFE standards probably helped to bring about some of the 80 percent improvement in fuel economy that occurred between 1975 and 1988. But it notes that fleet fuel economy has declined since then, as drivers have switched back to heavier and more powerful automobiles.

Increasing fuel prices is an alternative to CAFE standards that "warrants consideration," the NRC group urges. For example, vehicle registration fees and even insurance premiums might be paid at the pump as a supplement to the cost of gasoline. The NRC also gives a provisional approval to "feebate" schemes in which buyers of vehicles with above-average fuel economy would get a refund. Others would pay a fee. Meserve's study may never leave the garage. On such vote-sensitive issues, minds are usually made up without reference to the facts. *—Tim Beardsley*

Stained Glass

Low-melt glass may be the key to a solid state dye laser

In the late 1970s two chemists at Corning Glass Works—Paul A. Tick and Leon Michael Sanford—came on a type of glass that would melt and flow at a fraction of the ferociously high temperatures used to make the common silicate product found in Coke bottles and windowpanes. In some cases, these glasses based on lead, tin and phosphorus can be formed with as little heat as it takes to make tea or coffee.

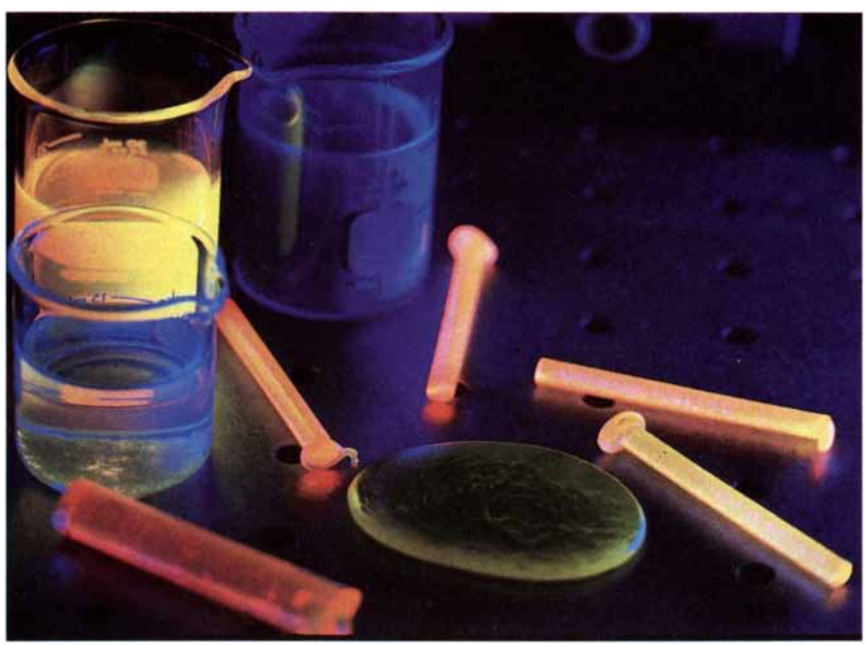
For now, the glasses are still an oddity confined to Corning's upstate New York laboratories. At $50 a pound or more, these low-melting-point glasses could cost about 100 times more than does one made from common silicates. But Tick hopes that his invention will soon become a valued part of a new class of materials from which to fabricate lasers and other components for optical communications and computing. Cost would be less of a drawback for such high-performance applications.

In contrast to a number of previous glasses with low melting points, the material is the first that is not quickly attacked and destroyed by water. "Before Corning's work, you could leave one of these glasses on the countertop and come back in the morning, and it would be a puddle. It would absorb so much water from the air that it literally dissolved," says James E. Shelby, professor of glass science at the New York State College of Ceramics at Alfred University.

The glasses for which Tick received a patent in 1982 (Sanford died soon after the two finished their initial work) are made by melting together lead, tin and phosphorus in the presence of oxygen and fluorine. The lead-tin fluorophosphate glasses are special because they can be processed in the same low-temperature range as many organic materials to which they bond readily. The glasses also join with copper, aluminum and stainless steel at temperatures below those that would disturb soldering connections. In addition, they are impermeable to gases and water.

Although the glasses are potentially useful for hermetically sealing electronic components from air and water, the most promising application is for lasers and the ragtag collection of waveguides, amplifiers and other so-called nonlinear optical devices. Researchers at the University of Rochester, led by optics professor Robert W. Boyd, were the first to demonstrate in 1987 the nonlinear properties of the glass when it was doped with an orange or yellow organic dye called acridine. When two light beams intersected within the glass containing the dye, a small amount of energy was transferred from one beam to another—a potential way to pass information between separate signals.

Sometime this year Tick and his colleague David L. Weidman, a Corning physicist, plan to demonstrate the first



***LOW-MELTING-POINT GLASSES** contain the same type of organic dyes that are shown in the beakers. Corning wants to use these glasses to change light in ways that may be useful for optical communications and computing. Photo: Robert Prochnow.*

tunable laser made from the glasses by doping an optical fiber with another organic dye, rhodamine. When the dye is excited by the relatively short wavelengths of light produced by an argon laser, it should be capable of lasing within a band of longer wavelengths. An optical element—a plate that adjusts polarization of the light—would be used to select the desired wavelengths.

Before they can produce an efficient laser, however, the researchers must find a way to make low-loss fibers from lead-tin fluorophosphate glasses. So far Tick and Weidman, who are working on the project part-time, have made fibers with losses of 10 decibels per meter in an undoped fiber. They must do better by a factor of 10 to make a practical device of a few meters in length.

The Corning researchers are confronting problems that have led other investigators to eschew the use of organic materials for optical devices—the tendency of some dye molecules to break down when excited by a light source, for one. "We have spent time thinking about organics, but because of longevity problems they're not ready for device applications," says Mohammed N. Islam, an AT&T Bell Laboratories research scientist. Sealing the dyes in the glass and picking ones that resist optical and thermal degradation may help counteract these difficulties, Tick and Weidman says.

Besides lasers, the two investigators believe doped fibers of their glasses could be used to make optical switches or other nonlinear devices. Another possibility is an optical amplifier. Conventional glass fibers doped with the rare-earth element erbium are now being tested as replacements for the "repeaters" that restore signal strength in long-distance fiber-optic communications networks.

Dye lasers do not emit light of the proper wavelengths for telecommunications systems, but Tick and Weidman believe the lasers might be used at shorter wavelengths to amplify signals in optical local-area computer networks. One potential application is an amplifier that could boost a signal before it is split down separate pathways in the local-area network. Each of the diverging signals would then retain sufficient power.

Tick and Weidman hope these devices may open opportunities as broad as the wavelengths emitted from dye lasers. "Rare earths emit only at discrete wavelengths, and you have only about a dozen of these elements," Tick says. "With organics, you have tens of thousands of possibilities to choose from." —*Gary Stix*

The MBAs of Summer

The national pastime is a strange business. Indeed, many observers have denied over the years that baseball is a business at all. According to the traditionalists, it is played for the very love of it by young men who smite the horsehide with their straight-grained bats of ash and run the limed diamond or sprint across the verdant outfields in pursuit of high flies. Owners, in this idyll, bring a team to their home city and at best break even as they public-spiritedly provide a spectacle to throngs of loyal fans.

That may have been baseball in the good old days, but it certainly is not baseball today. Star players pull down salaries that would make some Fortune 500 chief executives blush. Club owners pull up franchise stakes at the drop of a new stadium. Has greed overcome a sport whose nobility is so ingrained in U.S. consciousness that it is even exempt from the federal antitrust laws?

Economists don't think so. Under their sharp pencils, the National and American Leagues reveal themselves as always having been governed by the same profit motive as any other enterprise. The bizarre constraints under which baseball's markets function have simply obscured this fact, according to Gerald W. Scully of the University of Texas, an economist and author of *The Business of Major League Baseball.*

Consider the free-agent rule and its effect on players' salaries. From 1903 until the "reserve clause" was abandoned, players had a choice between playing for whoever owned their contract and retiring from the game. As a result, their market value was determined by opportunity cost: the amount of money they could earn in some other profession (which was often not much). In 1975 the balance of power (and profits) shifted away from owners and toward players; stars could sell their services to the highest bidder. Their market value is now determined by what other owners are willing to bid: in short, the value of adding a particular player to their franchise.

Baseball is replete with statistics, and so Scully and others have estimated not only the contribution various free agents make to their teams' won-lost percentage but also the proportion of ticket sales, broadcast revenues and other income they generate. Whereas the top players in the old days received no more than 10 percent of the money that they earned for their ball clubs, Scully's data suggest that by the mid-1980s typical free agents could haul in about a quarter to a third of the revenue they generated.

Since then, according to Rodney D. Fort of Washington State University, some stars have negotiated contracts that net 100 percent and occasionally more of the marginal revenue they contribute. Not that owners are stupid; such overpayments are simply an example of the "winner's curse" that besets any bidding war. The high bidder is the one who has the most optimistic valuation of the asset being sold; often as not, that optimism is misplaced.

Luckily for owners, the curse of buying high-priced free agents is counterbalanced by the blessing of deductibility. Since the 1950s, tax laws have allowed those who buy a baseball franchise to earmark part of the purchase price (currently no more than half) to "the value of player contracts" and depreciate that amount over five years. As a result, a club that has recently changed hands may take in millions of dollars more than it pays out and still show an accounting loss.

Under the economists' sharp pencils, baseball's profit motives emerge.

Owners may also make helpful arrangements with other businesses they run. For example, the St. Louis Cardinals, which are owned by brewer August Busch, Jr., pay a higher-than-average rental to the owner of the team's stadium, a subsidiary of Anheuser-Busch. Yet the team receives none of the revenue from stadium parking or other concessions, several million dollars every year.

Owners have a full rotation of accounting curves, sliders and spitters. In 1982, the worst year for baseball's finances in current memory, Scully reckons that unraveling the sport's unique accounting practices converted an apparent $105-million league-wide loss into an $11-million profit.

Until 1953, the year the first major league teams abandoned their hometowns, most clubs built the stadiums they played in and paid for them directly, recalls James Quirk, a retired California Institute of Technology economist. Today that number has shrunk to a handful, and the rest play in publicly owned parks built at taxpayer expense—often specifically to attract a new team or keep an existing one in town. Quirk estimates that overall local subsidies to professional sports teams (football, baseball, basketball and hockey) exceed half a billion dollars annually.

Although many municipalities (not to mention engineering firms pushing stadium projects) have proclaimed the benefits of a team in residence, Quirk contends that no studies have ever demonstrated that a city actually reaps increases in local business income or economic growth as a result of a major league franchise. "Any notion that a city can break even on these facilities is just wild imagination," he says. Intrigued by this observation, Fort has begun investigating just why cities continue to build stadiums but has found no convincing answers as yet.

If players can achieve cislunar salaries thanks to a reallocation of power in the labor market and owners can make money while apparently losing it, is there anything fans can do to better their lot? Curiously, says Philip K. Porter of the University of South Florida, the most rational thing they can do is to be fickle. Loyal fans, who come to the ballpark regardless of whether their team wins or loses, free owners to hire cheaper players and so increase profits.

If a pennant-winning season fills the park but a year in the cellar empties it, then owners who want to make a profit will be forced to hire top-quality, top-dollar stars. Indeed, Scully has developed an economist's equivalent of the team slugging average: his "quality-adjusted ticket price" measures dollars per game won. In 1991, for example, Atlanta rated best at $11.41 and the New York Yankees worst at $24.11. If your team isn't supplying enough bats for the buck, just stay away from the ballpark and, in the immortal words of Red Sox fans through the generations, wait till next year.

—Paul Wallich and Elizabeth Corcoran

The Riddle of the Vanishing Camel

The Bedouin patriarch Mustapha ibn Mokhta successfully defended his small tribe against a fierce rival, thanks to Allah. But Mustapha had been mortally wounded in the fight and had fallen unconscious. His lifelong friend, Ali the barber, tended his wounds and then carried him for miles across the northern Arabian desert to their camp.

Mustapha awoke surrounded by his wives, sons, daughters and grandchildren. "Allah be praised, I am still alive. But I must get back to the fight." He could barely lift his head up.

"Please rest now, Great Mokhta," his first wife pleaded, offering him water from a goatskin. "You have led your tribe to victory. How do you feel?"

"Like I have been trampled by a thousand camels," Mustapha groaned. "Who saved me?"

"Ali the barber," his first wife replied.

"Bring him to me quickly." His first son left to summon Ali, and the family dispersed, leaving Mustapha to lie peacefully in his tent.

Ali was busy, as usual, trimming the beards of all Bedouins who do not trim their own and wondering who would trim his beard. Hearing that Mustapha had regained consciousness, he ran to visit his friend.

Ali entered Mustapha's tent. "Salaam aleikum. You look much better."

"Aleikum salaam. Thanks to you and Allah, I have had a chance to see my family again. Yet my body is broken beyond repair, and I fear I will die soon." He waved away the protest of his friend. "There is no need to pretend. I want to talk to you about how I should divide my wealth among my three sons. I am very fond of them, but they are sometimes slow-witted. I believe before they inherit anything they should demonstrate their intellectual prowess."

Ali looked perplexed. "I do not understand, Mustapha."

"Among my possessions is an ancient arithmetical treatise, handed down, it is said, from the great Al-Khowarizmi himself. It tells of a wealthy merchant who owned 17 camels. He decreed that on his death the eldest son was to have one half of the herd, the second son one third, and the third son one ninth."

"I remember some such conundrum. Of course, it makes no sense to offer the eldest son eight and a half camels."

"Nor the youngest son one and eight ninths. But there is an ingenious solution to the problem."

"Yes, I remember. A wise man brings an extra camel of his own, raising the total to 18. The eldest son takes half of that number, namely, nine camels; the second son takes one third, or six camels; and the youngest son takes one ninth, or two camels. Those numbers total 17, whereupon the wise man departs once more with his own camel, and all are satisfied."

"Or at least, everybody thinks so. The psychology of the puzzle is almost as fascinating as the mathematics."

"But, Mustapha, you have more than 17 camels."

"Indeed, Allah has blessed me with 39. Moreover, I promised my father on his deathbed never to sell a camel. So it is not possible to reduce the number to 17. Of course, it would not be difficult to purchase a few extra camels should that prove necessary. The question I am unable to answer is whether some other collection of numbers would permit a similarly curious course of events."

"You could always triple everything," Ali said. "Start with 51 camels and the same disposition into fractions."

Mustapha nodded again, grimacing with pain. "I have thought of that, Ali. But then it would be necessary for the wise man to introduce three extra camels. That lacks elegance."

Ali rubbed his beard. "So the question is, what other numbers of camels would behave in this curious manner?"

"Yes. I had in mind assigning to each son some appropriate fraction of the total that would permit the introduction, and subsequent removal, of just one extra camel."

Ali leaned back and smiled. "Numbers, Mustapha, were always a strong point of mine. I wonder—" He gazed into space for a few seconds. "By the grace of Allah, there may be a way. But

***THREE SONS** share ownership of seven camels. The first son claims half the herd; the second son wants a quarter; the third demands an eighth. Can they each take their share without chopping up a camel?*

first we must understand how the original trick works."

Mustapha scratched his head. "I confess I am sorely puzzled. The crucial camel appears and vanishes like a jinni from a lamp with a defective wick."

"It must be some quirk of the particular fractions chosen," Ali said. "For example, had there been 12 camels, with the sons getting one half, one third and one sixth, then the eldest would get six camels, the second four and the third two. No extra camel would be needed.... Aha! I believe I see a ray of light. The three fractions cannot possibly add up to one. If they did, such a trick would never work—for all camels would be divided with none left over. Let me see. What is the sum of $1/2$, $1/3$ and $1/9$?

"Ah, $17/18$," Mustapha said. "Of course! The sons inherit only $17/18$ of the total number of camels. If the total is 17, they can't divide the herd evenly. But if the total is 18, each son takes a portion of the 18 with one camel left over." A thought suddenly entered his mind. "He wasn't really a wise man, was he? He never pointed out to anyone that the fractions don't add up."

"In that omission lay his deepest wisdom," Ali countered. "The trick works because the sum of the three fractions assigned to the sons is a fraction whose denominator exceeds its numerator by one," Ali said. "Here the numerator is 17 and the denominator 18." He grinned broadly. "There are many such fractions. For any whole number *d,* they take the form $(d-1)/d$.... I've got it! You have 39 camels. Right?"

"Yes."

"Then all we need to do is choose fractions that sum to $39/40$," Ali said. "For example, $1/2$, $1/4$ and $9/40$." He turned in triumph, but then his face fell. "You seem unimpressed, Mustapha."

"It lacks simplicity, Ali. Each fraction should be one out of something. One out of three or one out of 19. Like that. Not nine out of 40."

"Ah. You require numerators of 1."

"Precisely."

"In short, you need a solution in whole numbers to the equation $1/a + 1/b + 1/c = (d-1)/d$. That is, the number $(d-1)/d$ must be expressed as a sum of three reciprocals. Egyptians often wrote down fractions in terms of a sum of reciprocals. Hence, the sum of $1/a$, $1/b$ and $1/c$ is known as a three-term Egyptian fraction."

"I found a way to simplify your equation," the patriarch said. He wrote down the following equation:

$$1/a + 1/b + 1/c + 1/d = 1.$$

Ali smote his thigh in delight. "So if a is 2, b is 3 and c is 9, then d must be 18 since $1/2 + 1/3 + 1/9 + 1/18 = 1$. And now all we have to do is find some other solutions to your four-term Egyptian equation. That is, find four numbers whose reciprocals sum to 1." He paused. "A reciprocal agreement, so to speak."

Mustapha's brow furrowed. "I can certainly think of one other solution," he said. "Namely, $1/4 + 1/4 + 1/4 + 1/4 = 1$. So what now?"

"We will find all possible solutions to your equation." Ali reached for a sheet of paper. "It is a delicate matter, for we are dealing with what mathematicians call a Diophantine equation, one that must be solved using only whole numbers. Indeed, in this case, positive whole numbers. Such equations were discussed by Diophantus of Alexandria around the third century."

Mustapha turned himself awkwardly in his bed to ease his shattered bones. "Are you not being overambitious, Ali, to seek all solutions? There could be a large number of them?"

"Diophantine equations tend not to have very many solutions," Ali replied, "although there are exceptions. And in this case—"

He began scribbling on the paper. "I believe we can prove that only a finite number of solutions exist. Moreover, the proof allows us to find them all in a systematic manner. Among them may be one that suits you. Suppose that the numbers are arranged in order of size, so $a \le b$ (a is less than or equal to b) and $b \le c \le d$. Then a must be at most 4. If a were to equal 5 or more, then b, c and d would equal five or more, and therefore the sum of their reciprocals would never equal 1 and would always be less than or equal to $1/5 + 1/5 + 1/5 + 1/5$, or $4/5$."

Mustapha stared at him. "This helps?"

"Yes. You see, we also know that all four numbers must be at least 2. Otherwise the sum begins $1/1$ and will always be too large. Therefore, only three cases need be considered: a equals 2, 3 or 4. In the first case, where $a = 2$, the equation becomes $1/2 + 1/b + 1/c + 1/d = 1$." He simplified this equation a bit and then wrote down the three cases. When $a = 2$, the sum of the reciprocals b, c and d equals $1/2$, that is $1/b + 1/c + 1/d = 1/2$. When $a = 3$, the sum must be equal to $2/3$, and when $a = 4$, the sum is equal to $3/4$.

Mustapha looked puzzled. "But, Ali, all you have done is replace one equation with three."

"Yes, Mustapha—but now each has only three variables instead of four! Moreover, I can repeat the same trick on each. For example, consider the first of the three equations, $1/b + 1/c + 1/d = 1/2$. It is apparent that the second smallest number, b, must be no more than 6. Otherwise, the sum would be less than or equal to $1/7 + 1/7 + 1/7$, or $3/7$, which is less than $1/2$. In the same manner, for three reciprocals that add up to $2/3$, b must be at most 4; and for a sum of $3/4$, b must also be at most 4. Thus, each of the three cases for the number a breaks up

into a finite number of subcases for *b*."

"And then," Mustapha said in excitement, "you use the same trick again!"

"Precisely. As I have said, if $1/b + 1/c + 1/d = 1/2$, then *b* must be at most 6. And since *a* is 2 in this case, *b* must be at least 3. Suppose, for example, that *b* is 3. Then $1/2 + 1/3 + 1/c + 1/d = 1$. That is, $1/c + 1/d = 1/6$."

"From which," Mustapha cried, "we deduce that *c* is at most 12, since $1/13 + 1/13$ equals $2/13$, which is less than $1/6$."

"Exactly. And that gives only a finite set of sub-subcases for *c*, after which *d* has a unique value that we can calculate precisely. For example, if $a = 2$, $b = 3$ and $c = 11$, then *d* must satisfy $1/2 + 1/3 + 1/11 + 1/d = 1$, which implies that *d* is $66/5$. But that is not a whole number, so there is no solution with $a = 2$, $b = 3$ and $c = 11$. On the other hand, if $a = 2$, $b = 3$ and $c = 10$, then $1/2 + 1/3 + 1/10 + 1/d = 1$, which implies that $d = 15$. This time a solution appears. In general, if *d* turns out to be a whole number, then we have found a solution; if not, then that particular sub-subcase does not lead to any solution.

"Moreover, the same argument applies to any equation of the form $1/a + 1/b + \ldots + 1/z = p/q$, where *a, b,..., z, p* and *q* are positive whole numbers. There are only a finite number of ways to write any given fraction as an Egyptian fraction with a fixed number of terms. The solutions can be found by a series of simple deductions."

Mustapha coughed, then spat blood. "You seem to have proved a very general theorem, Ali."

"Precisely. Now, allow me a few moments while I calculate all possible solutions to your equation." Ali scribbled away furiously [*see table at left*]. "I find exactly 14 different solutions."

"And now the manner of your bequest stares us in the face," Ali pointed out. "The very first solution in the table is $1/2 + 1/3 + 1/7 + 1/42 = 1$. Mustapha, if you owned a total of 41 camels, you could decree that your eldest son should inherit one half of the herd, your second son should receive one third and your third son should get one seventh. Then if you die, Allah forbid, they will need to find a 42nd camel to satisfy your wishes. Then the eldest son will have 21 camels, the second son 14, and the third son six."

The dying man clasped the barber's hand. "Ali, you have answered my prayers. It merely remains for me to procure two more camels. Have the terms of the bequest drawn up immediately—"

There was a commotion outside the tent. Suddenly a small boy shot in through the flap. "Yes, Hamid? Do you normally approach the head of your family in such a precipitate fashion?"

"I apologize, master Mustapha ibn Mokhta. Your third wife, Fatima, has just borne you a son! Your fourth son!"

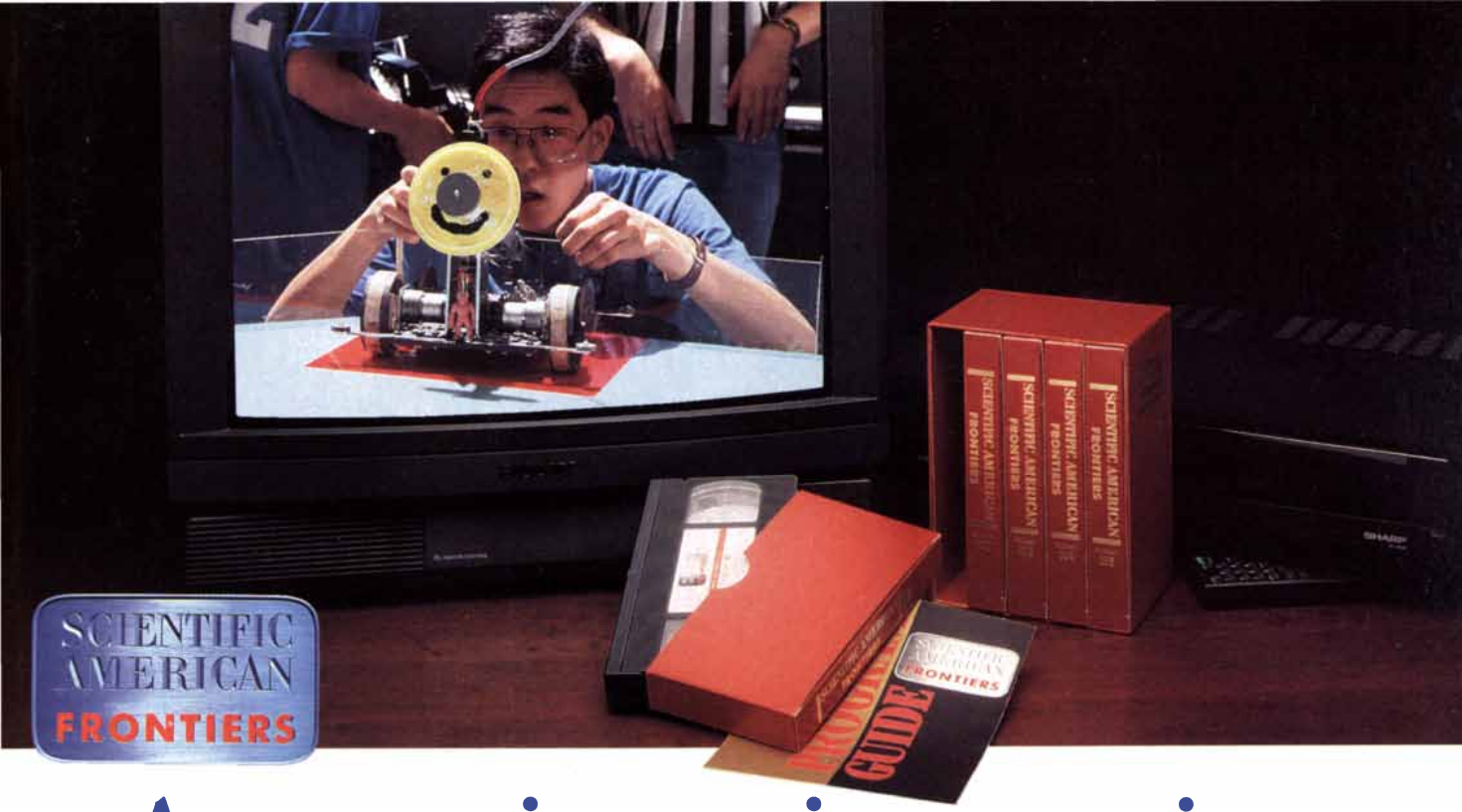
a	1−1/a	b	1−1/a−1/b	c	1−1/a−1/b−1/c	d
2	1/2	2	0		0	
		3	1/6	6	0	
			1/6	7	1/42	42
			1/6	8	1/24	24
			1/6	9	1/18	18
			1/6	10	1/15	15
			1/6	11	5/66	
			1/6	12	1/12	12
	1/2	4	1/4	4	0	
			1/4	5	1/20	20
			1/4	6	1/12	12
			1/4	7	3/28	
			1/4	8	1/8	8
	1/2	5	3/10	5	1/10	10
			3/10	6	2/15	
			3/10	7	11/70	
	1/2	6	1/3	6	1/6	6
3	2/3	3	1/3	3	0	
			1/3	4	1/12	12
			1/3	5	2/15	
			1/3	6	1/6	6
	2/3	4	5/12	4	1/6	6
4	3/4	4	1/2	4	1/4	4

MUSTAPHA'S EQUATION*—$1/a + 1/b + 1/c + 1/d = 1$—*has exactly 14 solutions if* a, b, c *and* d *are positive whole numbers and if* $a \le b \le c \le d$. *The colored boxes indicate cases in which* a, b, c *or* d *must equal a fraction or zero.

FURTHER READING

RIDDLES IN MATHEMATICS: A BOOK OF PARADOXES. Eugene P. Northrop. Krieger, 1975.

UNSOLVED PROBLEMS IN NUMBER THEORY. H. Croft and R. K. Guy. Springer-Verlag, 1981.



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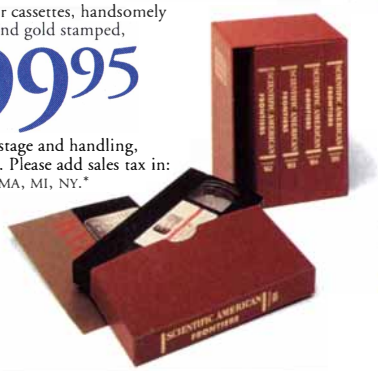

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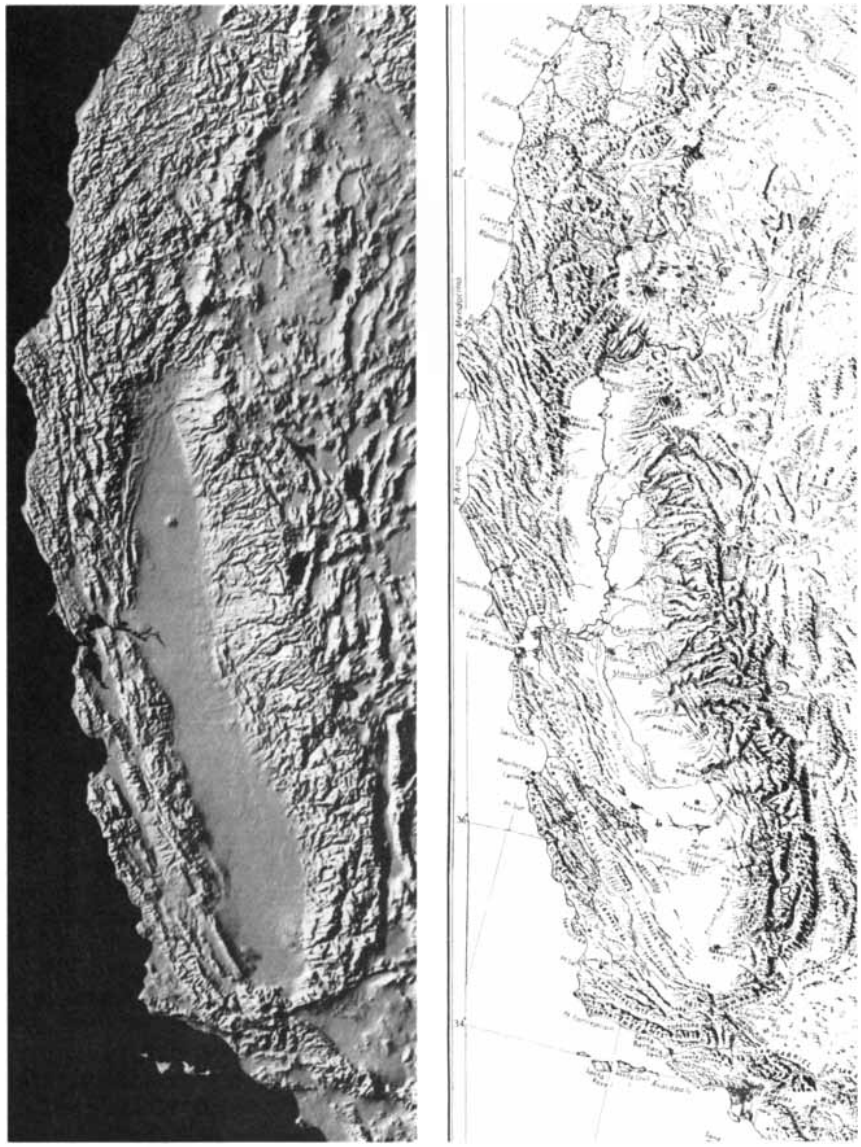
BOOK REVIEWS by Philip Morrison

One Topography Two Ways

LANDFORMS OF THE CONTERMINOUS UNITED STATES, Map I-2206, compiled by Gail P. Thelin and Richard J. Pike, with accompanying brochure. U.S. Geological Survey, Branch of Distribution, Box 25286, Federal Center, Denver CO 80225 ($5, postpaid). **LANDFORMS OF THE UNITED STATES,** by Erwin Raisz. Sixth revised edition, 1957. Raisz Landform Maps, P.O. Box 2254, Jamaica Plain, MA 02130 (map sheet $2, plus $5 shipping).



DIGITALLY SHADED RELIEF MAP produced by the USGS* (left) *contrasts with traditional hand-drawn map by Erwin Raisz* (right). *These details from the maps show California's coastline and Central Valley.

The purity of this large USGS map catches every eye. It appears to be the photograph of a wonderfully wrought silver plate, gleaming from a black-velvet ground almost five feet wide, its outline that of our nation's continental borders. The lustrous texture is roughest to the west, smooth and subtly undulating across the wide midcontinent, then somewhat rougher again along the eastern portion, all rendered in expressive shadow.

On this big, digital, shaded relief map, the stones, soil and sand of the 48 contiguous states are represented by no less than 12 million tiny gray squares, or pixels, each about one-quarter millimeter on edge, whose image is printed in still finer halftone dots. Each pixel reports by its tone the elevation above sea level of one sampled square of terrain, its edge about a half mile on the ground.

For every pixel, a gray value is calculated from the local slope, estimated by averaging the elevations of a number of neighboring pixels. Steep slopes appear nearly black on their shadowed eastern sides, nearly white where they are on the sunlit side; lower slopes are intermediate in tone. The height is then visually coded by the width of each patch of tone seen by a viewer looking straight down. Some simulated light enters to be reflected in all directions, like sky light; it is added to soften the direct beam of the simulated sun coming from low in the west-northwest. The total surface reflectances computed by that recipe, pixel after pixel, form the work of art we see. Shadows cast by the hills are not shown. (Heights are exaggerated over horizontal distances by a factor of two.)

The height data do not come from satellite images but are sampled from *two billion* mapped elevations, all digitized from hundreds of big topographic contour maps prepared since World War II. Rounding, interpolation between contours, and the survey errors yield a vertical accuracy of 100 or 150 feet. Horizontal errors are much smaller than pixel size, apart from some systematic flaws in matching adjoining large blocks of data and a few minor mysteries, mere flotsam in this flood of numbers.

The richly textured plaque is the result, a detailed, precisely defined and strongly evocative physical map. Smaller features, even salient places like Meteor Crater or the Delaware Water Gap, are missing or barely appear. This is a map of solid landforms alone, the bones of the land, somewhat larger than the scale of the field geologist. Here are no crops or forests, no streams, towns or roads. River valleys are wide and prominent, but no watercourses are marked within them. All natural lakes above 20 square miles in area were added in black. Jet black, too, renders everything outside our national borders, so that the Great Lakes lack many shorelines,

and even Niagara Falls is missing its western hinge. Mountain ridges and basins become dramatic; gentler landforms disclose low relief over wide areas, often patterns that can be noticed in almost no other way.

The USGS authors of this product of modern minds and machines include a 16-page brochure, mildly technical (explicit enough for the software buffs) as a guide to their gift. Three double-spreads in that paper show their map with strong overlays added, one to mark state boundaries, one to outline the physiographic divisions and geologic provinces standard since the 1940s, and the third indexing a couple of dozen topographic features discussed in the text. The San Andreas fault zone, the Valles caldera and the Ozarks are to be found here as on every good map. But what become conspicuous are such features as the low-relief Nebraska Sand Hills, "largest sand-dune area in the... Hemisphere"; the broad, flat Alluvial Plain of the lower Mississippi; and the complex textures that recall the comings and goings of glaciers across the northernmost states. The filigreed shoreline of Virginia and North Carolina is especially beautiful, as is the smooth floor of the long Central Valley of California, whose only lesion is an enigmatic old volcano near Marysville on the Sacramento.

Improvements will come; a geologic map should be an "ongoing experiment." Extending the map to include Alaska and Hawaii, filling in the blackness to reveal nearby Canada and Mexico, fixing a variety of awkward little errors and showing the streams seem priorities. Color for altitudes? Perhaps; that would lose the luminous serenity of the unequaled image.

No doubt this 1991 map is a triumph for digital mapping by machine. But there is still time to celebrate a tireless worker by hand, the John Henry of cartography, the late Harvard cartographer Erwin Raisz, who drove a steel pen. Long ago he drew the U.S. landforms at very similar scale, using a clear vocabulary of hatch marks, stipples and shading to represent relief symbolically. Moreover, he lettered right across his map a whole gazetteer, naming a couple of thousand towns, streams and forms. The scale of the digital USGS map is 1:3.5 million; the Raisz map is only a little smaller, one inch to one degree of latitude. Generously recommended by Thelin and Pike, it is an available index to their austere and silvery elegance. You will find Meteor Crater easily here, and all our rivers labeled, from the Chehalis across to the Caloosahatchee. Raisz left us a legacy of many other fine pen-and-ink maps as well.

Even in Switzerland

MALARIA: OBSTACLES AND OPPORTUNITIES, edited by Stanley C. Oaks, Jr., Violaine S. Mitchell, Greg W. Pearson and Charles C. J. Carpenter. National Academy Press, 1991 ($39.95).

The veterans of the grand campaign against smallpox are still here to recount their global victory. Our current engagement with the subtlest, most implacable of hostile viruses—HIV and its fatal sequel, AIDS—rages on, outcome still in the balance. This study, well edited from the reports and discussions of some 60 diverse experts for the cognizant committee of the Institute of Medicine (U.S.), is sobering news from the Million Years' War we are losing against malaria. That ancient scourge tightly couples the lives of three disparate organisms: a subgroup of mosquito species, all within a single large genus; a few strains of parasitic, specialized eukaryotic microbes called plasmodia; and our own world-girdling, protean species.

Oh, we have had our triumphs, all right. In 1699 a New York observer wrote of malarial "agues and fevers": "Many dead, but not yet soe many as last yeare. The like is all N. Engld. over, especially about Boston, where have dyed verry many." Well-drained lands and roads, better food, tighter housing have served our kind well, especially in lands where winter's writ runs. The main theater of war today is the tropical belt right around the world, where that obligate mosquito-to-person link of malarial transmission remains common. The zone is home to two billion people, most of them poor villagers long adapted by genetic inheritance to suffer but to survive the tides of malarial fever.

A hundred million of them fall clinically ill each year, and one or two million die of malaria. Four out of five of those patients and nine tenths of the ones who die are African, mostly in the savanna regions south of the Sahara but north of the high veldt. There malaria, which arrives with the seasonal rains, is most serious as a disease of childhood—virtually everyone becomes infected early in life. The children who manage to survive, liberally inoculated by the three abundant species of *Anopheles* mosquitoes, acquire partial immunity. Those mosquitoes prefer to lay eggs in natural sunlit pools of standing water; a photograph documents that pleasant locale, adjoining newly cleared garden patches of the slash-and-burn farmers along the forest's edge.

In mainland Southeast Asia and in much of the Amazon basin, forest ma-

laria is becoming a disease of young adults. Almost all the young men who venture into the forests, to sleep in open lean-tos while they scrabble for gold or for gems, come down with the fever. In India the larvae of the chief mosquito vector breed by choice in the rainwater held in tanks, buckets, even in tin cans; malaria in south India has become mostly an urban disease.

In San Diego County the female mosquitoes pick up the parasites along with the first nourishing blood meal they take from sleeping migrant workers, to transfer by bite a week or two later an inoculum of thriving microbes. Malarial cases by the dozen are reported there, some during every one of the past few years. Even in meticulous Geneva, a few malarial cases recently astonished the Swiss physicians: their patients had never traveled, but they shared one trait. All lived within a mile of the busy international airport. Those infected vectors had been jet assisted all the way from the tropics, to fly only one last mile on their own. Plasmodia prosper within those flying, searching and incubating insect syringes for up to a month.

Back in the late 1950s the full eradication of malaria, ending not only the fever but all new infections, seemed within reach. The wartime insecticide DDT, cheap and powerful, had allowed broad reduction of mosquito populations. Exposed people were well protected by steady prophylatic doses of the drug chloroquine, another wartime find. It was held that a winning strategy was to kill the mosquitoes that came near people often enough to make sure there was no time for multiplication of parasites within the insects.

Early results were promising. Malaria was so plainly on the run that health officials often reallocated funds to other pressing needs. Then malaria made its powerful counterattack. The mosquitoes began to survive their contact with well-sprayed house walls; soon there were vector strains so well adapted that they would not even rest on a sprayed surface. By the 1970s cheap, overused DDT had poisoned the food chain, to be replaced by pesticides that were dearer, even more toxic, and sparingly used. Worst of all, the plasmodia were rapidly selected for their resistance to the best drugs. The most resistant species of the parasite, *Plasmodium falciparum,* has by now spread almost globally. "The situation for drug treatment and prophylaxis" for this fast-growing form of malaria "is desperate." Other drugs we know are slower, more expensive and less sure; multidrug resistance is spreading as well.

Among the dozen chapters that con-

sider the relevant intricacies, from the treatment of plantation labor to new diagnostic polymerase chain reactions, four or five treat molecular biology at a rather technical level. One urgent aim is a good vaccine, which might act at any of a variety of target structures along the eventful life cycle of the parasites. It is simply impractical to follow the classical route of smallpox or rabies vaccines, by growing weakened infectious particles to inject as antigens. Vaccines based on subunits, key protein fragments of these big plasmodia, are for now the only hope.

The readable, many-sided volume ends with a brief, eloquent note of dissent, entered by a committee member, a World Health Organization expert close to the field of battle. He argues that what is needed is quick, generous support of direct prevention and control, not the long chain of research and study outlined in the book. The majority offers a high-minded defense of prudent, balanced effort. An unwritten question remains. In 1958 Senators Humphrey and Kennedy acted to commit the U.S. to support world malaria eradication for five years. It was, this report remarks, an "enormous investment for the time." The unprecedented sum would have bought as many as one or two squadrons of Phantom jet fighters, also brand-new that very year. During the next decades, the U.S. Air Force and Navy would acquire well more than 100 squadrons of that famous aircraft. An analyst might well judge as the more cockeyed policy not the urgency of the dissenting World Health Organization expert, but prudence, American-style.

Inconstant Sunshine

THE SUN IN TIME, edited by Charles P. Sonett, Mark S. Giampapa and Mildred S. Matthews, with 83 collaborating authors. University of Arizona Press, 1991 ($60).

The appeal of this chunky, expert and fascinating text is its novel topic: change in the proverbially constant sun. To be sure, our grasp of stellar evolution in the large has become so robust that we are pretty sure about the far prophetic future, say, five billion years out, time enough for exhaustion of the sun's available thermonuclear fuel. After that the sun will swell grotesquely to become a red giant, engulfing its inner planets. Waiting only a modest interval, that giant radiator will again transform, blowing away its great swollen envelope, to dwindle into a commonplace, long-lasting but dim and tiny white dwarf. The neighborhood of a spent sun is no place to live.

The changes this volume so closely examines are not such apocalyptic events, but rather the normal course of the geologic past and the brief time of human presence. Life bears witness that the sun has functioned recognizably for a very long time, although never free of important change. Since 1945 we have learned that certain solar-type stars with unusual hydrogen emission lines are suns still in the womb, enveloped in placental clouds of molecular gas and dust, rapidly evolving toward birth. A sun can be said to be born once the newly stable globe of gas, which has mass, temperature and rate of rotation roughly matching our own sun, begins its long, independent life of slow nuclear burning. During that career, spin, spottedness, magnetic fields, unusual radiations and incessant outgoing winds are in persistent change. For two decades now, spectral evidence has allowed us to follow in many distant sunlike stars both what look like regular solar cycles and such less repetitive features as the absence of sunspots in the years after Galileo's discovery.

We were not around at the sun's birth; our time machine is inferential, from theory and from the modern multiband examination of sun surrogates, some older, some younger than our sun. Newborn suns are rotating and magnetic; some sport a circumstellar disk, often with polar jets of gas, like the "solar nebula" postulated since Laplace's time. A smaller class among such stars have disturbed surfaces but lack the conspicuous dusty disk, cleared away by star winds and powerful radiation. Then direct starlight can illumine the equatorial neighborhood of the new sun. The disk has dissipated or even condensed to form planetesimal precursors and, eventually, real planets. That process would certify the birth of a true planetary system; it is conceded that we have yet to see the planets.

The meteorites and the moon rocks give mineral evidence of earliest days, when the sun was still in gestation, unstable and dust obscured. The asteroid-size parent bodies of the meteorites endured that very time. Strong interior heating, even real melting, is still present. Only two sources of so much power flung far into space now seem plausible. One is decay heat from short-lived radioisotopes of aluminum, whose million-year lifetime fits the presolar schedule. The other is electrical heating of the orbiting bodies as they circled in a strong early magnetic field, stirred by fierce pre-solar winds. Two chapters assess the processes in detail;

the reflective experts flatly disagree.

Half a billion years later—planets well formed, solar space cleared of dust—old earth rocks disclose warm and sunny shores, sediments formed in liquid water, even microbial growth: no signs of glacial ice. But the stellar evolutionists maintain that the sun took longer than that to warm up; its central thermonuclear source had to be weaker in those days, by perhaps a third. The young sun was faint, yet the earth was not cold. Was the sun perhaps more massive and brighter to begin with, to reach its present mass by heavy losses to strong early wind? That would be even worse; a hotter earth might have lost its oceans altogether. The present best answer is as familiar as the daily papers: a greenhouse atmosphere of carbon dioxide was released from inorganic rocks by huge impacts and by hyperactive volcanism, enough to overcompensate for the intrinsic dimness of the young sun.

Ever since, the sun's changes have been more subtle: sunspots and their half-chaotic cycles, frequent but small changes in size and brightness, high winds in space or none at all, declining spin, transient flare-ups of harder radiation than the dominant sunlight. Instrumented satellites of the 1980s show by direct measurement the reduction of solar power, if only by parts in 1,000, whenever the sunspots abound.

So far we have been led by the accounts of only a third of the papers in the book, the more astronomical moiety. For the rest, the story lies neither in the bright disk of the sun nor faraway in the night sky. Instead it is read right here on the earth—in exotic radioactive traces in molybdenum ore taken from the base of one red mountain in Colorado, in ice cores drilled out of the polar caps, in particle tracks artfully etched in mineral grains taken from meteorites, even in fine alternating layers seen in some old limestones and in less ancient tree rings. Two general methods are used: material traces ascribable to one or another kind of radiation of solar origin or to the telltale periodicities to be read in any earthly process that the sun might modulate.

Curiously, the grand rhythms of recent ice ages may be an exception: glaciers come and go, not mainly because the sun's output changes but more in time with minor gravitational forces from the other planets that tweak the tilt of the poles and the orbit of the earth. Those small variations in sunshine received are amplified by enigmatic feedbacks in the global climate engine to bring or banish the ice sheets... maybe.

ESSAY by Peter W. Huber

Junk Science in the Courtroom

The opportunities for peddling bad science in a court of law cut across our litigious landscape. May a public school consider excluding a child who is HIV positive because someone clothed as an expert declares there is a risk of contagion, or would that amount to unlawful discrimination based on paranoia, not science? May Texas courts rely on a psychiatrist's predictions of "future dangerousness" in deciding whom to electrocute, or would sentencing on that basis be unconstitutionally arbitrary? May a public school in Arkansas teach "creation science" alongside Darwinian evolution, or would this violate our separation of church and state? And in civil litigation, what kind of evidence should be admitted as to whether tobacco causes cancer or breast implants don't? Cases like these often involve pitched battles among experts. Many cases are decided by—or quickly settled because of—pretrial rulings on whose experts will be permitted to testify.

Should judges screen such "expert" scientific testimony? Since the early 1970s, many courts have drifted toward what has been dubbed the "let it all in" approach, preferring that 12 stout citizens in the jury box draw the lines between real science and junk.

The stakes riding on the answer that the courts ultimately reach are high. Highest of all are those in civil litigation. And it is here that evidentiary standards have declined the most, even as standards for liability itself have grown more strict. Thus, "clinical ecologists," who claim to detect links between stray chemical pollution and something they term "chemically induced AIDS," have become a powerful force in worker's compensation litigation. Obstetricians have been sued in record numbers on the (erroneous) theory that the doctor's performance at the time of delivery significantly affects a child's risk of cerebral palsy. The quality of testimony in cases involving chemical pollution is especially variable. Stuart F. Schlossman of the Dana-Farber Cancer Institute dismissed the testimony in one major and much publicized case not only as "outside the mainstream of science" but as "outside its widest perimeter."

Scientists from within the pale may scoff at courtroom antics, but what passes for science in court affects them, too. Over time, trials can define the meaning of "good" performance for entire professions and industries. Cerebral palsy litigants, for example, frequently argue that an electronic fetal monitor or cesarean delivery would have saved the child. Science offers little support for this view. And yet electronic monitors and aggressive surgical intervention have become the professional norm, because peer review for an obstetrician too often means review from an iconoclastic medic on the witness stand, followed by the vote of a jury.

Courtroom experts may likewise trump professional societies, journals or administrative agencies in judging how drugs, pesticides or cars should be designed. The Food and Drug Administration, for example, relied on several orthodox epidemiological studies to conclude that Bendectin, a drug for morning sickness, did not cause birth defects. But armed with a barrage of inflammatory publicity and a single researcher's limited animal tests (later exposed as fraudulent), lawyers conducted some epidemiology of their own: in 1984 they assembled more than 1,000 Bendectin claims in a single court case. With "people power" like that, one attorney cheerfully observed, conventional epidemiology might not matter so much. Bendectin was withdrawn from the market, leaving what the American College of Obstetricians and Gynecologists describes as a "significant therapeutic gap."

The legal climate may even shape what reputable researchers should publish—and when. In 1981, for example, a paper suggested a possible link between spermicides and birth defects. This led to a $5-million verdict against a leading contraceptive manufacturer. But the research was not corroborated by subsequent studies, as the original authors themselves have since acknowledged. "I believe our article should never have been published," one frankly conceded. "In our present litigious environment, the reservations and qualifications written into a published report are often ignored, and the article is used as 'proof' of a causal relationship."

What can or should be done? The thought of some judge deciding what passes for "science" and what does not undoubtedly evokes unpleasant memories of Galileo. But in the American legal system today, juries already pass judgment on scientists, engineers and physicians all the time. With that the established fact, judges should, at the very least, ensure that science in court has more in common with *Scientific American* than *The National Enquirer*.

A slowly growing number are looking for ways to do just that. Most judges recognize that screening an expert's qualifications is necessary but not sufficient. Some are willing to insist that an expert rely on facts and methods of a kind generally accepted by a wider scientific community. The *Frye* rule, based on a landmark criminal case, is being gradually resurrected to require, once again, that a scientific witness's methodology or mode of reasoning be "sufficiently established to have gained general acceptance in the particular field in which it belongs."

Scientific communities should be asking their members some searching questions, too. Should a scientist or doctor accept the same lawyer's (well-paid) invitation to testify on the same issue again and again? Can a true expert derive much of her income from scientific exposition aimed more at jurors than at scientific peers? At the very least, the individual scientist should reflect on the counsel once offered by Nobel physicist Richard Feynman. A true scientist approached for advice on public matters must commit to come forward with his ultimate findings regardless of whose position they may favor.

One way or another, lawyers and scientists alike must recognize that the delivery of babies or the redesign of drugs on the witness stand is also a form of professional practice—or malpractice. If courts aspire to maintain high standards of performance among professionals summoned to court as defendants, they must find ways to maintain equally high standards among the professionals who accuse them. Otherwise, there is a real risk that the least competent fringes of a scientific community will end up, through the courts, prescribing standards for the rest.

PETER W. HUBER is a senior fellow of the Manhattan Institute and author of the recent book Galileo's Revenge: Junk Science in the Courtroom *(Basic Books).*

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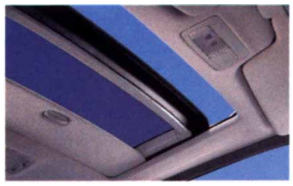

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