# SCIENTIFIC AMERICAN

AUGUST 1991
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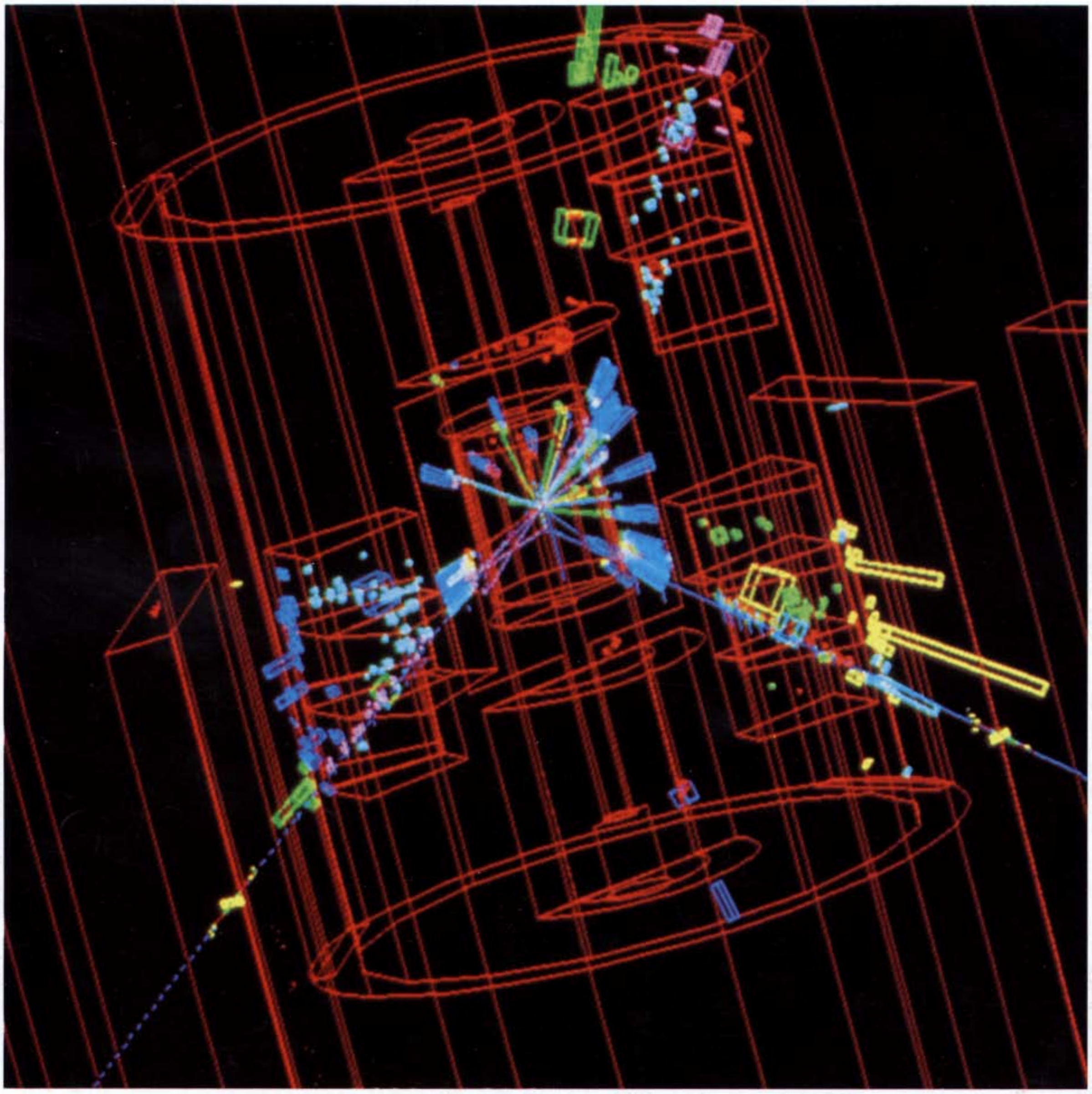
*The smart genes that control cell differentiation.*

*What happens when galaxies collide.*

*Can antichaos explain the origin of species?*



***Computer images** let physicists "see" the fates of fleeting particles.*

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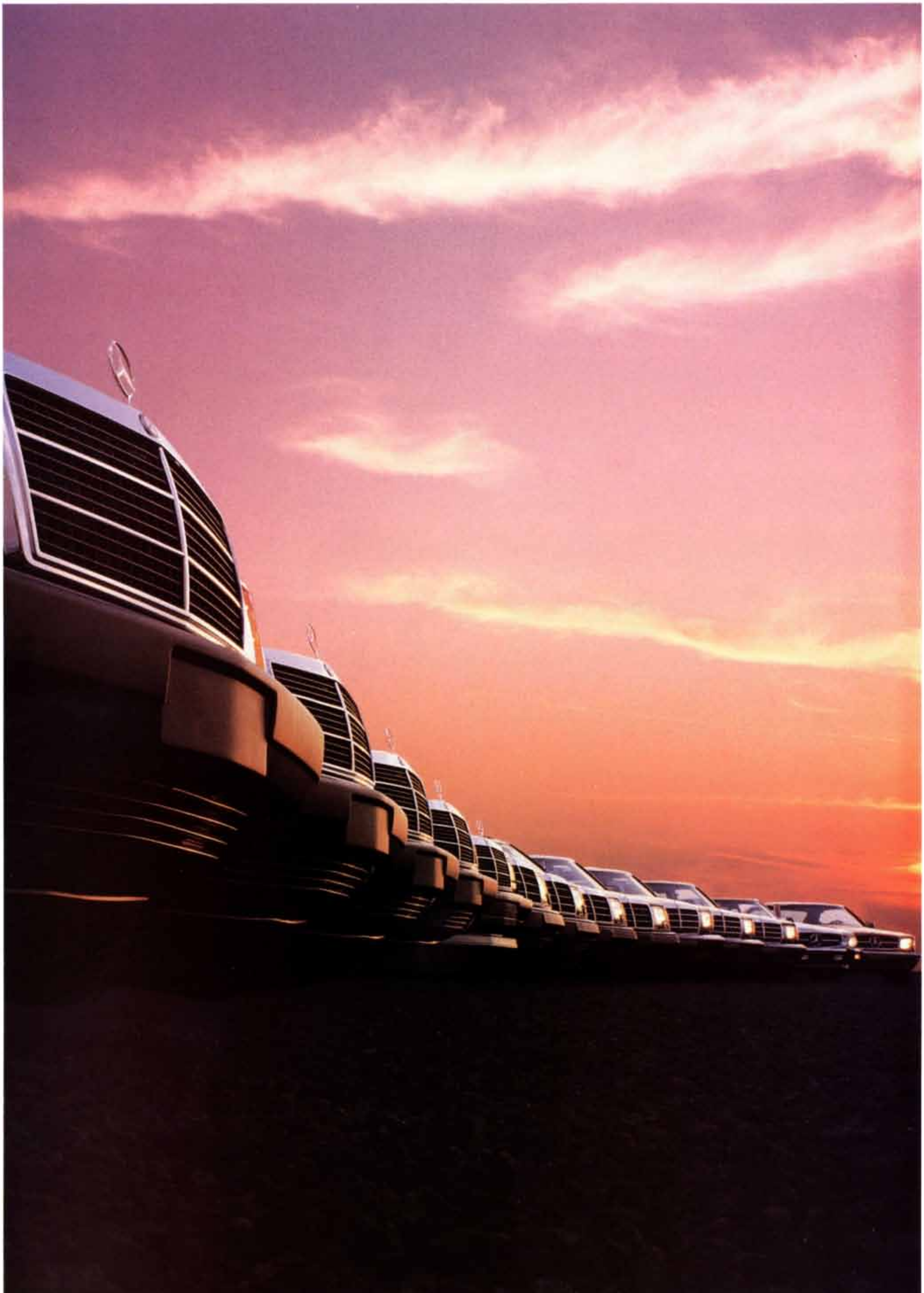

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*System 7 makes Macintosh computers even easier to use.*

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That's why we make the Apple® Macintosh® personal computer.

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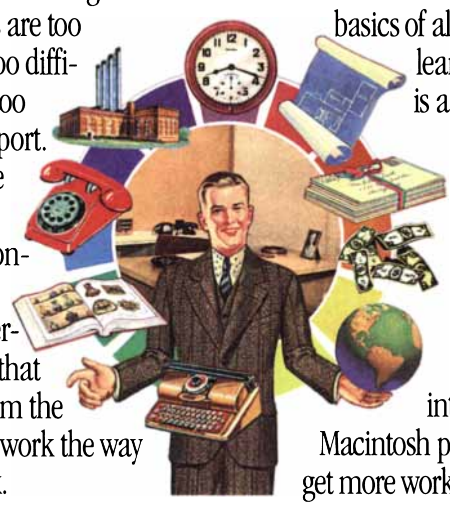
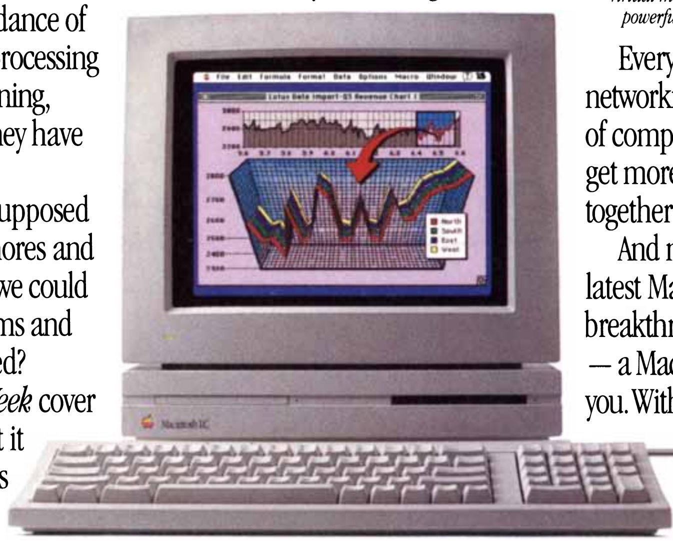


A computer that has been consistently rated significantly higher for user productivity than other PCs, including computers running Windows 3.0.*

The only computer to be named one of the best designed products of the last decade by *Time* magazine.



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Now if you have a question about anything on a Macintosh screen, you can just point at it. A balloon like this appears to tell you what it is. And how to use it.

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*The figures don't come from us. They're from "The Peat Marwick Macintosh Effectiveness Study," April 1987, "Macintosh or MS-DOS?" Diagnostic Research, Inc., March 1990 and "Macintosh or Windows 3.0?" Diagnostic Research, Inc., February 1991.*
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# Work less.

System 7 for Macintosh.

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# SCIENTIFIC AMERICAN

August 1991 Volume 265 Number 2





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## DEPARTMENTS





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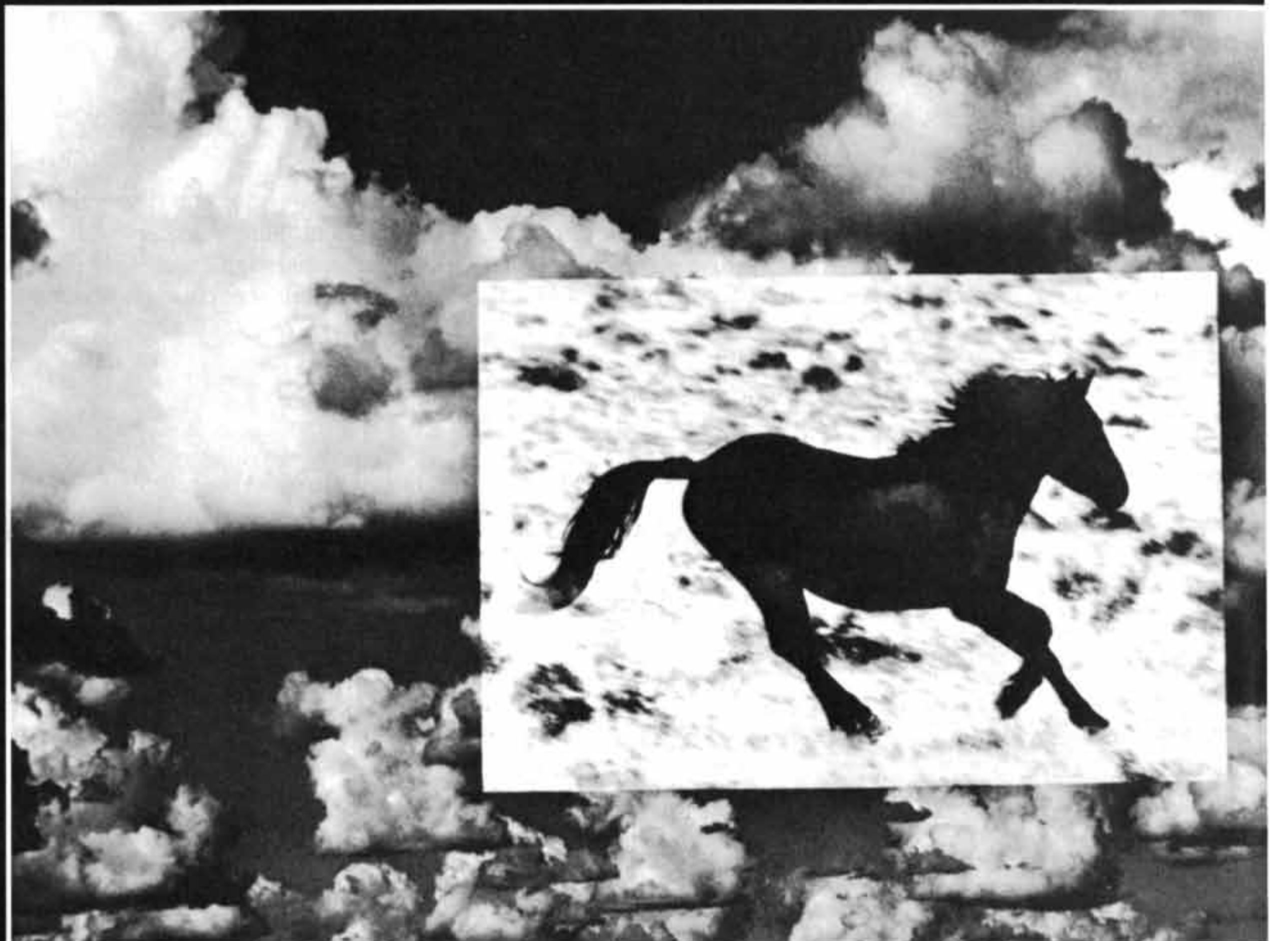

Photograph by Pete Turner

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"Nothing great was ever achieved without enthusiasm."

*Ralph Waldo Emerson*

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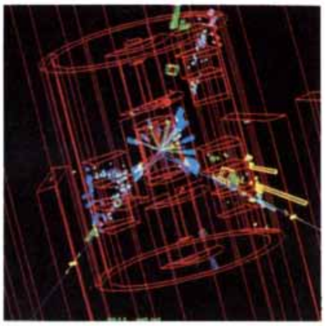

THE COVER image shows the explosion of particles created when electrons and positrons collide in the L3 detector at CERN. For each collision, the detector generates 500,000 bits of information. The authors of "Tracking and Imaging Elementary Particles" (page 58) program computers to translate these data into images, a crucial step in analyzing such events. The red lines trace the structure of the detector. Multicolored curves represent the trajectories of particles. The boxes reveal where the particles hit the detector and how much energy they released.

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Jeanne remembers looking at the plain brown Lands' End shipping box. And looking. And thinking, there's got to be something more we could do with this.

"In the end, I drew on my own experience of Christmas," says Jeanne. "Of playing with the box instead of the toy."

So Jeanne created a shipping box that turns into a cow. Or a sheep. Or a horse. Something a parent and child could play with together. Something to say, "Thanks for ordering from Lands' End!"

As head of our Customer Relations Department, it's part of Jeanne's job to come up with surprises like that. Extras. Things that add to the magic of the mail-order experience.


Most of the surprises we include with Lands' End orders (not all orders, mind you, for what would be the surprise in that?) are more on the practical side.

A skirt hanger. A cedar block. A shoehorn. All extensions of our early days, when we gladly enclosed extra buttons with every buttondown Oxford, extra laces with every pair of boat shoes. (Something we still do.)

"THESE ARE NOT LURES!" exclaims Jeanne. "We never mention them in the catalog. We want people to buy from us based on the quality of our products. But we also like to send them things to help them enjoy the products long after they've paid their Visa bill."

Recently, Jeanne even masterminded something called "The Book of Caring." Actually a booklet, full of tips on how to rid your silk tie of a stain, or store your wool sweater for its long summer's nap. It's available to anyone just for the asking.

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## The Dinosaur Derby

As a child, I fell in love with dinosaurs, and I have been a dinosaur lover ever since. As an adult, I suppose it's more accurate to refer to myself as a paleontology enthusiast (but still I prefer "dinosaur lover"). It was therefore with great enthusiasm that I read "How Dinosaurs Run," by R. McNeill Alexander [SCIENTIFIC AMERICAN, April]. That stimulating, thoughtful paper reached the conclusion that large dinosaurs were perhaps less than fleet-footed.

I was somewhat surprised, however, that the work of Robert T. Bakker (*The Dinosaur Heresies,* William Morrow and Co., 1986) was not cited as an alternative view of this interesting topic. Both Bakker and Alexander use analyses based on physical, engineering and comparative anatomical and physiological principles. Nevertheless, they arrive at very different conclusions: Bakker finds that dinosaurs such as *Tyrannosaurus* and *Triceratops* were quite swift, if not downright fast. It is clear from the unsettled issues that we dinosaur lovers will have stimulating reading for a long time to come.

THOMAS P. KNECHT
Iowa City, Iowa

If merely for aesthetic reasons, I prefer to believe that *Tyrannosaurus rex* probably could have outrun me in my 1986 Subaru from a cold start. Somehow the idea that this most terrible of monsters was only a slue-footed slowpoke leaves much to be desired.

ROBERT P. TURNER
Denver, Colo.

## UFO Bashing

If SCIENTIFIC AMERICAN has chosen to address the UFO topic, it might find a book reviewer more qualified than Philip J. Klass ["Books," SCIENTIFIC AMERICAN, February]. He is as blindly adamant in his dismissal of UFO phenomena as the most dedicated UFO buff is assertive. In 1983 the *New York Times* quoted Klass as saying that in 17 years of investigating cases, he had "yet to find a single one that is inexplicable." Because it is widely accepted that some UFO reports have so far defied convincing explanations, Klass's claim speaks eloquently of his bias.

A useful perspective on the UFO situation was offered by Philip Morrison in "The Nature of Scientific Evidence" (*UFO's: A Scientific Debate,* edited by Carl Sagan and Thornton Page, W. W. Norton, 1974). Morrison compares the UFO issue to the meteorite controversy of 200 years ago. In that case, skeptics, who were in the vast majority, dismissed each occasional report of stones falling from the sky. They turned out to be quite wrong.

EDSON C. HENDRICKS
San Diego, Calif.

***Klass responds:***

The meteorite controversy was resolved within several decades, when proponents acquired credible physical evidence to demonstrate that reports of "stones falling from the sky" were fact, not fantasy. In contrast, UFO proponents—after more than 40 years—are still unable to come up with any scientifically credible evidence that alien spaceships are in our skies.

## Not So Stupid

In "A Modest Proposal on Altruism," ["Science and the Citizen," SCIENTIFIC AMERICAN, March], John Horgan reports that Herbert A. Simon takes the causes of altruism to be, in essence, stupidity and docility.

But it is hardly a modest claim to assert that the final standard for judging what we ought to do is the interests of our genes. Among other things, that idea implies that not only altruism but also the pursuit of a career, instead of having as large a family as one can support, is stupid. It seems to me the more modest proposal is to recognize that although we are products of evolution, we have interests that go far beyond what evolution alone can give us.

ALEC WALEN
Department of Philosophy
University of Pittsburgh

I enjoyed Horgan's article, which gave an accurate account of my altruism theory (although I don't quite understand the Swiftian comparison implied by the headline). At the probable cost of being insufferably pedantic, I would like to explain my preference for the phrase "bounded rationality" over "stupidity."

I coined the phrase many years ago to serve as a contrast with the unboundedly rational person of classical economics, who chooses optimal behaviors without concern for the superhuman feats of computation required to select them. Real-world economic behavior is to an important extent shaped by limits on our knowledge and on our ability to compute the consequences of our actions. That is the theme I extrapolated into genetics. It does not connote cynicism about human nature unless it is cynical to believe that not all human beings have godlike intelligence.

HERBERT A. SIMON
Department of Psychology
Carnegie-Mellon University

## Hard to Swallow?

"Hard Words," by Philip E. Ross [SCIENTIFIC AMERICAN, April], uncritically quotes an assertion that humans are the only mammals incapable of drinking and breathing at the same time. An accompanying figure illustrates the preposterous idea that a chimpanzee can breathe while swallowing.

Both notions originated in the 1920s from studies of dead animal anatomy. X-ray motion pictures of living mammals in the 1950s, however, clearly showed that the old reasoning was unsound. As far as is known, no mammal can breathe and swallow at the same time. Unfortunately, the error persists as an article of faith among many writers on linguistics.

B. RAYMOND FINK
Department of Anesthesiology
University of Washington

ERRATUM

The table on page 14 of "Science and the Citizen" [SCIENTIFIC AMERICAN, April] contained errors. Domestic oil production would increase by 3.8 million barrels per day, not 3.8 billion. Oil imports would be reduced by six million barrels per day. Barrels of oil consumed per $1 million of gross national product would be reduced from 2.4 per day to 2.0 per day by 2010.



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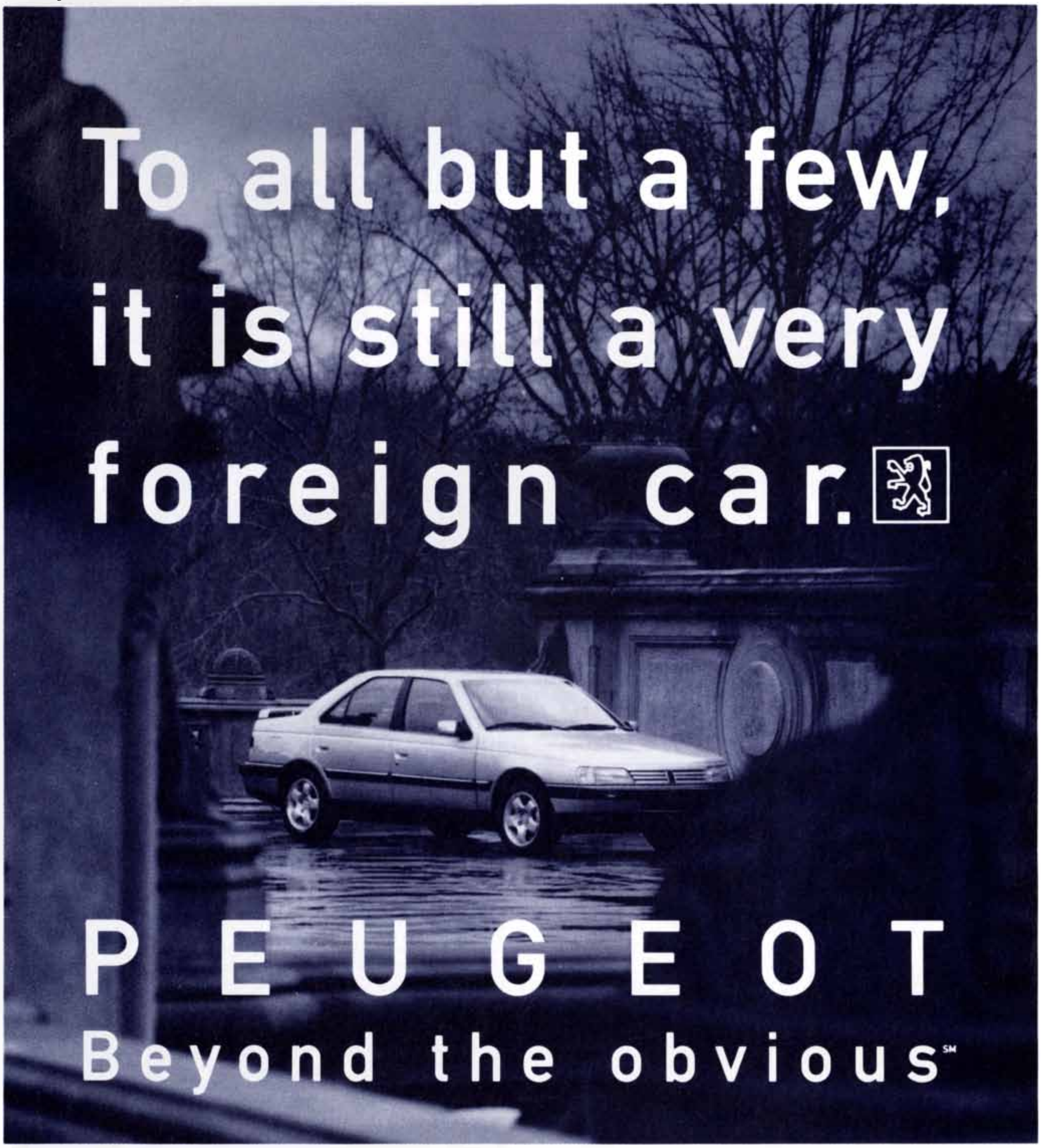


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ENOUGH INFORMATION ABOUT SCOTCH TO ORDER A DRINK.

You're thirsty for Scotch and water. But if you just say "Scotch and water," you're taking a chance on mediocrity. Say "Ballantine's and water," and you'll get a smooth, mellow, smoky Scotch with a hint of Island peat and a breath of Highland smoke. Your water will taste a lot better, too.


Ballantine's
THE TRUE TASTE OF SCOTCH.

Ballantine's Blended Scotch Whisky 43% Alc./Vol. (86 proof). ©1989 Maidstone Wine & Spirits Inc., Los Angeles, CA.

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ENOUGH INFORMATION ABOUT SCOTCH TO HAVE A CONVERSATION.

You're out on the town with a friend. But you hesitate before ordering the same old Scotch.

Peering over the bar, you spot a bottle of Ballantine's Finest.

"Hmm. I haven't had that in a while."

"One of the better blends," your friend says. "Number one in Europe."

So you order Ballantine's and water.

"It has 42 different single malts in it," he says.

"Really? Does that matter?"

"Only if you like your Scotch to be smooth."

You take a sip.

"It is smooth. How come it tastes smoky?"

Your friend explains, "That's from Highland single malts in the blend. Taste it again. It has an earthy flavor, too."

You do and it does.

"That's peat. From the Scottish islands. See, with blended Scotch, the single malts are married together to enhance each other. But you can still taste the individual flavors."

"You know too much. How am I supposed to keep up with that?"

"We have time," he says. "Another round?"

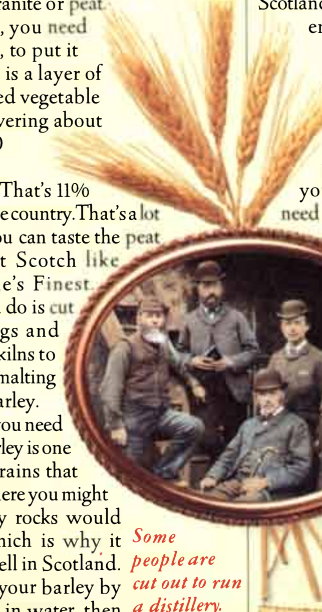
Ballantine's
THE TRUE TASTE OF SCOTCH.

ENOUGH INFORMATION ABOUT SCOTCH TO OPEN A DISTILLERY.

First, you need water. Scotland has more than enough, because it rains so much. And the best, because on its way to the burns and lochs, Scottish water is naturally filtered and purified as it flows through granite or peat.


*Aristotle. He would have enjoyed Ballantine's.*

Second, you need peat. Peat, to put it delicately, is a layer of compressed vegetable matter covering about 1,700,000 acres in Scotland. That's 11% of the entire country. That's a lot of peat. You can taste the peat in a great Scotch like Ballantine's Finest. What you do is cut it into logs and burn it in kilns to stop the malting of your barley.

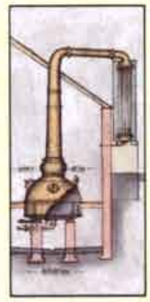

*Some people are cut out to run a distillery. Some aren't.*

Third, you need barley. Barley is one of those grains that thrives where you might think only rocks would grow. Which is why it does so well in Scotland. You malt your barley by soaking it in water, then drying it over the peaty fire. Then you grind it, mix in hot water and let it sit for a few hours. Add a little yeast to the liquid and the sugars turn into alcohol. The barley has done its job. You can feed it to cattle.


*The handsome Highland cattle.*

Fourth, you need cattle. Some of the happiest cattle in the world live in Scotland. (Not to mention some of the best tasting.)

Fifth, you need a still. These are the funny looking copper pots without which there would be no Scotch. It is said that Aristotle invented distillation. But sadly, he never lived to taste a fine Scotch like Ballantine's. After distillation, you have whisky. Which longs for barrels in which to grow old.


*Save your pennies for a copper still.*

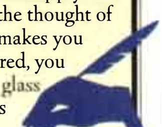
Sixth, you need barrels. There aren't many oak trees left in Scotland. At least not enough to age Ballantine's Finest. So you need oak barrels imported from America. Once your Scotch is in the barrels, you need to put them away for a long time.

Seventh, it helps to have an ocean. There's a refreshing scent of sea air in a select few of the single malts used in Ballantine's. Some say it creeps into barrels stored near the ocean. In any case, it adds distinction to the Scotch. It may be that Scotland is the best place to make Scotch precisely because there's no point more than 70 miles from the sea. Kansas is not a good place to make Scotch.


*Kansas. Too far from the North Sea.*

And last, you'll need patience. The only thing left to do is wait. If you want your Scotch to be part of Ballantine's Finest, you'll have to wait quite a while, because we don't blend any malt whisky younger than five years. Patience is essential when starting your own distillery. But, as you've read this far, it would seem that you have a good supply of it.

Whew! If the thought of all this work makes you feel a bit tattered, you might enjoy a glass of Ballantine's Finest. Maybe you don't need your own distillery after all.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# 50 AND 100 YEARS AGO

AUGUST 1941

"If ways and means are found to decimate the enemy's ranks by communicable diseases or by deadly poisons, carried into the enemy's territory, this 'cruel' and 'inhuman' method of fighting will be generally adopted, despite all sentimental objections. Fortunately for the human race, the situation is such that exaggerated fears of the devastating effects of bacterial warfare are without foundation. A spoonful of toxin of the bacillus botulinus would be enough to poison the whole population of a large city. A single airplane could carry enough botulinus toxin to destroy the world's entire population. But it is not so simple in practice. While it would not be difficult to manufacture the necessary amount of botulin and to transport it, the real problem is how it should be administered. There were over 100 billion bullets manufactured during World War I, enough to kill the entire population 50 times; but a few of us are still alive."

"Complete control of gonorrhea is promised by a new treatment which cures in 100 percent of the cases, Dr. William Bromme, of Detroit, has declared. Complete cures in three days of 100 out of 100 men were achieved by sulfathiazole treatment, Dr. Bromme reported. All previous methods of treating gonorrhea have failed because the drugs could not get at the germs, which quickly get below the surface of the skin to the deeper tissues where the gonococci live. Dr. Bromme predicted that within 20 years there will not be a case of gonorrheal crippling or other complication to demonstrate to medical students."

"The next step in the experimentation was to find out what would take place if the bats were made voiceless. The Harvard biologists, Galambos and Griffin, were able to gag an animal temporarily by first binding its snoutlike mouth with linen thread and then sealing the lips with collodion. The result was that the score of collisions again jumped to 65 percent. The supersonic broadcaster—that is, the bat—could no longer give off volleys of sound as it flew. Just to make doubly sure that the supersonic sounds really were cries rising in the animal's larynx, the investigators held the bat's head for short periods under water. During these periods no high frequency sounds came forth from the recording apparatus."

"That modern steel automobile bodies are effective shields against lightning was recently proved in the laboratories of the Westinghouse Electric and Manufacturing Company, where a 3,000,000-volt stroke of man-made lightning was directed against the top of a car. Although the bolt struck the car top within a few inches of the head of the engineer seated within, the only traces of damage were small burn marks on the metal top."

SCIENTIFIC AMERICAN

AUGUST 1891

"Nature in the tropics lends herself readily to the uses of the poisoner. On every hand abound vegetable products from which the deadliest poisons may be extracted by easy processes. Lobelia, nux vomica, belladonna, prussic and oxalic acids, urichitine, manchioneal, and many other less well-known substances are all abundant. In the animal kingdom the potency of putrid blood and the venom of tarantulas, scorpions, centipedes and, more rarely, serpents are well understood."

*A safe way to handle a boa constrictor*

"Chicago is a great city, enterprising to an astonishing degree, and in more than one respect is unlike any other city on this continent. She gained the world fair site over all her competitors, and she now has a woman engineer. A contemporary says she was not let off easily either because she was a woman; in fact, the writer says her examination was, if anything, a little more severe than usual. Among other questions she was asked was the size of the blow-off required for a seven horse power engine, and what she would do if the valve stuck fast. When the examination was finished, the examiners wrote at the end of her paper 'accepted,' and Miss De Barr is now a full-fledged licensed steam engineer."

"The worker of the nineteenth century works beyond his strength, and in order to keep it up he resorts to stimulants—coffee, tea, spices, alcohol, tobacco. These produce a superexcitation of the nerves, which brings in its train insomnia; and to overcome this he resorts to narcotics, at the head of which stands morphine. The danger of falling into the habitual use of this drug arises from the cowardice and degeneracy of our times. No one will suffer pain, no matter how transitory. Not a tooth can be drawn, not a child born into the world without the use of an anodyne, and when death comes we must have euthanasia."

"The banana belongs to the lily family, and is a developed tropical lily, from which, by ages of cultivation, the seeds have been eliminated and the fruit, for which it was cultivated, greatly expanded. In relation to the bearing qualities of this fruit, Humboldt said that the ground that would grow 90 pounds of potatoes would also grow 33 pounds of wheat, but that the same ground would grow 4,000 pounds of bananas."

"Mr. G. R. O'Reilly has traveled much in search of snakes and reptiles, and finds no difficulty in making captive, in a live state, the most dreaded serpents. Our illustration shows his easy manner of handling a boa constrictor at the Central Park Museum."



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And our quality control checks are so exhaustive that they even include x-rays.

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True, there may be cheaper tires. But if they don't last like a Michelin, are they really less expensive?

So the next time someone tries to save you a few dollars on a tire, tell him this: It's not how much you pay that counts. It's what you get for your money.

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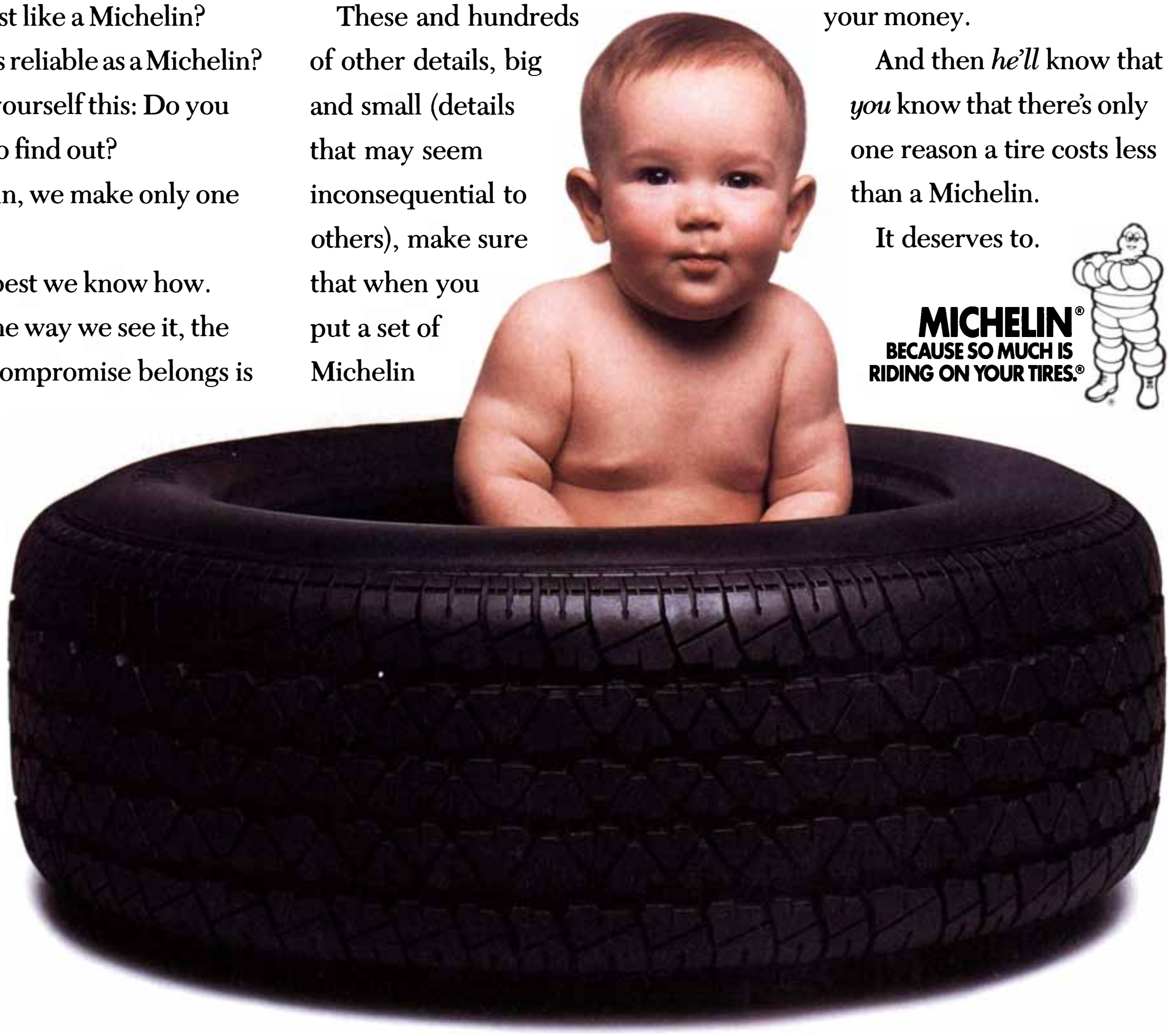

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## Exporting Misery

*A U.S. abortion ruling affects women's health worldwide*

On May 23 the U.S. Supreme Court upheld Title X regulations issued by the Reagan administration in 1988 that prohibit federally funded family-planning clinics from providing women with any information about abortion. The decision, which came on a 5-4 vote, provoked extensive media coverage, brought satisfaction to antiabortion advocates and outraged pro-choice groups and their supporters.

Only 11 days later the Supreme Court quietly issued another abortion-related decision that, while provoking relatively little public comment, has even more far-reaching consequences. The ruling, which was issued by the high court without comment, sanctions another Reagan policy that exports the gag order on abortion to developing countries.

Called the Mexico City policy because it was announced at a family-planning conference in Mexico City in 1984, the rule denies U.S. foreign aid to any organization that performs abortions, advises women on abortion or lobbies on behalf of abortion rights—even if these activities are supported by non-U.S. funds. Like Title X regulations, the Mexico City policy was challenged in court by the Planned Parenthood Federation of America.

Antiabortion groups, whose lobbying helped to bring about the Mexico City policy, have nothing but praise for the court's decision. Richard Doerflinger, a spokesperson for the National Conference of Catholic Bishops, calls it "good common sense and good morality." He contends that the policy has helped decrease the number of unintended pregnancies and promote "true family planning" in developing countries.

That view cannot be further from the truth, according to family-planning experts. Sally J. Patterson, a spokesperson for Planned Parenthood, contends that the Mexico City policy may actually have led to a rise in the number of unintended pregnancies and abortions in the Third World by reducing the availability of other forms of contraception. "We suspect," she adds, that the policy has caused "an increase in the number of women dying from unsafe abortions."

The policy has denied U.S. funds to many international organizations—notably Planned Parenthood, which was once the largest recipient of U.S. money—that offer contraception as well as abortion-related services. Some funds have been diverted to groups opposed not only to abortion but to all forms of artificial contraception. The Agency for International Development (AID), the primary dispenser of U.S. foreign aid, recently provided a $200,000 grant to a Catholic organization that advocates the rhythm method and sexual abstinence as the best forms of birth control. The money will be spent in Zambia—a country with a soaring rate of AIDS.

AID once led the world in promoting birth control, including abortion, in developing nations. Adrienne Germain of the International Women's Health Coalition, a group based in New York City that supports medical and reproductive services in Third World countries, observes that in the 1960s and early 1970s AID helped to develop a simple abortion procedure for health care providers with limited training and resources. "It is the ultimate in appropriate technology," Germain says.

The Reagan and Bush administrations cut AID's annual budget for family planning from a high of $300 million in 1985 to $270 million in 1990. Meanwhile pressure from conservative groups has helped shut down research that could provide alternatives to abortion in developing and advanced nations alike.

Other nations have taken up some of the slack. France, for example, is promoting the use of the chemical abortifacient RU 486 in developing countries. But these nations, like the U.S., are increasingly constrained by pressure from antiabortion groups. No other country, moreover, can match the financial and scientific potential of the U.S. "If you cut back on U.S. research,"

**Maternal Deaths Caused by Illegal Abortions**

| COUNTRY | SHARE (PERCENT) |
|---|---|
| CHILE | 36 |
| ARGENTINA | 35 |
| JAMAICA | 33 |
| BANGLADESH | 31 |
| COSTA RICA | 30 |
| COLOMBIA | 29 |
| ZIMBABWE | 28 |
| ETHIOPIA | 25 |
| NIGERIA | 25 |
| TANZANIA | 21 |
| SRI LANKA | 13 |

*SOURCE: World Health Organization, Population Council and Worldwatch Institute*

***THIRD WORLD WOMEN wishing to limit their number of children will get less advice as a result of a U.S. Supreme Court ruling. Photo: J. P. Laffont/SYGMA.***



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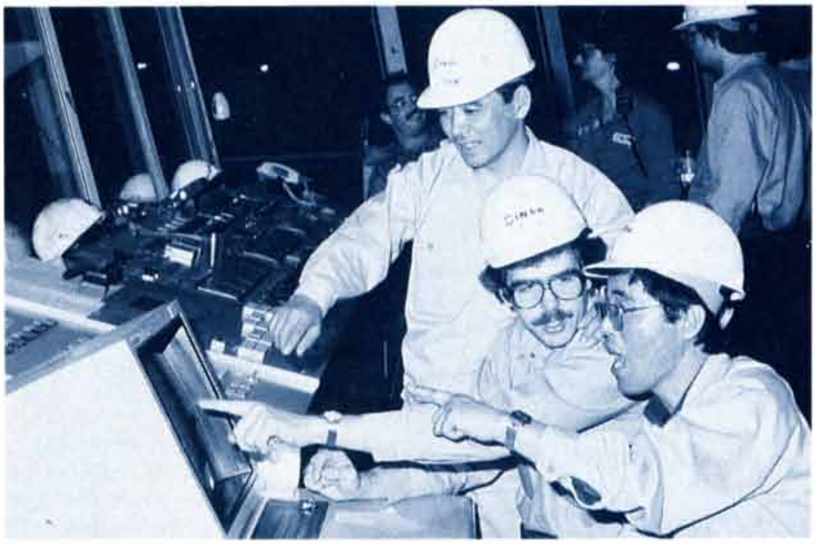
# *Doing Our Best....To Achieve the Best*



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Germain says, "you're cutting it off at the source."

Not surprisingly, birth control remains largely unpracticed in many nations. A report by Jodi L. Jacobson of the Worldwatch Institute, a research group in Washington, D.C., concludes that 50 to 60 percent of couples in Latin America, 60 to 80 percent in low-income Asian nations (China excepted), 75 percent in the Middle East and North Africa, and 90 percent in sub-Saharan Africa do not use any form of modern contraception. Yet most couples in Latin America and Asia and a growing percentage in the Middle East and Africa, Jacobson says, "wish to space the timing or limit the number of their children."

The inevitable result of these trends is that more women are turning to unqualified abortion practitioners or trying to abort their pregnancies themselves. According to Jacobson, abortion-related deaths are rising throughout Asia (China excepted) and Africa. Such deaths now account for 31 percent of all recorded maternal deaths in Bangladesh and 25 percent in Ethiopia. In six Latin American countries, Jacobson adds, unsafe abortion is already the leading killer of women in their twenties and thirties and the second leading cause in another six. The World Health Organization has estimated that some 200,000 women die every year of complications from improper abortions.

These estimates may even be low. According to a 1988 study by the Population Crisis Committee (PCC), a private group in Washington, D.C., the Mexico City policy has discouraged U.S.-funded clinics from reporting abortions, legal or otherwise. Some clinics have expunged any records of abortion-related treatment from their files out of fear that they could endanger their U.S. funding.

For the same reason, clinics have refused to treat women suffering from botched abortions. A worker at a clinic in Bangladesh told PCC researchers that even if a woman showed up bleeding and in severe pain, she would be turned away without treatment or even advice. "We can't touch abortion," the worker said.

Technically, the Mexico City policy applies only to private groups and not to state-run hospitals and clinics. Yet PCC vice president Sharon L. Camp says the policy has led some governments dependent on U.S. foreign aid to limit or to eliminate abortion-related services—even if their own laws permit the procedure. Camp recalls asking a health official in Kenya, where abortion is officially legal for some health indications, why his agency was acting as if it were subject to the Mexico City policy. "One does not bite the hand...," the official replied.

Now that the Supreme Court has upheld the Mexico City policy, family-planning groups are lobbying the U.S. Congress to reverse the policy through legislation. Representatives Olympia J. Snowe of Maine and Chester Atkins of Massachusetts have co-sponsored such legislation, which was passed by the House on June 12. But Senator Jesse A. Helms of North Carolina has predicted that the Senate will not follow suit.

Carol A. Miller, a member of Snowe's staff, points out that an appropriations bill could still overturn the Mexico City policy, although President Bush might then use his power of veto. Still, Miller notes that opponents of the policy have a trump card: the outrage of many Americans over the gag rule placed on U.S. clinics. "We hope that will carry over" into the struggle for the rights of women in the Third World, Miller says. *—John Horgan*

## Do DNA Fingerprints Protect the Innocent?

Since 1987, DNA fingerprints have been allowed into courtrooms as proof of guilt or innocence. But the method of identifying individuals by unique patterns in their DNA is still controversial. At issue is the lack of standards to ensure that the tests have been properly performed. Although a growing number of courts in 38 states are now admitting DNA fingerprints as evidence, neither the states nor the federal government regulates the forensic tests.

As a step toward resolving the uncertainties, Congress is considering the DNA Proficiency Testing Act of 1991. The bill, which was proposed by Representative Frank Horton of New York, would authorize spending $5 million so that states could acquire DNA testing equipment. In order to get a share of the money, states would have to agree that laboratories performing the tests meet standards guidelines and also agree to participate in proficiency testing at least every six months.

So far, though, the questions of who will set standards and how they should be implemented have not been answered. At congressional hearings held by House and Senate judiciary subcommittees in June, the Federal Bureau of Investigation, which has performed more forensic DNA analyses and trained more investigators than any other group, attempted to decline responsibility for oversight. "We do not want to be a regulatory agency," says John W. Hicks, the FBI Laboratory's assistant director. Other potential candidates include the National Institute of Standards and Technology, the American Society for Crime Lab Directors and the College of American Pathologists.

Developing technical standards, such as rules for matching DNA patterns, will probably be easier than setting procedural standards for licensing, accreditation, data storage and proficiency testing, points out Robyn Y. Nishimi, who headed a study of DNA fingerprinting at the congressional Office of Technology Assessment. Because various methods of analysis are now used, data cannot be shared between states via computer. "Standardized data are critical to a successful national DNA information data base," Nishimi says.

A likely model for DNA proficiency requirements are rules put in place for clinical testing laboratories when Congress amended the Clinical Laboratory Improvements Act in 1988. These laboratories are required to use a "blind" external testing system, in which neither the laboratory nor the individual examiner knows when any given sample received is actually a test. Such a system is being used in Britain, where forensic DNA testing was pioneered. The blind-test methodology is "the linchpin of clinical laboratory amendments," declares Barry C. Scheck, a professor of law at New York University. "Why should tests that may be used to deprive someone of their freedom be subjected to any less rigorous treatment?"

A report due from the National Academy of Sciences this fall will explore other issues raised by DNA fingerprinting. Along with quality control and standards, the academy will address the growing concern over what happens to DNA samples after the information pertinent to the criminal investigation is collected. Unlike regular fingerprints, DNA contains information about hereditary disorders and predispositions for disease—knowledge that will become ever more accessible through testing. *—Deborah Erickson*



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## A Small Disturbance

*Did experimental obstacles leave Brown motionless?*

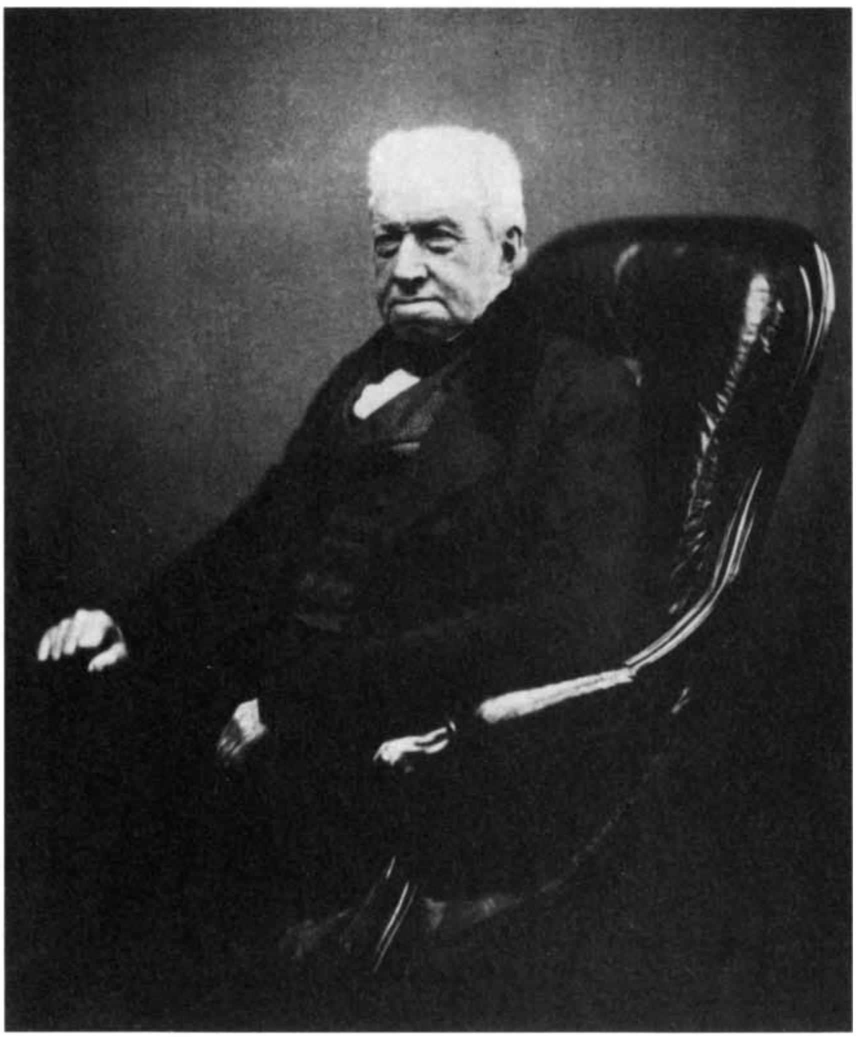
In 1827 the Scottish naturalist Robert Brown peered through a microscope and saw specks of pollen dancing a chaotic Highland fling in a water droplet. Notwithstanding the small scale of those random movements, inquiry into Brownian motion yielded discoveries of great magnitude during the 20th century: the first definitive evidence for the existence of atoms, estimates of the physical constant known as Avogadro's number, a mathematics for describing randomness in quantum mechanics and a metaphor for small fluctuations in economics.

Yet in an abstract published recently in the *Bulletin of the American Physical Society,* Daniel H. Deutsch of Pasadena, Calif., a consultant to the chemical industry, suggested that what Brown saw was not real Brownian motion at all. The tiny perturbations he observed may have been no more than—well, tiny perturbations.

Although several early microscopists had noticed the small, aimless motions of tiny floating bodies, Brown was the first to study the phenomenon in detail. By repeating his observations with bits of glass and rock as well as pollen, Brown demonstrated that the strange motions were not a property of living matter alone. Physicists unsuccessfully puzzled over the cause of Brownian motions throughout the 19th century. They considered the possibility that convection currents in the drop were moving the particles but abandoned the idea when observations showed that the motions of neighboring particles did not correlate.

Albert Einstein found the source of Brownian motion—inadvertently—in 1905. While seeking proof that atoms were real physical entities and not just useful abstractions, Einstein realized that the pressure of molecules bombarding a suspended particle would vary randomly on different sides. Consequently, the particle would jiggle and wander in its medium. Only after making his insight public did Einstein learn that Brown and others had already seen such a motion. Jean Baptiste Perrin of the University of Paris later verified Einstein's work by measuring the Brownian motions of suspended particles and using them to calculate Avogadro's number. Perrin received the Nobel Prize in Physics for his accomplishments in 1926.

But according to Deutsch, Brown could not have observed true Brownian motion—the kind that Einstein described—with the equipment available to him. Brown's original single-lens microscope magnified images only about 350 times; at that scale, Deutsch calculates, true Brownian motion would be resolvable only for particles that were about one micron (a millionth of a meter) across. Many of the pollen grains and bits of rock that Brown studied were 10 times or more that size and would have moved imperceptibly.



**ROBERT BROWN** ***is credited with having studied the phenomenon now called Brownian motion—but did he really? Photo: The Granger Collection.***

So what did Brown see? The particles may have been moving because of environmental vibrations and convection currents, Deutsch says. Whereas modern microscopes are "built like a 16-inch gun on a battleship" to eliminate vibrations, he explains, Brown's microscope was virtually "an inverted pendulum." Cover slips—thin sheets of glass that hold samples and prevent them from drying out—were not used by microscopists until the mid-19th century.

The particles that Brown observed might therefore have been driven by evaporation after all. Later, microscopists using sturdier instruments and cover slips did see the effects of random molecular bombardments, but Deutsch believes they mistakenly assumed that it was the same phenomenon Brown had reported.

Still, no one is as yet leading a charge to strip Brown's name from the famous motion. Joachim Burgdeorser, a physicist studying the liquid phase of matter at the University of Tennessee, has read Deutsch's abstract but says that he would need to see a more detailed version of the argument before he could be convinced. "I'm a little bit skeptical of people who try to reevaluate work ages after it's been done and say, 'Well, we know much better what really happened,'" Burgdeorser adds. Deutsch says he is currently planning a fuller exposition, which he hopes to have ready in about a year. —*John Rennie*



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# Waves Are Waves...

*...and particles are particles, and never the twain shall meet*

A bit of matter or energy can appear to act like either a wave or a particle. But both behaviors can never be observed simultaneously. That is one of the most fundamental principles of quantum mechanics, known as complementarity.

Proving it, of course, is not quite so simple. Physicists once believed that every experiment designed to test complementarity would, in some sense, be too clumsy to do the job. Indeed, some physicists thought that the "clumsiness" inherent in all experiments was the very reason why an object had never been seen acting like a wave and a particle at the same time.

The recent development of such technologies as the one-atom maser has made possible a delicate apparatus that measures the position of an atom and, at least in theory, alters its wave behavior in a predictable manner. The apparatus gave physicists a glimmer of hope that they might actually be able to catch an atom behaving like a wave and a particle at the same time.

No dice. Theory claims that as soon as the apparatus measures the position of atoms, all associated wavelike behavior is lost. And like it or not, experiments have confirmed every observable aspect of the theory.

The apparatus designed to test complementarity is a clever variation of the famous two-slit experiment. In the original version, a gun shoots an atom in the direction of a screen that has two tiny slits. If the atom passes through a slit, it produces a white spot on a photographic emulsion placed behind the screen. After a million or so atoms have been fired at the slits, a pattern of bright bands emerges on the emulsion.

Quantum mechanics accounts for the pattern of bands in the following way. Once the atom leaves the gun, it behaves like a wave that can either combine with other atomic waves or cancel them. The two slits act like breakwaters in a harbor, splitting the atomic wave into two pieces that spread out and interfere with each other. The atom is more likely to be recorded at a point on the emulsion where the waves interfere constructively. After many atoms have run the gauntlet from the gun to the emulsion, the regions most likely to be hit by atoms emerge as the bright bands of the resulting interference pattern.

All well and good, except that this explanation implies that the atom has traveled through both slits and interfered with itself. Surely individual atoms must have gone through one slit or the other. But all previous attempts both to find the path of the atom and to preserve its wavelike behavior have been foiled by Heisenberg's uncertainty principle or, to put it simply, clumsiness.

The principle states that as soon as the position of the atom is measured, its momentum will change to an unpredictable value. When the momentum changes, the wavelike properties of the atom are disturbed, and the interference pattern disappears. "No one has ever found (or even thought of) a way around the uncertainty principle," remarked the late Richard P. Feynman in his *Lectures on Physics,* published in 1965.

Some 26 years later workers have finally thought of a way. Julian Schwinger of the University of Southern California and Marlan O. Scully of the University of New Mexico, together with Herbert Walther and Berthold-Georg Englert at the Max Planck Institute for Quantum Optics, have conceived of a modified two-slit experiment that bypasses the uncertainty principle. In their version of the experiment, published in the May 9 issue of *Nature,* two small cavities are placed on the gun side of the slits. Each cavity has holes that allow atoms to pass through. A laser beam illuminates the atoms as they enter the cavities. The laser beam is tuned in such a way that whenever an atom passes through the beam, it becomes "excited" by absorbing a high-energy photon. The cavities are designed so that whenever an excited atom passes through the cavity, it releases a low-energy photon. (Such cavities were key to the development of the one-atom maser.)

The experiment begins when atoms pass, one by one, through the laser beam, the cavities and the slits. Each atom absorbs a high-energy photon and then releases a low-energy photon inside one of the cavities. The presence of a photon in one of the cavities indicates which slit the atom passed through.

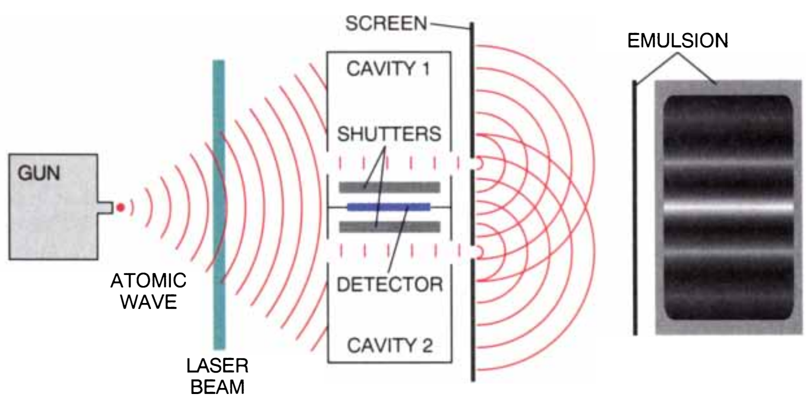
Because the atom absorbs the high-energy photon before it enters the cavity-slit system, the influence of the high-energy photon is irrelevant. Indeed, if the experiment is performed without the cavities and the atom remains in an excited state, the results are the same as the original two-slit experiment.

With the cavities in place, however, the outcome is very different. When an atom releases a low-energy photon, its momentum changes in a predictable way. The momentum does not change randomly, as in those systems in which the uncertainty principle plays a role. The cavity experiment succeeds in discovering which slit the atom passed through without scrambling the atomic wave.

Even so, when the atom signals its position by releasing a low-energy photon, it loses the ability to interfere with itself. More specifically, the loss of interference in these experiments can be traced to correlations between the atomic waves and the act of measuring the paths of the atoms. As a result, the pattern of bright bands does not appear. Thus, the principle of complementarity is enforced by a mechanism other than the uncertainty principle.

Physicists are now preparing anoth-

## An Experiment to Test Complementarity




**As an atom crosses the laser beam, it absorbs a photon. The atom then deposits a photon within one of the two cavities. The detector can capture this photon if the shutters are open. The atom passes through one of the two slits in the screen and strikes the emulsion. After millions of atoms run the gauntlet, a pattern emerges on the emulsion.**



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**The United States Academic Decathlon**

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er test that should reveal one of the most bizarre aspects of complementarity. The experiment, known as the quantum eraser, should demonstrate that if information about the path of an atom is stored and then erased, the wavelike properties of the atom should survive. The quantum-eraser concept was proposed in the early 1980s by Edwin T. Jaynes of Washington University in St. Louis and Scully.

In this case, a detector is positioned between the two cavities, and one wall of each cavity is replaced with a shutter. Photons from either cavity can reach the detector if the shutters are open. The experiment begins with the shutters closed. An atom enters one of the two cavities, where it deposits a photon. While the photon bounces around in the cavity, the atom passes through the corresponding slit and hits the emulsion, producing a white spot.

An instant later, the shutters are opened simultaneously. The photon, which is still moving around in the cavity, has a 50 percent chance of being absorbed by the detector, according to quantum theory. If the detector captures the photon, the spot on the emulsion is marked. This may be accomplished by some mechanism that colors the spot blue. The blue spot represents an atom whose path information was definitely erased after the atom hit the emulsion. If the detector fails to absorb the photon, the spot is colored red, indicating that the path information might or might not have been destroyed. After many atoms have passed through the apparatus and the resulting spots on the emulsion colored, theory predicts that the result should be bands of blue and red.

Remarkably, the pattern should appear even though the information about which path the atom took was erased after the atom hit the emulsion. Atoms seem to "know" where to land on the emulsion before the apparatus "tells" them where to go. Recently Scully and his collaborators have resolved this paradox within the mathematical framework of quantum mechanics.

What if actual experiments do not produce a pattern of blue and red bands? "I'd say there was something wrong with the experiments," Scully says.

He's got good reason to be confident. "Quantum mechanics can be compared to a car that we bought 60 years ago," Scully proclaims, "and after 60 years, we've never seen it break down once." Few physicists would dispute that statement, but most would feel more comfortable about driving the quantum car if they could get a better look at the engine. *—Russell Ruthen*

# Caribbean Killer

*Did an impact off Mexico kill the dinosaurs?*

Ever since scientists proposed that the impact of an asteroid some 10 kilometers in diameter wiped out the dinosaurs about 65 million years ago, skeptics have asked: Where is the crater? Numerous candidates have been proposed over the years, but all have been dismissed, generally because they are too small or are not the right age.

Now a once rejected crater, which straddles the coast of Mexico's Yucatán peninsula, has regained the status of leading contender. "It looks to me like the best candidate crater we have," says Walter Alvarez of the University of California at Berkeley, who with his father, Luis, proposed the impact hypothesis in 1980.

In 1981 two geologists for Mexico's national oil company, Pemex, first suggested that a crater 180 kilometers wide lay beneath about a kilometer of rock in a region centered on the coastal town of Chicxulub. Glen T. Penfield and Antonio Z. Camargo based their conclusion, which they presented at a geology meeting in Houston, on maps of gravitational and magnetic anomalies in the region.

If the geologists were correct, the Chicxulub crater would be the largest one ever identified. It would also fall within the range of sizes that the Alvarezes had predicted. The hypothesis was almost universally ignored, however. Acceptance was stymied initially by Pemex's refusal to release geologic data and later by a fire that destroyed core samples taken from the Chicxulub region.

Alan R. Hildebrand, then at the University of Arizona, had never heard of the Chicxulub crater when he indepen-


***RING OF SINK HOLES marks the rim of a huge buried crater in the Yucatán.***



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dently began to suspect, some nine years later, the Caribbean as the site of the killer impact. Sifting through sediments deposited at the boundaries between the Cretaceous and Tertiary periods, when the dinosaurs and many other species are thought to have become extinct, Hildebrand turned up signs that they had been disturbed by a tremendous tidal wave.

The findings led Hildebrand to conclude that the impact had occurred somewhere in the Caribbean—but where? Geologists had identified several potential crater sites in the area, but none were satisfactory. Then, in March 1990, Hildebrand learned about the Chicxulub site from a reporter for the *Houston Chronicle* who had written about it in 1981. Sixty-five million years ago the site would have been entirely under water, and the impact would have created an enormous tidal wave.

Hildebrand contacted Penfield, and before long, the two succeeded in locating some old drilling samples from the Chicxulub region. Together with other scientists from the University of Arizona, including William V. Boynton, Hildebrand's thesis adviser, they did an analysis of the samples that supported Penfield's earlier conclusion.

Boynton says the data have set an upper limit on the age of the impact of 67 million years and a lower limit of 55 million years. An analysis of radioactive decay in rocks from the crater, he adds, should provide a more precise date in a month or two.

Meanwhile other positive evidence is accumulating. In May a group led by Kevin O. Pope of Geo Eco Arc Research, a company in La Canada, Calif., reported in *Nature* that it had found a ring of sink holes marking the edge of the land-based part of the crater. The sink holes were probably formed, Pope explains, by groundwater seeping through fractured rock at the rim of the crater.

Of course, some scientists still find all the evidence for the asteroid-impact theory unpersuasive. One is Charles B. Officer of Dartmouth College, who has vehemently opposed the theory from the beginning. Asked to comment on the Yucatán findings, he snaps, "It's utter crap, and I don't want to say any more about it."

Yet Pope contends that the evidence for a devastating impact at the Cretaceous-Tertiary boundary "is piling so high that it is really difficult to discount." He acknowledges that scientists "need to be cautious" before concluding that the impact occurred at the Chicxulub site. "But every time we turn a corner," he adds, "this thing looks better." —*John Horgan*


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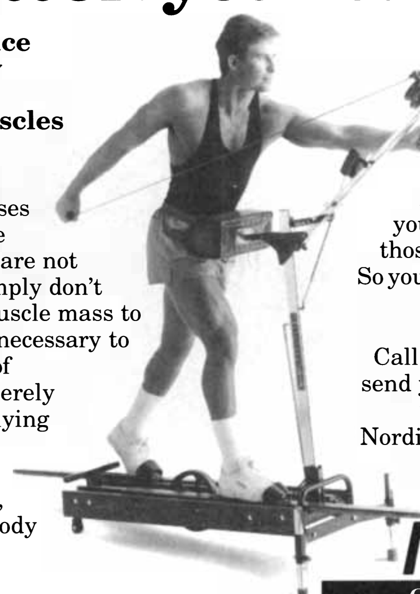


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# The New Moon

*Taking a fresh look at a familiar cosmic face*

Like a partner in a good romance, the moon, although familiar, can still offer surprises. While more glamorous distant planets grab the headlines, the earth's faithful companion continues to reward the scientists who lavish attention on it.

At a recent meeting of the American Geophysical Union, some two dozen researchers announced the results of their recent lunar investigations. The National Aeronautics and Space Administration's *Galileo* spacecraft, which swept by the far side of the moon last December 8, provided material for several reports. The probe captured the first clear images of the Aitken basin, a vast depressed region of the moon about eight kilometers deep and as large as 2,000 kilometers across.

The Aitken basin presumably formed when a meteorite collided with the moon. Judging from the basin's size, the meteorite "was close to the size needed to bust up the moon," notes James W. Head of Brown University, who coordinated *Galileo*'s lunar encounter.

The *Galileo* images reveal that the basin contains material that is darker and probably richer in iron and magnesium than the surrounding surface. Possibly the meteorite blasted through the lunar crust, exposing chemically distinct underlying mantle material. Or it may have created a giant crater that flooded with lava and then was partially buried under material from other impacts.

If lava did flood the basin, the moon may have been volcanically active earlier than astronomers realized. The Aitken basin appears to be distinctly older than the lunar "seas" that mark the visible hemisphere of the moon, which are thought to have been created by huge lava flows some 3.9 billion years ago.

Paul D. Spudis of the Lunar and Planetary Institute in Houston presented photographs that imply volcanism may have occurred on the moon as recently as 900 million years ago. If so, the moon has been active through much of its 4.5-billion-year history. Spudis notes that these findings call into question the conventional view that all lunar volcanism occurred in one enormous pulse, a kind of cosmic burp, that ended three billion years ago.

*LUNAR FAR SIDE was photographed by the* Galileo *spacecraft. The darkish region at the lower left is a scar from a giant meteorite. Photo: Jet Propulsion Laboratory.*

Another intriguing report concerned observations that reveal the moon to have a subtle cometlike appearance. In 1988 researchers discovered that the moon, like Mercury and Jupiter's moon, Io, is surrounded by extraordinarily thin wisps of potassium and sodium; other elements also probably encircle the moon, but these two are particularly easy to detect from the earth.

Most lunar scientists think the moon's tenuous atmosphere consists of bits of the surface vaporized by tiny meteorites, although it may also represent material that diffuses directly from lunar rocks. Because of the kick from the meteorites, the atmosphere is extremely hot, about 1,500 kelvins.

Radiation pressure from the sun appears to sweep away the moon's atmosphere as it is created. Michael Mendillo and his colleagues at Boston University's Center for Space Physics have observed a cloud of sodium atoms around the moon and a sodium tail that stretches at least 25,000 kilometers in the direction away from the sun. The tail, which, sadly, cannot be seen without specially designed instruments, extends more than 10 times the moon's diameter across the sky.

New insights into the history and origin of the moon still lurk in two-decades-old data from the Apollo missions. A close examination of lunar rocks indicates that the moon once had a substantial magnetic field much like the earth's. Scientists think that such a field requires the presence of a molten, electrically conductive core.

The moon's magnetic field vanished some 3.6 billion years ago as the moon cooled off, but signs of the lunar core linger on. Christopher T. Russell of the University of California at Los Angeles presented an analysis of magnetic measurements made during the Apollo missions. From these measurements, he estimates that the moon's core has a radius of about 400 kilometers, distinctly larger than most previous estimates.

A complementary theoretical study of the chemical evolution of the moon by Marc Hirschmann of the University of Washington suggests that the moon's core may be rich in nickel. The presence of so much nickel could create problems for the much publicized theory that the moon formed when a Mars-size object smashed into the newborn earth. Present models imply that a large impactor would release mostly nickel-poor material. "The origin of the moon," Hirschmann says, "is still very much an open question." —*Corey S. Powell*



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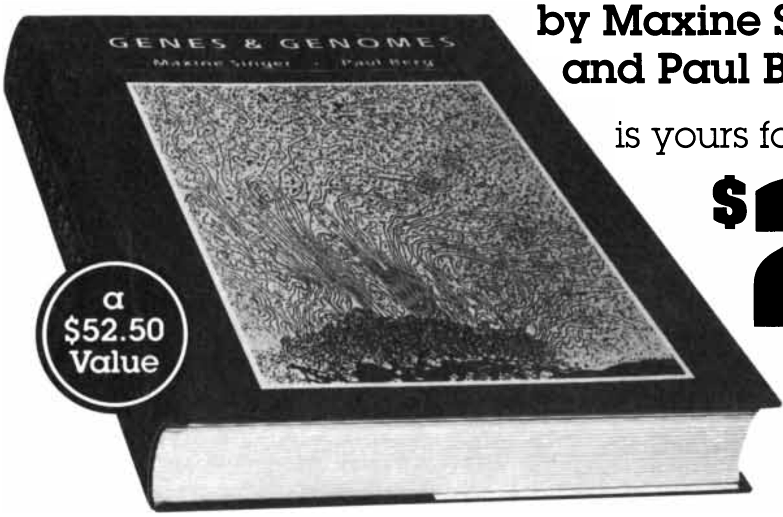


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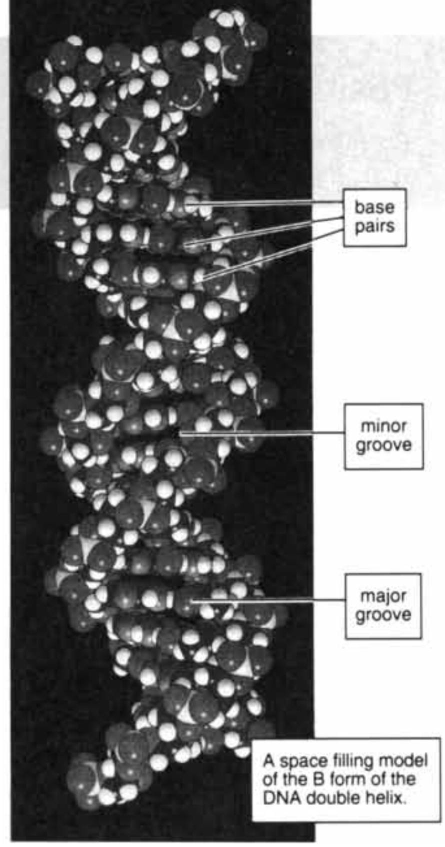


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## Positive Response

*Encouraging results in the search for an AIDS vaccine*

When someone becomes infected with the AIDS virus, the immune system attempts to fight it off by producing antibodies. Usually the attempt is ineffective. The virus keeps on multiplying, slowly destroying *T*4 cells, a key component of the immune system.

Hence the excitement over a report from the Walter Reed Army Institute of Research on a preliminary trial of a genetically engineered AIDS vaccine made by MicroGeneSys, Inc., of Meriden, Conn. In 19 out of 30 volunteers with early-stage infection with HIV, the AIDS virus, the vaccine stimulated not only production of new antibodies but also specific *T* cell responses to the protein used in the vaccine.

The results from the small test of the MicroGeneSys vaccine are the first to show clearly an enhanced immune response in patients. Nevertheless, the researchers and others are quick to point out that the trial was to establish merely that the vaccine was safe and that it had some effect. "By no stretch of the imagination is this a major breakthrough in therapy—we don't know whether it will turn out to be clinically relevant or even effective," says Anthony S. Fauci, the director of the National Institute of Allergy and Infectious Diseases.

Even so, the patients' responses provide substantial evidence that it may be possible to slow the progress of AIDS with a vaccine. Vaccines are usually given to prevent against becoming infected with a disease, not to help those already infected. (Rabies vaccine, which is given to persons who have been bitten by a rabid animal, is an exception.) The idea of postinfection immunization against HIV was suggested in 1987 by Jonas Salk, the inventor of the first polio vaccine. But many researchers thought it unlikely that giving a vaccine to people infected with HIV would have any effect.

The Walter Reed study, which was published in the *New England Journal of Medicine* in June, showed that line of reasoning to be wrong. "One of our hopes is that many of our scientific colleagues who were not enthusiastic about this approach will get actively involved," says Robert R. Redfield, who led the team that performed the trial [see "HIV Infection: The Clinical Picture," by Robert R. Redfield and Donald S. Burke; SCIENTIFIC AMERICAN, October 1988]. Six of the patients who did not respond have completed supplementary vaccinations, and all of them now have enhanced immune responses to HIV, Redfield says.

Fauci says he is encouraged that in those patients whose immune systems responded (generally those given more frequent injections), the vaccine appeared to slow the depletion of *T*4 cells. Patients whose immune systems were in better shape at the start of the 240-day trial responded better than did the others, suggesting that the response was genuine. A larger trial is now in progress to assess clinical benefits.

Researchers have followed two basic approaches in trying to develop an AIDS vaccine. One concentrates on making antibodies against an "envelope" protein that is displayed on the outside of the AIDS virus, known as gp120. This protein binds to a molecule found on *T*4 cells known as CD4, allowing the virus to gain entry to the cells. The other approach targets so-called core proteins: proteins found within the virus and on the surfaces of some infected cells.

The MicroGeneSys vaccine uses an envelope glycoprotein called gp160, which occurs in immature virus particles and is later split in two to make gp120 and another glycoprotein called gp41. Redfield notes that 70 percent of those given the vaccine developed *T* cell responses, which are rarely observed in natural infections. He points out that some of the antibodies produced by the 19 patients who responded to the vaccine recognized parts of the gp160 molecule that do not normally elicit an immune response in persons infected with HIV. Moreover, some of the antibodies resisted several different strains of HIV in laboratory tests.

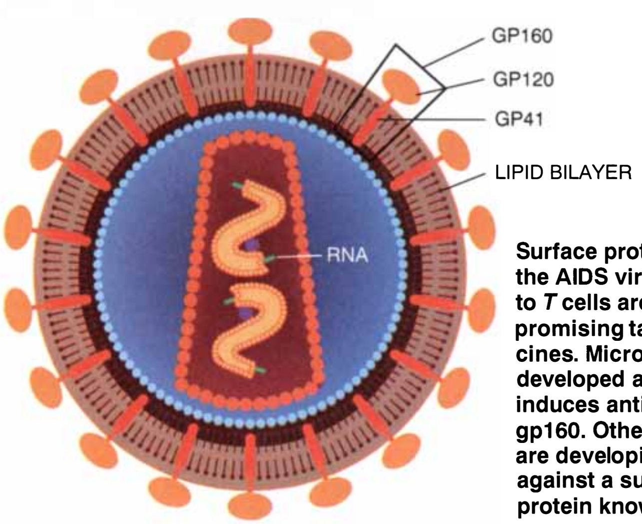
These observations suggest that the engineered vaccine might display the gp160 protein to the immune system in a way that the virus does not. "The observation that you can broaden the antibody response, if it is verified, is quite attractive," notes Jerome E. Groopman, an AIDS researcher at New England Deaconess Hospital.

Numerous vaccine trials are now under way, and more results can be expected in the next two years. Others developing vaccines based on bioengineered envelope proteins include Chiron Corporation and Genentech, Inc. Repligen Corporation and Merck & Company have collaborated to develop a vaccine based on a synthesized fragment of gp120. According to Emilio Ermini of Merck, the vaccine protected chimpanzees from infection with HIV.

A few companies are working on core proteins. MicroGeneSys has developed a vaccine that includes an HIV core protein called p24 as well as gp160. Allan L. Goldstein of George Washington University believes a successful vaccine may need to contain core proteins because they can stimulate the immune system to kill infected cells. Alpha 1 Biomedicals, Inc., which Goldstein founded, has participated in a "very encouraging" trial of a core protein vaccine in uninfected volunteers in London, Goldstein says. The Salk Institute for Biological Studies is testing a vaccine made from killed HIV.

Fauci raises the possibility that if postinfection immunization does prove to be feasible for AIDS, it might help in other chronic diseases. Chronic tuberculosis and leprosy, as well as major killers such as hepatitis, might be amenable to the approach. —*Tim Beardsley*

### How Vaccines May Foil AIDS




**Surface proteins that help the AIDS virus gain entry to *T* cells are proving to be promising targets for vaccines. MicroGeneSys has developed a vaccine that induces antibodies against gp160. Other companies are developing vaccines against a subunit of that protein known as gp120.**



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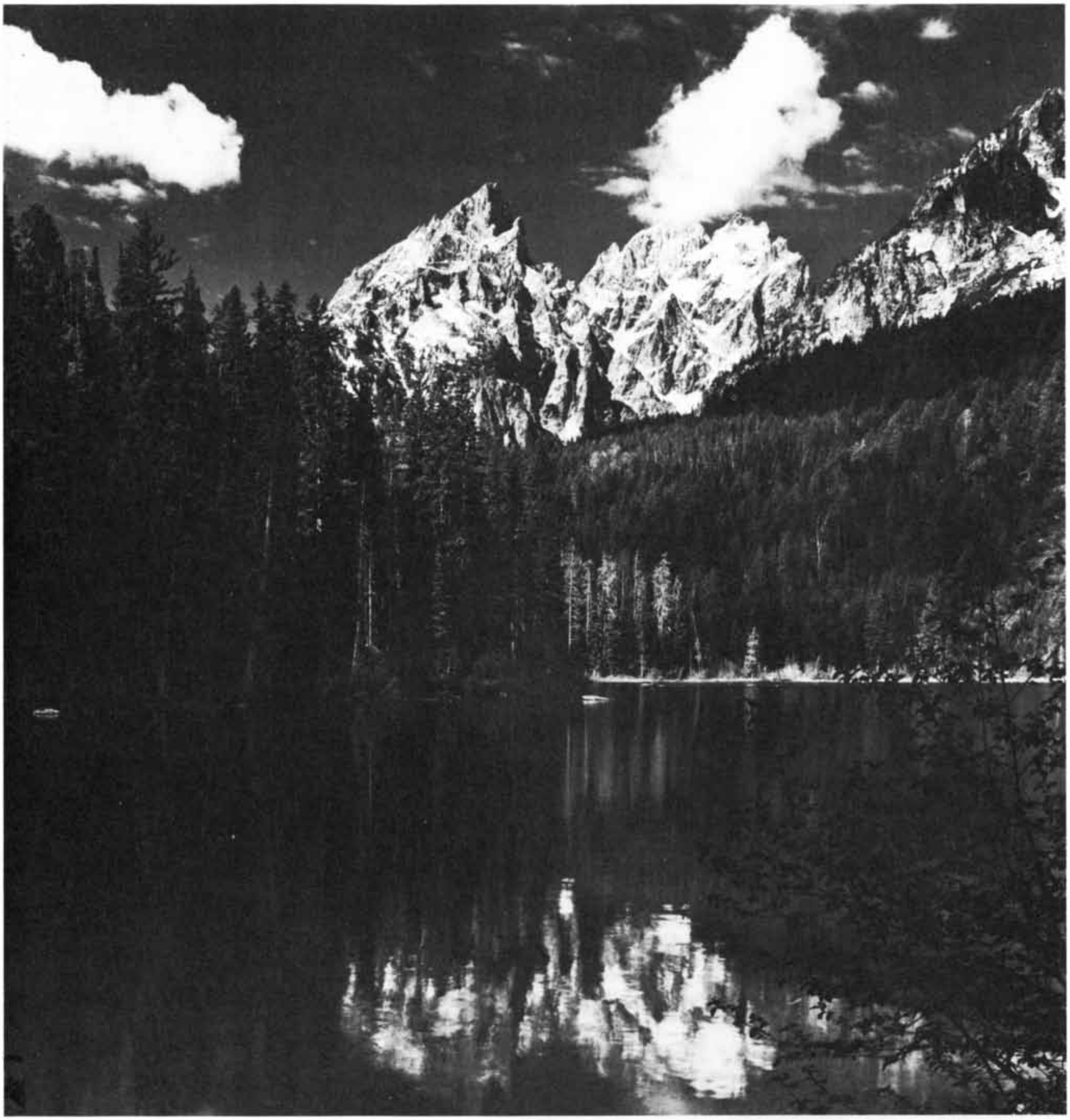

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## Man's Best Friend

*Veterinary research provides clues to human diseases*

Three years ago N. Sydney Moise was making a routine electrocardiogram when her very young patient fell asleep on the examination table and nearly died. The larger cardiac chambers were misfiring—a condition known as ventricular arrhythmia—so she jolted them back into step with a defibrillator. Moise is a researcher at the New York State College of Veterinary Medicine at Cornell University; her patient was a German shepherd.

That unfortunate puppy joins a long list of animal models for human disease that has emerged from veterinary research. The result of Moise's work is a true-breeding line of dogs that can be used to study cardiac arrhythmias, which afflict millions of people. Most intriguing of all, the model may be able to test the hypothesis that such arrhythmias play a role in some cases of sudden infant death syndrome (SIDS), the major killer in the U.S. of infants younger than one year. Through inbreeding, Moise was able to produce puppies predisposed to infantile arrhythmias.

"Our hypothesis is that the distribution of nerves in the heart is abnormal," Moise says. "We will first see if the arrhythmia is exacerbated during sleep. But even if it isn't, this wouldn't negate the importance of the model: cardiac arrhythmias are a major reason why people die in the U.S." Studying them in animals, she adds, may lead to better diagnosis and treatment.

Indeed, many disease models bred to find cures to the afflictions of animals later find application in humans. A drug, ivermectin, which was developed to purge heartworms from dogs, is showing promise against the parasites that cause African river blindness. Another wormer for horses, levamisole, in combination with surgery and conventional chemotherapy has turned out to increase by a third the survival rate of people with advanced colon cancer. Retroviruses were studied by veterinarians long before physicians suspected that the organisms might cause human diseases, such as AIDS and leukemia.

Data gleaned from animal models are often superior to those from human clinical trials. For one, animals take their medicine, whereas humans say they do but often don't. "People typically follow veterinarians' prescriptions more closely than they do their own doctors'," says Fred W. Quimby, director of research animals at Cornell. Animal subjects can also be kept free of all diseases except those that veterinarians want to study. Human patients are often riddled with infections.

Diseases of the immune system, such as AIDS, produce so many opportunistic infections that the cause and effect of each symptom cannot always be identified. Physicians would like to know whether AIDS-related dementia is directly caused by HIV, without the mediation of other organisms. To find out, Quimby says, veterinarians at Cornell and other institutions are studying changes in the nervous systems of cats infected with the feline analogue to HIV.

Animals with exotic syndromes are often donated to veterinary schools, where they found family lines and serve up genetic material for direct biochemical study. Ronald R. Minor of Cornell, Donald F. Patterson of the University of Pennsylvania and their colleagues have studied "stretchy" dogs and cats by such methods. The skin of these animals has only 5 percent of the normal tensile strength. Stretchy skin is rare in humans, as are such other connective tissue disorders as brittle bone disease and Marfan's syndrome (which may have affected Abraham Lincoln).

Normal animals also bring potential medical applications to the attention of veterinarians. This is demonstrated in the panicked reaction of some pet owners to the Lyme disease epidemic. Veterinarians reassured owners that their dogs were quite unlikely to pass the parasite directly to humans and in the process learned that the animals make a splendid model of the disease. Study of dogs with Lyme disease has already produced more sensitive diagnostic tests. "The next step is to improve the specificity of the test," says Richard H. Jacobson, a Cornell immunoparasitologist.

Veterinarians are particularly sensitive to the ethical problems of animal modeling—love of animals, after all, was what brought most of them into the field. But vets point out that their job is not to prolong life but to reduce the suffering of as many animals as possible. Human medicine, they aver, is in many ways more heartless: "We're allowed to give suffering animals euthanasia," Quimby says. "Physicians have to keep their patients alive no matter what the cost." —*Philip E. Ross*

***N. SYDNEY MOISE poses with the progenitor of her animal model for infantile cardiac arrhythmias. Photo: David Grunfeld.***



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## The Reward of Ideas That Are Wrong

The soft-backed chair is too small for him. With his long legs and arms extending at odd angles, Solomon H. Snyder shifts and stretches, crossing and uncrossing his legs while he plays with the Johns Hopkins University I.D. card strung around his neck, moving his hands now across his face, now down to his ankles to pull up his socks. "You've got to be an optimist because you have got to have ideas you are pretty sure are wrong," says Snyder, first picking up and shuffling the coasters on his office coffee table, then stuffing his fingers under his belt as if to keep them still for a few moments. "And, as you know, you have to be relatively relaxed to be enthusiastic."

The only thing that seems relaxed about Snyder, one of the country's most prolific and creative neuroscientists, is his voice. In a near drawl, Snyder discusses his research and his personal interests, while his hands and eyes, perhaps eager to get back to the business of designing experiments, continue to wander.

The 52-year-old researcher is best known for his work in the 1970s on isolating the opiate receptor and the body's own opiates, the enkephalins and endorphins. But Snyder's contributions to other areas of neuroscience, including the development of techniques to study receptors, the elucidation of aspects of neuronal communication and of olfaction, the in vitro cultivation of continually dividing human neurons and, most recently, the discovery of what may be a novel class of neurotransmitters, has kept him at the forefront of the rapidly expanding field.

Like some senior researchers, Snyder clearly prefers thinking up new ideas to the grind of conducting experiments. As a result, the dozen or so students working with him do most of the hands-on research, according to Snyder. He claims that he is a klutz and that leaving laboratory work to his students ensures the success of the experiments. His mentor, Nobel laureate Julius Axelrod, a biochemist at the National Institute of Mental Health, thinks otherwise: "It sounds good; he likes to say that, but he really isn't a klutz."

For his part, Snyder compares research to musical composition and almost calculatingly—as though he wants his interviewer to use the colorful metaphor—describes how music is a recurring theme in his work. His office, which resembles a comfortable living room, is filled with pictures and models of his instrument, the guitar. Although Snyder's parents encouraged him to become a musician, he resisted: "I was more conservative than my mother and father." Instead Snyder wanted to become a psychiatrist. Hoping, he says, to muddle somehow through the science required for his chosen profession, he entered Georgetown Medical School.

*NEUROSCIENTIST Solomon H. Snyder insists that he is just a "klutz." Photo: Chris Usher/Black Star.*

Snyder credits the guitar with leading him to his first research job. At the age of 19, he was giving guitar lessons, and one of his pupils was a scientist at the National Institutes of Health who needed a technician for the summer. Snyder took the job. "I realized that research was not at all like science. Science means you take these measurements and numbers and analyze them—yuk. But research is really creative," Snyder says. "You're discovering, composing."

Several years later, after medical school, Snyder spent a year as an intern in San Francisco, where a personal experiment with the hallucinogen LSD underscored his strong interest in psychopharmacology. Although he reached a state of panic after many hours of the drug's influence, Snyder says the experience made him "realize that there is more to awareness than ordinary awareness and that there are incredible things going on in the brain."

He continues to value drugs as probes to study brain function. "Most of what we know about neurotransmitters comes from the drugs that affect them," he explains. In fact, Snyder sees pharmacological ignorance among many neuroscientists today as a shortcoming in the field. "They are missing a terrific tool."

Snyder himself has wielded these tools with consummate skill. His early fame came from his work on the actions of opiates in the brain. In 1971, during President Richard M. Nixon's war on drugs, the federal government began to fund research to clarify the neurochemical basis of heroin addiction in the hope of finding a cure. Snyder, who had worked in Axelrod's laboratory studying neurotransmitters and the effect of drugs on the nervous system, was by then a professor of pharmacology and psychiatry at Johns Hopkins.

By designing a straightforward experiment, Snyder and Candice Pert, a graduate student, were able to isolate the opiate receptor in 1973. Their work opened up the field of psychopharmacology: it promised the potential of binding receptors to alleviate pain without causing addiction and of treating



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addiction and, perhaps, mental disorders as well.

The technique that the two tailored to study the brain's receptors—reversible ligand binding—is still pivotal to neuroscientific research. Snyder and Pert used opiates labeled with highly radioactive isotopes to bind to the receptor. They then washed the cells quickly so that only the opiates that bound to the receptors remained. With the indiscriminant opiates that stuck loosely to any tissue flushed away, the researchers could then identify the binding sites and characterize the receptor.

Elegant experiments are the key to good research, Snyder believes. "If you can do an experiment in one day, then in 10 days you can test 10 ideas, and maybe one of the 10 will be right. Then you've got it made." He says this approach to research was one of the most valuable ideas Axelrod taught him.

Shortly after the discovery of the opiate receptor, the body's own natural painkillers were identified by John Hughes, now at Parke-Davis in England, and Hans W. Kosterlitz of the University of Aberdeen. Pert and Snyder published the same results several months later, but they had been scooped. In 1978 Snyder, Hughes and Kosterlitz shared the Albert Lasker Award for basic biomedical research for their work on the opiate receptor and the enkephalins.

Pert, who was not so honored, leveled charges of sexism because she was first author on the 1973 opiate receptor paper. Although Pert says she greatly respects Snyder as a mentor, she remains convinced that "there was definite sexism going on. Women are low on the scientific hierarchy and that has not changed."

Snyder shrugs off questions about Pert. "Actually, it was sort of a noncontroversy," he says, speaking in a soft monotone. Snyder lauds Pert's work and matter-of-factly describes how many students and colleagues are involved in every discovery. Citing Axelrod, who won the Nobel Prize in 1970, as an example, he says "it is not unreasonable to say that Dr. Axelrod gets credit for what Dr. Axelrod's laboratory turned out."

Snyder has continued to pursue classical receptor-based research. For instance, his laboratory is now studying the benzodiazepine receptor, the site where valium binds. And in 1982 he and venture capitalists David and Isaac Blech founded the biotechnology firm Nova Pharmaceutical in Baltimore. Although the company has not yet produced any drugs based on receptor technology, Snyder says several such compounds are in clinical trials.

But what most excites him at the moment is an entirely new idea. Snyder explains that he and his students are exploring what may be a new kind of neurotransmitter—one that does not act on traditional receptors. Certain highly reactive chemicals, such as nitric oxide and carbon monoxide, may be more than just common air pollutants. They appear to diffuse from one nerve cell to another to deliver messages, bypassing the classical receptor model.

A decade or so ago nitric oxide was identified in the endothelial, or inner, cells of blood vessels. Originally called endothelial-derived relaxing factor, nitric oxide diffuses from the blood vessel wall to the adjacent muscles, causing the muscles to relax and the blood vessels to dilate, Snyder explains. The compound, which has a half-life of five to 10 seconds in the body, was also found to be the active metabolite of nitroglycerin, a fact that might account for the efficacy of that substance in treating heart disease.

*"If you can do an experiment in one day, then in 10 days you can test 10 ideas, and maybe one of the 10 will be right."*

"We couldn't help but study it," says Snyder of himself and his student David S. Bredt. "I mean, Jesus, it's a new kind of messenger." The two decided to determine whether nitric oxide is made in the brain—an idea that had been suggested by John Garthwaite of the University of Liverpool and Salvador Moncada of Wellcome Laboratories in England—and, if it is, what role it plays.

Again, by devising a simple assay, Snyder says he and Bredt were able to measure levels of a by-product of the creation of nitric oxide, a substance with a much longer half-life than that of nitric oxide. They discovered that nitric oxide is indeed present in the brain and that it binds with iron in an enzyme that makes cyclic guanosine monophosphate (cGMP), a compound involved in the chain of events that occur after a neurotransmitter binds with a receptor. They recently identified specific neurons that produce another enzyme, nitric oxide synthase.

"Who ever heard of a receptor as iron? Iron as a receptor?" asks Snyder, like a comic delivering a line. It is "a completely novel concept in neuronal communication," he says, his hands roaming ever more quickly over his chair, his temples, his hair. "This is the most fascinating thing I have seen in maybe 10 years: a new biological principle about how things act."

Snyder can barely rein in his enthusiasm. Since nitric oxide clearly plays a role in regulating blood pressure, what better candidate for a genetic abnormality responsible for hypertension, he asks. And recently, he notes, his laboratory has found evidence that carbon monoxide may work in a fashion analogous to that of nitric oxide.

Snyder says the idea of looking for nitric oxide in the brain is a perfect example of taking discoveries in other areas of science and applying them to neuroscience, a process he credits as a source of ongoing inspiration along with the insights and ideas of his students. "When I read something about the heart, I think 'Does that fit into the brain?' When I read about cancer genes, I think 'Do they fit into the brain?'" he says. "Some of the finest advances come from jumping fields."

Another recent discovery that for now is not as well understood as nitric oxide is the continued cultivation of human neurons in vitro. Four years ago researchers in Snyder's laboratory obtained cerebral cortex tissue from an 18-month-old child who was undergoing an operation for megalencephaly. Normally, neurons do not reproduce, or divide, but these neurons did and still are, although no one knows why or how. "We've mailed the cells to more than 200 laboratories so far," Snyder says. "They have all the properties of neurons; they do everything that neurons do."

Snyder, enthusiastic but hardly relaxed as he describes his vision, foresees using these neurons for brain transplants. "I mean, all this fuss about fetal brain transplants," he scoffs. Instead a surgeon could just implant these neurons in a certain region of the brain that has been damaged or possibly even ravaged by Alzheimer's disease and watch them grow, Snyder says. He adds that researchers in his laboratory have already done successful transplants in rats and plan to move on to monkeys in the next few months.

The thought of a new, elegant experiment never seems far from Snyder's mind. When asked about a possible connection between the mental impairment that can accompany iron deficiency and the importance of iron in binding sites for nitric oxide, Snyder's hands and eyes suddenly slow down—but his voice speeds up. Out loud, he quickly runs through the biochemical intricacies of iron, nitric oxide and cGMP. "Oh," he muses, "you could test that very easily."—*Marguerite Holloway*



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SCIENTIFIC AMERICAN

# Antiscience Trends in the U.S.S.R.

*A prominent Soviet scientist traces the reasons underlying the current surge in superstitions, cults and antitechnological protests in his country*

by Sergei Kapitza

The recent profound changes in the U.S.S.R. that we associate with *perestroika* and the policies of President Mikhail S. Gorbachev have, strangely enough, released a flood of antiscientific and antitechnological feelings. These public attitudes have found powerful expression in the rejection of nuclear energy in the aftermath of Chernobyl, in the general reaction against technological progress and in numerous manifestations of irrationality and interest in the supernatural.

In understanding these social aberrations, it is important not to confuse the visible symptoms with the deeper reasons for this dramatic change in a society that until recently was purportedly pro-scientific, rational and even "scientifically" designed. These external symptoms are important primarily as signals of the underlying crisis. But they may also be a sobering portent of a more dangerous development, to which I shall return.

To put the current tendencies in Soviet society into perspective, we must understand the magnitude of the transition through which the country is passing. The cold war is over. When war is over, there are the victors and the vanquished. We know who won—Japan and Germany. It is not my purpose here to discuss how the U.S. fared. But the clear loser is the Soviet Union.

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The war was indeed a cold one. If it had been hot, there would not be much to talk about and hardly anyone to listen. Nevertheless, the symptoms of defeat are just as real. Our troops, in humiliation and disgrace, are withdrawing from all fronts. Our former allies and client states have left or are leaving in haste—and going through rapid changes of their own.

The economy at home is in great disarray, with escalating inflation and a corrupt distribution system unable to feed the people. The centrally planned economy is moving toward a market economy, not only because of the expected efficiency of the market but because the centrally planned system was for the most part militarily oriented. Military defeat is one of the main forces spurring economic change.

The crisis is also a political one. The *ancien régime* is falling apart even more rapidly than the economy. The demise of the central authority is leading to an outright threat to the very existence of the Union. In fact, such economic ties as the electric grid, communications, railroads and airlines, all the complex connections of an interdependent and highly industrialized state, hold the Union together more strongly than does the waning power of the central authority. The central government may even have to resort to the last vestige of political power—military force—to save the Union.

We have to admit that, after 70 years of fighting for it, the main goal of the Soviet socialist state is lost. Gone is the grand concept of a socialist and Communist revolution, a great change that would lead to the global spread of these ideas through a worldwide upheaval. This is the fundamental struggle that we have finally lost and the ultimate reason behind our crisis. That is why today we have to demilitarize both our economy and our mentality, evolving toward a democratic society.

The entire concept of world revolution was based on Marxist ideology. Now we see the collapse of this system of ideas as the motive for the policies of the Soviet Union both at home and abroad. This collapse is the real measure of our defeat, the dimension of the historic transition through which we are now passing. In the unspoken laws of the cold war, one admits defeat before being coerced into submission by force, just as deterrence is the way of fighting the war without going to battle.

In the Soviet Union we are gradually becoming if not used to this point of view at least tacitly in agreement with it. Much is still said in support of some of the old ideas. Our military must still succumb to the realities of its new po-



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sition. Attempts are made to salvage what can be saved from the past: much in socialism and in public ownership and planning makes sense and works in many countries.

In this article I will not enter into this debate. What is worth mentioning is that some of the reasons for the Soviet crisis are of a more general nature, especially the use of military power as an instrument of politics. This trend we may see as one of the indications of the crisis of primitive rationality.

Rational issues in public policies and social thinking have existed since ancient times. I will go back only as far as the 17th century, to look into the roots of modern rationalism. The history of modern science—the ideas of Copernicus and Vesalius, Kepler and Galileo, Descartes and Bacon—is an essential part of the development of rational thinking. With spectacular effect, rationality was applied to mechanics. The remarkable success of the celestial mechanics of the solar system was certainly one of the greatest intellectual adventures of all time.

These developments in science, the emergence of capitalism and world trade, the decline of the authority of church and monarchy all happened in Europe at the same time. On all counts it was the great *perestroika* of Europe, the Reformation, with a 30-year war—which ran on for most of the century. During this upheaval, superstitions of all kinds flourished. I will note only that it was then that reportedly 50,000 witches were burned alive or drowned, more than at any other time. As an example of what was going on, it took Kepler extreme effort to save his mother from the stake. The end of a millennium of medieval ideology and a way of life did not pass without these painful indications of social unrest and insecurity. On a lesser scale we see them reappearing in mesmerism before the French Revolution and in spiritualism and "scientific" superstitions during the profound and rapid changes in Eu-


**SIGNS OF THE TIMES. Claims of supernatural phenomena, familiar to tabloid-browsing shoppers in the U.S. and to citizens of other countries, have surfaced in the U.S.S.R., capturing attention and credibility at all levels of society. The description of this photograph provided by the official news agency Tass, for example, tells us that the 10-year-old girl from Soviet Georgia is demonstrating her phenomenal ability to attract metal objects, "from teaspoons to irons," with her hands.**



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**"EXTRASENSORIAL HEALER" (*seated at right*) describes the woman in the print dress as unable to walk on her own when she came to him. After her first session, the healer says, she threw away her crutches; now she can jump as many as 70 times. But, he admonishes, "You can do better than that. You should be able to jump at least 200 times."**

ropean society preceding World War I.

The extent to which outward manifestations of irrationality are socially indicative is also illustrated by the hippies in the U.S. at the time of the Vietnam War. In the summer of 1968, on my first visit to the States, I flew into San Francisco from Sydney. On that very Sunday I was taken to Haight-Ashbury to meet the "flower children."

Superstitions, cults and mysticism appear with surprising consistency during a social crisis. Today it is ESP and UFOs, astrology and clairvoyance, mystic cults and mesmeric healers. The growth of interest in such things is a sure indicator of social unrest, personal uneasiness, frustration and loss of purpose. These symptoms are also present in the West, particularly in the U.S., where they are more chronic; in the Soviet Union, however, we have an acute fever.

Here we must consider the responsibilities of the media. In the U.S.S.R., *glasnost* has brought a remarkable change in public discourse. The whole pattern of social consciousness has changed. Unfortunately, together with all the positive results, forces of the irrational were also unleashed, forces that for so long were contained by the power of central authority and direct censorship.

Are we to publish all the nonsense that is fit to print? What today are the real responsibilities of the media in propagating the antiscientific and irrational? Are we to invite control, or should we rely on a sense of decency on behalf of the producer or publisher? In the case of outspoken violence and pornography, we have recently had a decree from Gorbachev asking the minister of culture to intervene in these matters. But it seems that no one is to protect the public from astrologers and soothsayers. It is interesting to note that at the same time the fortunes of these mystics have risen, the number of popular science magazines and television programs has declined markedly. This change is widespread and unfortunate, and the scientific community should take due action, if only to protect its own interests. For the Soviet Union, the attitude of society toward science and technology is the key to a sustainable future.

In many cases, there is a strong correlation of antiscience and antitechnology trends with publications on sex, violence and extreme social ideas, such as rampant nationalism and fascism. The traditional links between anti-Semitism and anti-intellectual tendencies are also present. These connections may truly signal danger, a threat that goes well beyond the irrational cravings of a fringe group of UFOlogists. Political extremism is what follows when these forces gain ground, and here we have a real menace to the important and welcome changes now happening. Another way of looking at what is going on in the Soviet Union is to say that we are changing from one set of myths to another. The "new" set is not in any way new or reasonable, for we are still in the domain of mythological thinking, the nature of which was explored in the seminal studies of Claude Lévi-Strauss, as a natural stage in the human story.

The regression into mythology in no way signals a new "science," an alternative science as some desire. On the other hand, many of the modern mystical trends try to call themselves scientific, be it Scientology or scientific astrology. Some say that modern science is authoritarian, nondemocratic and remote. The authority of science is based on the power of the scientific method and resides in proof by experiment rather than by pronouncements of the learned or the vote of the people.

The extent of the decay of the state ideology can be well illustrated by the case of Alexander Spirkin. For many years he was the principal philosopher of the Soviet Academy of Sciences, elected as the only alternate member to the chair of dialectical materialism. On this subject Spirkin wrote the standard text-



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book, which went through many editions. In spite of professional adherence to dialectical materialism, Spirkin became well known for his systematic support of ESP, witch doctors, clairvoyance and other modern pseudoscientific stuff. With apparent honesty, he thinks we have to explore these extreme dimensions of the human experience not as an aberration but as the real thing. Professionally and scientifically, however, he is in no way equipped to face these issues.

In the 1990 elections to the Academy of Sciences, the department of philosophy and law voted Spirkin a full member of the academy. The charter of the academy mandates that these primary elections be endorsed by the vote of all members. Happily, it was here that reason won, and Spirkin got 58 votes out of 240. Academician Ivan Frolov, perhaps the only professional and responsible member of the department of philosophy and law, called for its disbandment on account of incompetence. The Spirkin affair shows all the depravity and disgrace of our philosophical establishment. Unfortunately, the Academy of Sciences is not beyond reproach in what it prints. Recently its publishing house, Nauka [Science], released a large number of copies of a book on astrology and is promising more [*see also illustration on next page*]. On the other hand, we do have a vocal and growing number of writers on social matters who are seeking a new set of ideas and values. Apart from economic issues, this quest is the most important one for those who want in a responsible and creative way to help meet the challenges of our present condition.

The origins of the current critical events derive to a certain extent from simplistic, even mechanistic, ideas of social development. Indeed, many of our present social ideas are still dominated by positivist thinking, of which Marxism is perhaps the most pronounced (I hope readers will excuse this oversimplification). What I am suggesting is that the success of the natural sciences, of physics and of classical mechanics in the 17th and 18th centuries set an example for the social sciences and political theories. The ideas and the concepts, even the words of mechanics, dominate the vocabulary of much of social theory, especially in the 19th century. One spoke of social forces, masses of people, energy of nations, and described history as a movement governed by deterministic laws of social development in a causal process. In that same century, the concepts of many-particle systems and of statistical mechanics came into being, but somehow they did not have much effect on social thinking. The economists still prefer to speak of the balance of payments and conservation laws, disregarding that we are dealing with an open and nonequilibrium system where the concept of entropy is just as important as that of energy.

With the arrogance of a "natural" scientist, it is easy to ridicule the "unnatural" scientists for relying so much on the mechanistic concept of history as they try to understand the pattern of behavior of the real world. In the natural sciences, do we not now see a persistent craving for a mechanistic approach in our computer modeling, which promises to lead to magical insights, to forecasting and to resolving the complexities of the world? The computer is superb at handling data. But before using it we must know where we stand and where we want to go. At present, the limitations of human intelligence seem to be greater than the expectation of aid from an artificial one. We should keep in mind that social theory is much more demanding and complex intellectually than all our physics.

In the present political institutions in the Soviet Union, this mechanistic legacy is still powerful and intellectually dominates much of the public debate and performance of our newly born parliament. For that is how this generation of legislators was brought up and educated. One hopes that the next generation will get a more humanly oriented mind-set—and thus it is essential to give some direction as to where to go. Providing this guidance is the challenge for all of us who are engaged in exploring the novel and exciting opportuni-

**MEDITATION SÉANCE was held in the Central Army Sports Club Hall in Moscow in October 1990. The crowd—with the exception of one young skeptic (*at far right*)—concentrates as an Indian healer teaches, according to Tass, "moral self-perfection, self-regulation and self-treatment." The healer's plans include establishing a school in one of the city's clinics.**



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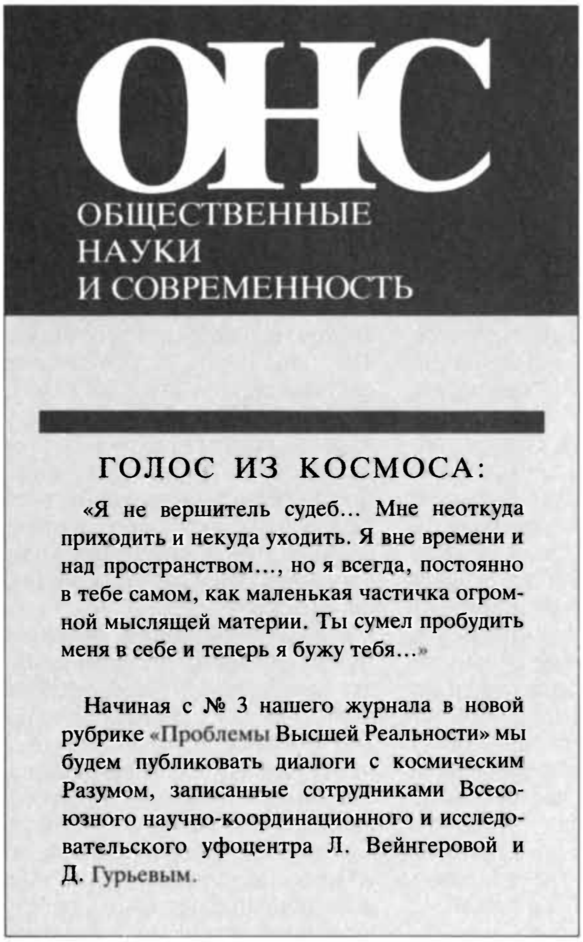

ОНС

ОБЩЕСТВЕННЫЕ НАУКИ И СОВРЕМЕННОСТЬ

ГОЛОС ИЗ КОСМОСА:

«Я не вершитель судеб... Мне неоткуда приходить и некуда уходить. Я вне времени и над пространством..., но я всегда, постоянно в тебе самом, как маленькая частичка огромной мыслящей материи. Ты сумел пробудить меня в себе и теперь я бужу тебя...»

Начиная с № 3 нашего журнала в новой рубрике «Проблемы Высшей Реальности» мы будем публиковать диалоги с космическим Разумом, записанные сотрудниками Всесоюзного научно-координационного и исследовательского уфоцентра Л. Вейнгеровой и Д. Гурьевым.

## SOCIAL SCIENCES AND MODERNITY

No. 1, 1991

### VOICE FROM SPACE:

"I am not an executor of fate.... I come from nowhere and there is nowhere I can go. I am beyond time and space ...but I am always, at all times, with you as a small particle of the great thinking matter. You managed to wake me up in myself and now I am waking you up in yourself—"

Beginning with No. 3, our journal, in its new department "Problems of Higher Reality," will publish dialogues with the Cosmic Mind, as received by the staff members of the All Union scientific coordinating study center for UFOlogy, L. Veyngerova and D. Gur'ef.

**SCHOLARLY JOURNAL published by the Academy of Sciences of the U.S.S.R. bears this message on its back cover.**

ties now open. A demand for new ideas, ideals and even ideology, despite all the negative connotations that last word evokes, is certainly the order of the day. I can hardly agree with those who say, with Francis Fukuyama, that history is finished. The old ideas have run their course, which does not mean they will not go on, now carried by the fundamentalism of various persuasions that is emerging and filling the ideological vacuum. This is an important and real signal of social distress.

One of the main concerns is that we should strive for evolution rather than revolution. Much of the hope of a revolution is the expectation of rapid change, a miracle offering deliverance from all ills through the magic of the new creed. In the past the promise was often religious and moral; now science and reason have become the passwords.

In many cases, this deliverance is the promise of the extremist, of the lone mind, often desperate and unhappy. It is he who challenges the laws of society and science, the conventional wisdom of the established order. And yet without these revolutionaries, these true pathfinders, no progress, however halting, would be possible. That is why we have to be tolerant of all those who want to break into the unknown, even allowing for some of the outright initial craziness and irrationality that we see. We know well that a society that persecutes all dissenters and imposes stability is bound for stagnation and decay. Where, then, are the limits? How much dissent is to be tolerated?

Today the power of political and social extremism is so great that the fragile forces of social order are often not sufficient to counter them. For this reason, the political support and media coverage of antiscientific and irrational ideas can be so dangerous.

A certain "extrasensorial healer" offers a case in point. Anatolii Kashpirovskii has appeared on many occasions on television. For an hour or more, he speaks, persuading the audience that their ills will leave them if they trust him. The medical profession has voiced only feeble opposition, which can in no way countermand Kashpirovskii's huge popularity. On New Year's Eve in 1990, the Communist party newspaper *Pravda* devoted half a page to the support of this "doctor." The same issue contained a detailed and sympathetic report on a seer from India who offers advice on political and personal matters. A few days later the same newspaper supported a woman who has novel ideas on "rotational" gravitation. In none of these issues was there a single item on science and technology. We also see the appearance of various movements of Oriental origin, be they Krishnaites or some other cult.

Because the spread of these ideas is not at all harmless, in 1988 the magazine *Priroda* [Nature] published a set of four papers, giving case studies and comments about these and similar developments. This publication of a scientific and critical nature in a journal founded by Chekhov went practically unnoticed, and now we have a veritable avalanche of the mystical, occult and pseudoscientific. Only Vitalii Ginsburg, the well-known physicist, has written to counter these tendencies, with a good article in *Izvestia*. One can only come



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to the conclusion that powerful irrational forces are at work, perhaps supported by obscure political motives.

So as not to be biased, we should recall Nancy Reagan's astrologer. And in the literature of the recent past we can go back to the treatment of power and mysticism by Leon Feuchtwanger in his 1949 book *The Lautensack Brothers,* depicting life in Hitler's Third Reich. In the more distant past we have the well-known chapters in Gibbon's *The History of the Decline and Fall of the Roman Empire,* which set forth a classic description of the symptoms of a collapsing society and emerging religion.

We may conclude that crises of reason and rationality are a chapter in social anthropology and should be treated as a subject for study, as a *petit mal* of a society, rather than anything else. In which case, the professional detachment of the physician or historian is more appropriate than the attitude of the scientist or journalist personally engaged in this bizarre debate.

Exacerbating the crisis of rationality in the Soviet Union, however, is the antitechnological mood brought on by the effects of Chernobyl. This accident, the largest in nuclear history, has been well publicized. I will note only that as a society the Soviet Union was not prepared technologically and psychologically, perhaps even intellectually, for the realities of the nuclear age. The forces at the command of nuclear technology are so vast that the corresponding social responsibilities and legislative guarantees must be developed. This is the main and very painful lesson that Chernobyl teaches, which makes it more than a mere technological accident.

We now see widespread reaction to this disaster. The major consequences of Chernobyl are direct and indirect losses to public health and well-being. Physicians are not sure what causes more suffering and unhappiness—radiation or fear of it. We also have to note the loss of public confidence in science, scientists and even the medical profession. Initially much was done to play down the magnitude of the event and even to mislead the public about the actual consequences: the coming of nuclear *glasnost* has been long and painful. Can we blame the public for the widespread resentment toward nuclear energy? And yet this resentment has led to a full stop of all new nuclear power stations.

The protest, even revolt, against nuclear testing in Kazakhstan is significant. It has become a major public issue that makes it practically impossible to go on testing in that nuclear-ridden republic. Conditions at the northern test ground at Novaya Zemlya are not much better for the bomb makers.

In a sense, these reactions against testing are benign. The nuclear testing issue as a whole is the result of the utterly monstrous and irrational accumulation of nuclear weapons as the outcome of the arms race. It is an issue of its own, going well beyond these local protests. One may even say that the arms race is a global demonstration of the mechanistic hope for a technological fix for social problems. Here the proof of the futility of power has been reached at too great a cost for all parties concerned.

**"SCIENTIST DISCOVERS BIOLOGICAL UHF" reads the caption line on this photograph from Tass. The Chinese-born scientist sits inside the ultra-high-frequency "biological electromagnetic plant" he has built in the basement of his apartment house.**

In the Soviet Union, outspoken movements against technology are not limited to things nuclear. In Moscow, public protests have halted construction of a large power station that was to be fueled by natural gas. The consequences may be grave, and the time scale of such decisions and the loss involved are immense.

Demands of the growing environmental movement have closed many metallurgical, chemical and biochemical plants. Long-term delays in industrial development may be the consequence. The prime minister has issued a strong warning on these matters. I am not sure who is right—the technocratically minded government, which did not recognize the environmental dangers, or the ecologists, who are at a loss as to how to face the pressures of the industrialized world. The result may be a general further decline in the standard of living.

The controversy between the rational that has become wrong and the irrational that is partially right but basically wrong is certainly best seen in science. Some years ago I conceived the idea of a public dialogue between an astronomer and an astrologer. The astronomer was the leading authority on the sun. For him, the important enigma was the discrepancy in the number of neutrinos measured from the sun and the flux of energy observed. In other words, he was not sure why the sun shines. This expert but hesitant scientist would certainly have lost in a debate with a slick astrologer whose powers of persuasion are the main source of his living, as a member of an ancient profession. I will remind you of the classic debate between Bishop Samuel Wilberforce and Thomas Henry Huxley. The great protagonist of evolution won more by his famous remark linking his origin to that of an ape than by scientific reasoning. Public debate is a powerful didactic device in science, but the professional discussion is usually carried out with little publicity and follows the established procedure of science. The case of cold fusion shows what can happen when this procedure is not observed.

Carl Sagan of Cornell University has told me that in the U.S. there are 15,000 astrologers and only 1,500 astronomers. On the other hand, Kepler, one of the foremost astronomers, was a practicing astrologer, having written three horoscopes for himself. In his horoscope Kepler notes that he was conceived on May 16, 1571, at 4:37 A.M. and born on December 27 at 2:30 P.M., after 224 days, nine hours and 53 minutes of pregnancy. And today our very popular and progressive *Young Com-*



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**CENTER FOR FOLK MEDICINE recently opened in a Moscow hospital. Tass reports that "now specialists in...unconventional medicine may at last give legal and open treatment," and thousands are on the center's waiting list. Among the center's sponsors is the city's Department of Health Protection.**

*munists of Moscow* newspaper gives in its daily horoscope detailed advice as to the proper hours for sexual activities. Astrology on all counts is both an exact and practical science!

It should be noted that with the comeback of traditional religion as a messenger of morals, we still have not built up the rational equivalent of these pressing issues left in the ashes of the totalitarian state ideology. It is fascinating that in the Soviet Union we are importing creationism from fundamentalists in the U.S. After decades of Darwinian indoctrination, we have our own creationists of a religious, rather than a Lysenkoist, persuasion.

The profound interest in the unknown, be it our personal future or the behavior of distant planets, has led humankind to the myriad discoveries of science. Can we really find blame because these inherently human trends are sometimes misguided and are hardly ever as direct and logical as they may seem later to the rational mind?

Today more than at any other time we should give attention to propagating the message of science and developing social attitudes toward matters scientific. And yet we cannot in a direct way fight the antiscientific trends. They are symptoms of a malaise lying at deeper levels, and social maladjustments are not so simply treated. A sustained and systematic effort in propagating science as part of modern culture is critically important for the future, for the generations yet to come, rather than for those who are here now.

With the emergence of symptoms of the crisis, seen in art and other expressions of the public mood, we must always ask to what extent they reflect a social phenomenon and to what extent they may be responsible for propagating these issues. In a fundamental way, this is what determines the ultimate responsibility of those who control the media and the artist or writer whose influence may be broadcast. In other words, should you stop Hitler by not publishing *Mein Kampf?* Could you?

I do not want to say that I offer a solution to such problems. Yet one cannot but think in these terms, especially at a turbulent period of critical change when causes and consequences are all mixed up.

What must deeply concern us are the limits to which this tendency may develop. Recently, following the demise of official Soviet ideology, attempts have been made to introduce the humanities into the curricula of our scientific and technical universities. At the Moscow Institute for Physics and Technology, on the initiative of the rector, Nikolai V. Karlov, a systematic effort has been made to offer lectures and courses on the history of culture, on religion and art and on the history of science and civilization. Critics ask what such courses contribute to training. The answer is that what really matters is education. Unfortunately, the importance of education is not properly appreciated, and it is this very lack of appreciation that ultimately led to Chernobyl.

The momentous changes happening now in the Soviet Union are the reason for this current upsurge of the irrational. What is important is the emerging extremism that they may signal. That is the real danger, one of our more observant social thinkers and writers has pointed out. Unfortunately, in the past, many intellectuals have supported the belief that the extreme may be right in public life just as it is in art and science. With the importance and responsibility of modern science and technology, we see that this simplistic attitude is not sufficient to resolve the issues at stake. In a basic way, we are once again looking at the fundamental disparities between our cultural experience and our technological civilization, between being and having. An age-old dilemma of the human predicament, it is now appearing in a new and less familiar way.

I can only hope that good will prevails. The price that the Soviet Union has paid in the past to the demands of vulgar and egalitarian rationality is so enormous that we may understand, if not excuse, the current outburst of irrationality.


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# Colliding Galaxies

*Violent encounters between galaxies appear surprisingly common. Computer models and observations indicate that these cosmic collisions may form elliptical galaxies and activate quasars*

by Joshua Barnes, Lars Hernquist and François Schweizer

Galaxies, like people, are social: they tend to gather in pairs, small groups and even large crowds. The Milky Way, for example, belongs to the so-called Local Group, as do the well-known Andromeda Galaxy and some two dozen lesser companions. In most such aggregates, galaxies are separated by large distances, typically 10 to 100 times their own diameters. Yet under the influence of gravity, these galaxies travel a galactic diameter every few hundred million years. Over the lifetime of the universe—10 to 20 billion years by most cosmologists' estimates—some galactic collisions are inevitable.

A decade ago many astronomers had serious doubts about the frequency or import of galactic collisions. But recent observations, combined with advances in theory and greatly improved computer models, have demonstrated that collisions must be far more common than previously thought. Moreover, mounting evidence suggests that colliding galaxies often merge into a new kind of object. We have become increasingly convinced that such collisions control the evolution of many galaxies and lead to the formation of a variety of peculiar objects, possibly including the distant and extraordinarily luminous quasars.

JOSHUA BARNES, LARS HERNQUIST and FRANÇOIS SCHWEIZER were drawn together by a shared fascination with interacting galaxies. They concocted the idea for this article while attending the 1990 Theoretical Astrophysics Workshop at the Center for Physics in Aspen, Colo. Barnes obtained a Ph.D. in astronomy from the University of California, Berkeley, in 1984. He recently joined the Institute for Astronomy in Honolulu, Hawaii, as an associate astronomer. In his spare time, Barnes has been known to attend Grateful Dead concerts. Hernquist received a Ph.D. in physics at the California Institute of Technology in 1985. He is currently professor of astronomy at Lick Observatory at the University of California, Santa Cruz. Schweizer earned his Ph.D. in astronomy from Berkeley in 1975. For the past decade, he has been a staff member at the department of terrestrial magnetism of the Carnegie Institution of Washington.

Interactions between galaxies are quite unlike those between everyday objects. Distances between stars in a galaxy are so great that very few stellar collisions actually take place even in the most violent galactic encounter. In some large clusters, pairs of galaxies approach each other at very high velocities—thousands of kilometers per second—and yet pass right through each other, suffering almost no damage.

Oddly enough, if the same galaxies were to approach at a velocity of only a few hundred kilometers per second, they would violently disrupt one another and probably would merge within a few hundred million years. Such seemingly paradoxical behavior reflects the fact that galactic interactions are governed by gravitational forces. The slower an encounter between two galaxies, the more time there is for gravity to produce huge, disruptive tides and the greater the resulting damage.

The twice-daily rise and fall of the ocean illustrates the nature of tidal forces. Ocean tides result from the fact that the side of the earth nearer the moon feels a stronger gravitational attraction than does the earth overall, whereas the opposite side feels a weaker attraction. As a result, the waters on the near side are pulled toward the moon, and those on the far side draw away (that is why there are two tides every day). Similarly, a galaxy in the gravitational field of a nearby companion develops extensions of both its near and far sides.

Tides between galaxies are much more disruptive than terrestrial ocean tides because galaxies pass much closer to each other, relative to their size, than do the earth and moon. If the moon orbited the earth at half its present distance, the gravitational force it exerts would increase by a factor of four, because gravity is inversely proportional to the square of the distance. But the *difference* between the forces on the near and far sides of the earth, which is what determines the height of the tides, would increase by a factor of eight. In other words, tidal forces are inversely proportional to the cube of the distance. In close collisions the tidal forces between a pair of galaxies can be strong enough to rip both apart.

Peculiar galaxies surrounded by narrow extended features, called bridges and tails, have been well known since the 1950s. For a long time, these objects were considered to be aberrations, and most astronomers did not think of galactic collisions as commonplace phenomena. A series of developments, involving better observations and more complete understanding of galaxy dynamics, is changing that view.

In 1983 the *Infrared Astronomical Satellite* (*IRAS*) provided surprising evidence of the widespread effects of galactic collisions. While surveying the sky at wavelengths of 25 to 100 microns (typical of the infrared radiation emitted by warm gas and dust clouds), *IRAS* discovered scores of galaxies that shine far brighter in the infrared than they do at visible wavelengths.

These galaxies appear to be experiencing intense bursts of star formation that release large amounts of infrared energy. Collisions or mergers between galaxies seem to provoke the sudden rash of stellar births. Indeed, many objects identified only on the basis of their conspicuous infrared brightness in low-resolution *IRAS* maps appear, on closer examination, to be interacting galaxies.

Increasingly sensitive observations made at visible wavelengths have also shown that even some apparently featureless and quiescent elliptical galax-



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ies exhibit signs of previous mergers. In 1979, while trying out new image enhancement techniques on photographic plates, David F. Malin of the Anglo-Australian Observatory in New South Wales found gigantic, faint shells of luminous matter surrounding otherwise normal-looking elliptical galaxies.

This discovery astonished many astronomers. Ellipticals were known for their smooth light distributions. Moreover, the large random motions of the stars within an elliptical galaxy should wash out any incipient clump or organized feature in approximately one hundredth the age of a galaxy. Shell-like features had previously been noticed only around a limited class of suspected merger remnants.

Astronomers immediately proposed several mechanisms to explain the presence of shells, including shock waves created by a galactic wind, huge galactic explosions and the accretion of stars through galactic mergers. Only the last hypothesis has stood the test of time. Shocks or explosions would be expected to create shells of gas and hot, young stars. The colors and spectral characteristics of the shells indicate, however, that they are predominantly composed of stars a few to 10 billion years old, much like those found in the disks of spiral galaxies.

The sharp edges of the shells signify that their constituent stars do not partake in the large random motions within ellipticals. These stars must therefore have originated in galaxies having relatively small internal random velocities. Only models that include stars captured from well-ordered galaxies seem capable of explaining the striking geometric patterns surrounding such galaxies as Arp 230 and NGC 3923.

Other studies of elliptical galaxies have found additional signs of recent merging. In some ellipticals, for example, the central region rotates in one direction, while the outer parts spin the other way. Such a counterveiling rotation pattern would be difficult to explain if these galaxies formed all of one piece but could come about quite naturally from a merger. Indeed, one of the first observed examples of a counterro-

**TIGHT-KNIT GROUPS of galaxies that are gravitationally bound to one another are likely to undergo extensive interaction. The above computer model began with six independent galaxies. As the simulation continues, two pairs of disk galaxies now tidally disrupt one another, sending out long tails of gas and stars. Eventually all six galaxies will coalesce into a single object. Such group interactions may be one mechanism by which large elliptical galaxies form.**



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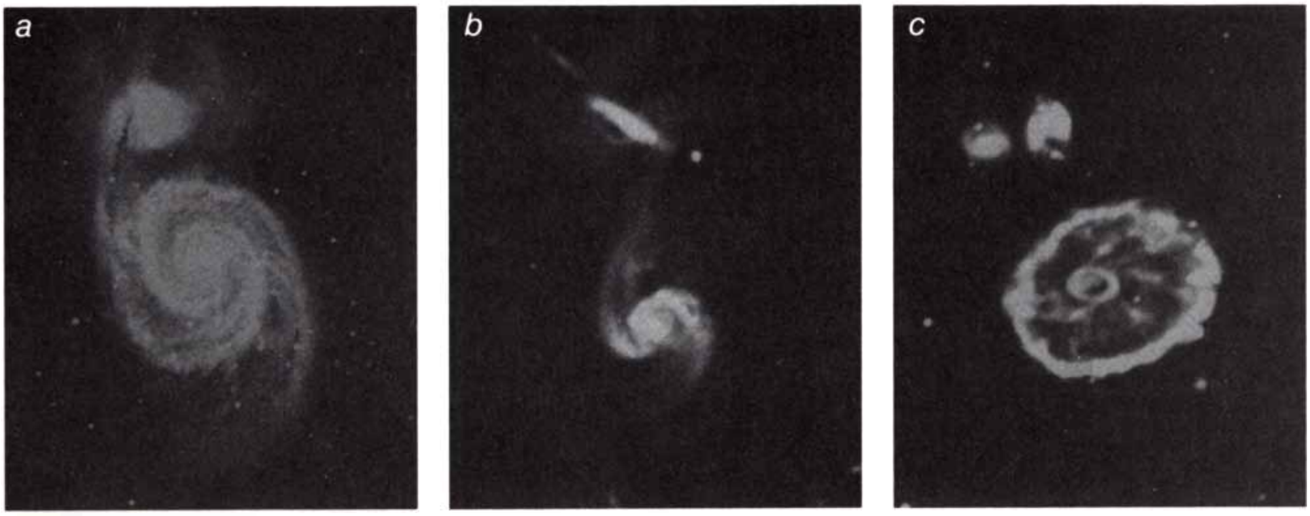



**GALACTIC COLLISIONS produce a remarkable variety of intricate structures. The beautiful spiral pattern of the Whirlpool Galaxy, or M51, resulted from the close passage of its small companion galaxy (*a*). In the system NGC 3808, stars, gas and dust are flowing from the large spiral galaxy to its companion (*b*). Two rings of stars formed in the Cartwheel Galaxy after one of its companions plunged straight through the main disk (*c*). Collisions between galaxies of similar mass-**

tating galaxy was the merger remnant NGC 7252.

Shells should remain visible for at least a few billion years, which would make them more persistent markers of merger activity than the more obvious tidal features. We and our colleagues have found faint shells around nearly half of all ellipticals observed to date and even around some disk galaxies that have large central bulges. The prevalence of shells suggests that collisions among galaxies must be relatively widespread.

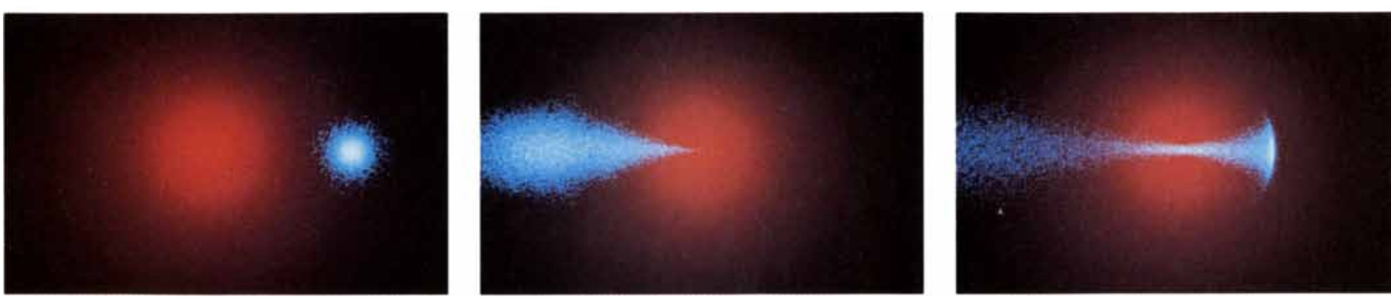
Advances in the understanding of galactic structure have bolstered that notion. Researchers have discovered that the dynamics of galaxies are determined not only by visible, luminous stars and gas clouds but also by halos of unseen "dark" matter that seem to represent a major fraction of a galaxy's total mass [see "Dark Matter in Spiral Galaxies," by Vera C. Rubin; SCIENTIFIC AMERICAN, June 1983]. Dark matter reveals its presence only by its gravitational effects and is otherwise invisible.

The presence of dark matter implies that galaxies are perhaps 10 times larger and more massive than they appear to be, greatly increasing the likelihood of encounters. Moreover, during a close approach, dark halo material carries off large amounts of angular momentum, making it easier for the galaxies to fall into one another and merge.

Even as observational evidence that galactic collisions are commonplace has accumulated, computer models have helped illuminate exactly what occurs during such encounters. Pioneering models developed in the early 1970s by Alar Toomre of the Massachusetts Institute of Technology and Juri Toomre, then at New York University, showed that long, filamentary structures develop naturally when a thin, rotating disk of stars is subjected to strong tides from a nearby companion [see "Violent Tides between Galaxies," by Alar and Juri Toomre; SCIENTIFIC AMERICAN, December 1973]. Tidal forces yank stars from the near side of the disk to form a bridge (which, despite the name, seldom actually connects to the other galaxy), whereas stars from the other side shear off to form a far-flung tail.

Depending on the type of galaxy and on the geometry involved, collisions can also produce spiral arms, masses of debris circling perpendicular to the plane of the galaxy, stellar and gaseous rings and all kinds of luminous filaments and appendages. Particularly intriguing are some galaxies that exhibit the telltale tidal signatures of two colliding partners despite the presence of only one messy body of stars.

Comprehending the origin and fate of interacting systems requires simulations far more elaborate than the Toomres' early models. In the examples shown here, each galaxy is modeled as 44,000 mass points, some representing the dark matter, others the stars or gas [*see illustration on page 44*]. The computer calculates the motion of each mass point as it moves under the combined influence of the grav-



**ORDERLY SHELLS of stars around elliptical galaxies may be artifacts of collisions. In this sequence from a computer simulation, a small, initially spherical galaxy (*blue*) is disrupted by the gravitational field of a larger elliptical galaxy (*red***



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**es tend to destroy the original structures of both objects. The Antennae (*d*) consist of two disk galaxies whose gravitational interaction has flung off two tails, each several hundred thousand light-years long. In NGC 520, the two colliding galaxies appear thoroughly intertwined (*e*). Such an encounter eventually evolves into a single messy-looking merged galactic mass like NGC 7252 (*f*), which may eventually settle down to become an elliptical galaxy.**

itational field of all the other points. Such elaborate simulations have become possible only with the advent of efficient software programs and powerful supercomputers.

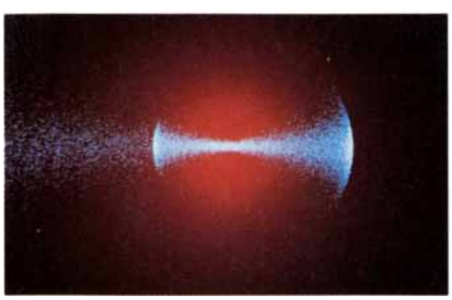
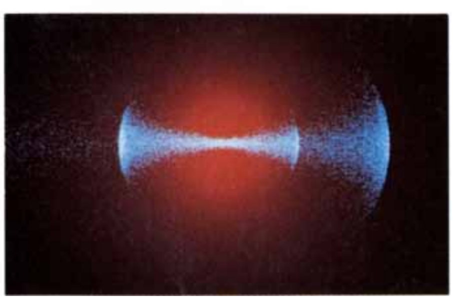
One of the most significant findings from our new models is that interacting galaxies have a very strong tendency to merge. For example, we simulated two galaxies approaching each other at velocities acquired by falling toward each other from a great distance. Common sense might suggest that such velocities should carry the objects about the same distance apart after their encounter. What actually happens, however, is quite different. The galaxies become trapped in tight orbits around each other, collide a second time and then coalesce, a process that takes a few hundred million years.

Researchers had anticipated that tidal effects would produce orbital decay, because each galaxy is attracted to the tidal features it induces in its partner. Nevertheless, few astronomers fully appreciated the fierceness of orbital decay produced by typical galactic encounters. The speed with which the orbits decay is largely caused by the gravitational interaction between the extended halos of dark matter surrounding these galaxies.

In the early 1980s computer models developed by Peter J. Quinn of the Australian National University confirmed that the shells seen around many galaxies could be the aftermath of mergers. His models showed that tidal forces distort and eventually destroy companion galaxies that collide with their larger neighbors. Because of the loss of orbital energy, much of the debris will be captured in tightly bound orbits around the more massive galaxy. Provided the internal random motions within the companion are small to begin with, the debris will retain much of its original order for some time. In this way, the stars captured by the more massive galaxy can form large, ordered structures.

If the infalling companion is a flattened disk, the gravitational field of the more massive galaxy tends to bend and to fold it into a curved surface. As seen from the earth, the edges of the surface appear relatively thick and therefore bright. Each time the companion wraps around the primary galaxy, it produces another thin, curved region of stars and a new associated shell.

No real galaxy is perfectly thin, of course. Computer models show that the small random motions responsible for the thickness of real spiral galaxies may blur the shells somewhat, although their essential appearance will survive. Even debris from small spherical galaxies can form shells in our simulations, as can mergers of equal-sized partners. The degree of blurring depends on the structure of the smaller victim galaxy, and so observations of shells can in principle be used to constrain the properties of the galaxies from which they formed. The variety of shells generated in computer models appears sufficiently diverse to account for the shells observed around elliptical galaxies.


***area*). Stars from the small galaxy form a series of semicircular shells that become fainter but more numerous with time. Similar shells are observed around many real galaxies, such as NGC 474, shown here in a false-color image (*far right*).**



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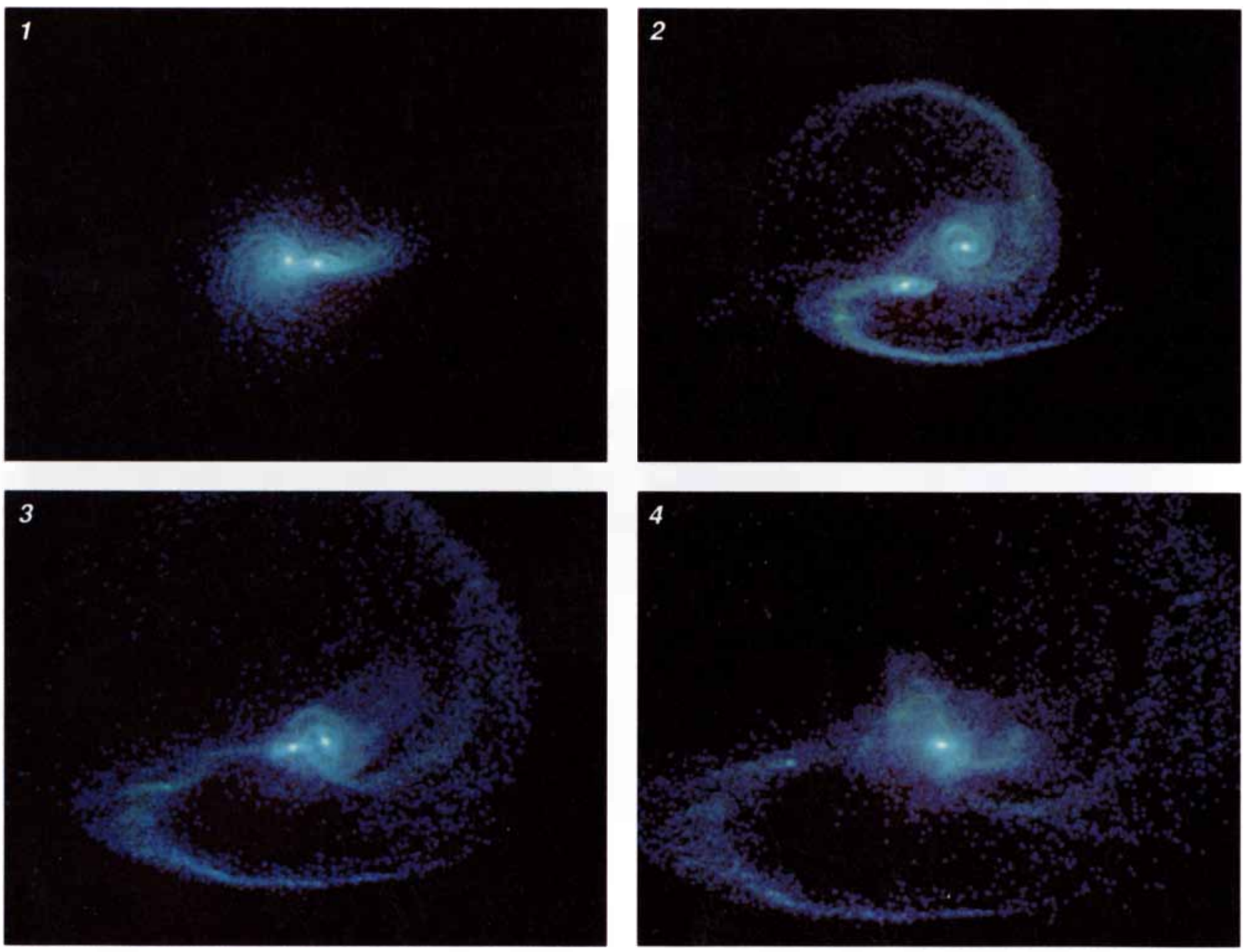
Modeling has also provided insight into the nature of a class of peculiar galaxies known as starburst galaxies. These objects were first identified by their distinctive colors. In 1978 Richard B. Larson and Beatrice M. Tinsley of Yale University showed that interacting galaxies tend to be bluer than average. These "blue" galaxies (the colors are actually quite subtle) owe their hues to the presence of large numbers of recently formed stars. Larson and Tinsley concluded that interacting galaxies undergo bursts of star formation lasting up to 100 million years, or about 1 percent of the age of a typical galaxy. As interacting systems age, their colors seem to fade gradually back to normal.

Stars form within massive clouds of dust and gas. These clouds absorb much of the visible light emitted by bright young stars and reemit the energy as longer-wavelength infrared radiation. Observations at infrared wavelengths might be expected to reveal otherwise hidden sites of star formation. Even so, it came as a shock when *IRAS* revealed a class of galaxies that emit as much as 99 percent of their energy in the infrared. Optical photographs showed that many of these galaxies are interacting systems surrounded by tails and bridges drawn out by nearby companions; others appear to be full-fledged galactic mergers.

The large amount of infrared radiation emitted by such galaxies implies that stars form at a prodigious rate. In some starburst galaxies, hundreds form every year, compared with an average of two to three a year in the Milky Way. The region where stars form rapidly is usually concentrated in a central part of the galaxy, which is often less than one tenth the diameter of the galaxy as a whole. Radio telescopes operating at millimeter wavelengths have detected vast clouds of gas at the center of many infrared galaxies. These clouds are sufficiently massive to fuel the observed rapid star formation for periods of several hundred million years.

Astronomers studying starburst galaxies naturally wondered where the central gas clouds come from. The total amounts of gas involved are comparable to the quantities found in typical spiral galaxies. But squeezing all of a galaxy's gas into a small central region poses a difficult problem. Conservation of angular momentum forces a rotating gas cloud to spin faster as it contracts. The faster the rotation, the greater the centrifugal acceleration that prevents the gas from falling inward. The gas distributed throughout the Milky Way, for example, already spins fast enough to balance out the gravitational forces pulling it toward the center. The gas therefore could not collect at the middle of our galaxy unless some kind of brake were to retard its motion.

Computer models solved this puzzle by showing that the necessary braking can occur during galactic interactions. As tidal forces deform a disk galaxy, stars and gas no longer move in unison.




**COMPUTER-SIMULATED ENCOUNTER between two spiral disk galaxies, generated at the Pittsburgh Supercomputing Center, illustrates how gravitational forces can transform these objects. As the galaxies approach each other, gravitational tides create long bridges and tails. After a second passage, the galaxies begin to merge. Each galactic disk (*blue-green*) is surrounded by a halo of dark matter (*red*) that plays an important role in the gravitational interaction of the two objects.**



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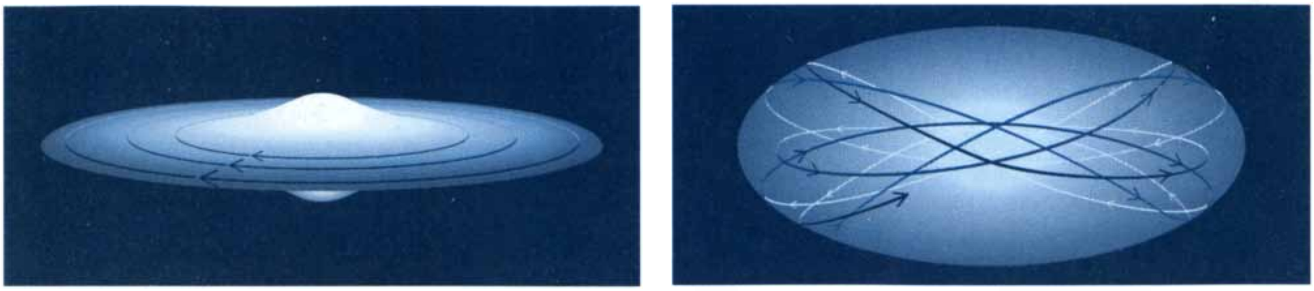

**SPIRAL AND ELLIPTICAL GALAXIES exhibit very different structures. In disklike spirals, stars move around a common center in approximately circular orbits that all lie in nearly the same plane (*left*). In ellipticals, there is no planar structure, and a significant fraction of the stars shuttle to and fro in orbits along the galaxy's long axis (*right*).**

Streams of stars in the disrupted galaxy freely interpenetrate one another. Flows of gas, however, interact strongly and create a spiral pattern of intense shock waves. The gravitational force of the stars tends to steal angular momentum from the shocked gas clouds, forcing the clouds to collapse inward.

Later, when two galaxies begin to merge, the gas remaining in the disks may collide at speeds of several hundred kilometers per second, creating huge shock fronts. Some stars undoubtedly form directly from the gas compressed in such shocks. But much of the gas, having already collected at the center of each galaxy, winds up at the center of the merged pair, where it may fuel a much larger burst of star formation.

Observations of the most infrared-luminous galaxies hint that the radiation comes not only from star-forming regions but also from a compact central source, possibly powered by material falling into a massive black hole. Black holes having masses as great as one billion times that of the sun are thought to be the central engines of quasars, some of the most distant and luminous objects in the universe [see "The Quasar 3C 273," by Thierry J.-L. Courvoisier and E. Ian Robson; SCIENTIFIC AMERICAN, June].

In isolation, a black hole gives no visible indication of its presence. But matter that comes close to the black hole will eventually spiral in, growing extremely hot and radiating powerfully before it vanishes forever. The central gas clouds created in mergers of disk galaxies may provide a source of fuel that activates the black hole.

Some nearby quasars do in fact appear to be interacting or merging systems. Galactic collisions are also often associated with various other kinds of active galaxies, including Seyferts (which appear to be miniquasars embedded in disk galaxies) and radio galaxies (ellipticals that are surrounded by enormous regions of radio emission). Many astronomers think these energetic objects are all disturbed galaxies in which matter flows into large central black holes. Quasars, Seyferts and radio galaxies seem to differ largely in the mass of the central black hole and in the rate at which matter falls into it.

The collapse toward the galactic center of gas clouds that sets off the observed bursts of star formation is insufficient to bring the gas into the vicinity of a central black hole. To be consumed by a central black hole of one million solar masses, the gas must contract by an additional factor of 10 billion. Once again, the angular momentum of the gas presents a barrier to its contraction.

More detailed computer simulations will be needed to understand the braking mechanisms that could enable the gas to fall all the way into the center of the galaxy, where the black hole lies. Nevertheless, the theory of galactic collisions promises to lead to a unified model that explains the observed characteristics of a wide range of active and peculiar galaxies.

Galactic collisions may also explain the origin and evolution of a much more common, if less remarkable, class of objects—elliptical galaxies. Ellipticals are an important class of galaxies, only a little less prevalent than the more photogenic spirals; the manner in which ellipticals form is a major open question of astrophysics. Ellipticals occur throughout the universe, but they tend to congregate in huge clusters having up to 1,000 members. They range from giant systems 10 times more luminous than the Milky Way to faint dwarf ellipticals, such as the satellites of the nearby Andromeda Galaxy (M31), that have as little as one hundredth the luminosity of our own galaxy.

Ellipticals are fundamentally unlike spirals. Spiral galaxies are disk-shaped objects, are generally rich in gas and contain many young stars in their outlying regions. Ellipticals, on the other hand, are almost featureless conglomerations, possess only trace amounts of cool interstellar gas and contain few if any young stars. The bulk of their light is emitted by stars estimated to be at least several billion years old. The dynamic distinction between ellipticals and spirals is quite simple. The orbits of stars in disk galaxies are highly ordered, and all lie in more or less the same plane; the constituent stars in elliptical galaxies move in random orbits.

Guided by this basic distinction, the Toomres suggested in 1972 that elliptical galaxies are the merged remnants of disks that collided. This merger hypothesis immediately proved controversial. The notion seemed plausible that the strongly fluctuating gravitational fields produced when two galaxies collide and merge could randomize stellar orbits, resulting in a disorganized accumulation of stars. At the time, however, there was no proof that the products of mergers would resemble elliptical galaxies in detail. Moreover, many properties of ellipticals could also be explained by the then more conventional hypothesis that such galaxies formed from slowly rotating clouds of gas, which cooled and collapsed within one or two billion years after the big bang.

To back up their hypothesis, the Toomres noted that disk galaxies of equal size merge relatively often in cosmic terms. Given the age of the universe, the number of mergers could total a significant fraction of the number of ellipticals. As a test, the Toomres examined a sample of 4,000 galaxies. They found 11 objects exhibiting either a pair of tails extending from a single messy-looking body or a pair of disks in a close and violent interaction. The former appeared to have merged within the past 500 million years, whereas the latter seemed likely to merge before another 500 million years pass.

If disk galaxies have been merging at the currently observed rate for 10 to 20



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billion years, one would expect to find at least 100 merger remnants among the 4,000 galaxies. In fact, the sample used by the Toomres contains about 400 ellipticals. If the merger rate had been only modestly higher in the past, galactic collisions could account for all elliptical galaxies. Conversely, if merger remnants were *not* turning into elliptical galaxies, then where were they?

Meanwhile improved understanding of the dynamics of elliptical galaxies offered a better understanding of how they might be produced by mergers. Astronomers had long assumed that overall rotation of some ellipticals accounts for their oval shapes. But in 1975 Francesco Bertola and Massimo Capaccioli of the University of Padua reported that the giant flattened elliptical NGC 4697 rotates with a maximum speed of only 60 kilometers per second. Apparently the distribution of the stellar orbits rather than the galaxy's rotation produced the flattening. Mergers might be able to create such asymmetric stellar distributions, a possibility that encouraged researchers working on computer models of galactic interactions.

**GALAXY CLUSTERS vary in shape, density and galactic population. The Hercules cluster (*top*) contains a number of interacting disk galaxies; the overall form of the cluster is irregular. In contrast, the Coma cluster (*bottom*) is a dense, generally spherical cluster rich in bright elliptical galaxies. The large number of ellipticals may indicate that the Coma cluster has experienced a high rate of mergers.**

The first simulations of the merging process considered simple interactions between spherical galaxies. Although very different in detail from the more realistic disk-galaxy simulations accompanying this article, these early experiments improved understanding of the effects of merging. When the surface brightness of an elliptical galaxy is plotted as a function of distance from the center, the shape of the resulting curve is always nearly the same. In the late 1970s Simon D. M. White of the University of Cambridge showed that mergers produce objects whose brightness profiles closely resemble those of elliptical galaxies. Further studies indicated that this characteristic light profile results whenever a galaxy evolves in a strongly varying gravitational field.

Early computer simulations of galaxies used only a few hundred particles. Those models sufficed for studying some aspects of the behavior of a spherical galaxy, but many thousands of particles are needed to approximate a rotating disk. Not until the mid-1980s was it possible to test the conjecture that two disk galaxies could merge to produce a single object with the properties of an elliptical. Recent calculations by us and by other research teams yield merger remnants whose brightness profile, shape and slow rotation resemble those typical of large elliptical galaxies.

The merger hypothesis predicts definite relations between the properties of ellipticals and those of the disk galaxies from which they form. As more calculations are run and more galaxies observed, it will be possible to make increasingly detailed comparisons between merger remnants and normal elliptical galaxies. In this way, astronomers are testing the validity of the merger hypothesis and determining how widely applicable it is.

Not all the properties of elliptical galaxies can be explained by mergers between ordinary disk galaxies. For example, bright ellipticals rotate slowly, but faint ones do not. The merging pro-



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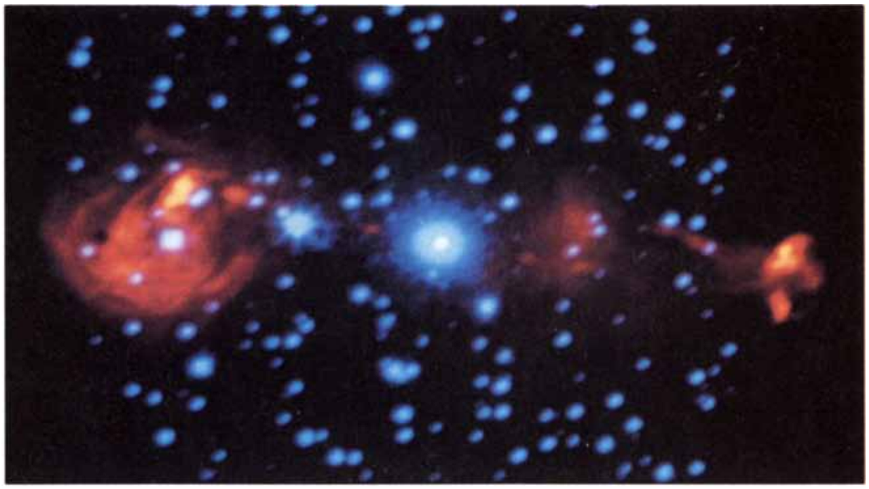
cess is insensitive to scale, so there is no obvious reason why bright merger remnants should rotate at a rate different from that of faint ones. The faintest ellipticals present a further embarrassment for the merger hypothesis, because no plausible progenitors have been identified.

Encounter velocities between these dwarf elliptical galaxies are high in relation to their internal velocities, with the result that dwarfs rarely if ever merge. These facts imply that either the faintest ellipticals were not formed by mergers or else they formed under circumstances very different from those that produced the bright ellipticals. One long-standing but speculative conjecture is that some dwarfs are fragments of tidal tails extruded during encounters between disk galaxies.

In fact, there is little direct evidence about the circumstances under which even the bright ellipticals formed. The largest elliptical galaxies reside in rich "regular" clusters such as the Coma cluster. These groupings contain hundreds or thousands of galaxies in a roughly spherical swarm. Collisions are not unusual in such clusters, but little or no merging takes place because the galaxies move so fast relative to one another that they have no chance to coalesce. Most mergers in these clusters must have taken place as the clusters themselves formed. The regular shapes and high central densities of these galactic groupings imply that they must have formed only a few billion years after the big bang.

Astronomers cannot yet look back far enough in space and time to observe rich galaxy clusters as they form, but they may be able to find nearby environments in which similar formation processes are occurring today. The most luminous ellipticals might have been built up by repeated mergers involving many disk galaxies. Such multiple mergers apparently occur in compact groups, which typically contain four or five interacting galaxies each. Numerical models indicate that the galaxies in these groups merge with one another over a period of a few billion years, producing ever more massive merger remnants that are structurally similar to elliptical galaxies.

Some galaxy clusters contain just such compact groups and so may resemble regular clusters caught in the act of formation. These clusters are irregular in shape, lack a definite center and generally contain a much larger fraction of spiral galaxies than rich clusters do. A quick visual examination of the irregular Hercules cluster reveals a large number of interacting galaxy pairs. Over billions of years, many of these pairs will probably merge. Meanwhile the entire cluster will continue to evolve, becoming less irregular and more spherical. The ultimate result of this process could resemble a regular cluster abundant in elliptical galaxies.



**POWERFUL RADIO EMISSION emanates from the galaxy 3C 353. Such radio galaxies, along with other kinds of active galaxies and quasars, may be interacting systems that harbor massive black holes in their centers. Gravitational interaction sends large amounts of matter into the central region, which causes a burst of activity when the material reaches the black hole. Blue shows the galaxy's visible form; red depicts its appearance at radio wavelengths.**

If the ellipticals in rich clusters did form by multiple mergers, those events must have occurred when the universe was only a fraction of its present age. The galaxies involved may have been immature forms of those observed today, containing more gas and perhaps differing in stellar content. Cluster ellipticals may be fossils that preserve some properties of the infant galaxies from which they formed.

That possibility might explain why some massive ellipticals are surrounded by remarkably large numbers of globular clusters, tight-knit spherical gatherings of up to a million stars that somewhat resemble miniature ellipticals. In the distant past, globulars may have been more common relative to stars in the main bodies of galaxies; an alternative explanation is that new globular clusters form during galactic mergers.

Quasars were far more abundant in the early universe than they are today [see "Black Holes in Galactic Centers," by Martin J. Rees; SCIENTIFIC AMERICAN, November 1990]. As we have seen, mergers between galaxies may activate quasar or quasarlike activity. If cluster ellipticals are in fact the result of galactic collisions, these events must have occurred in large numbers very early in the history of the universe, before rich clusters formed. Such a high merger rate may also account for the large numbers of quasars found when astronomers examine very distant, and hence very young, parts of the universe.

We are not yet able to test the hypothesis that distant quasars occur in interacting galaxies. Except in nearby cases, the glare of the brilliant nuclei all but eclipses the surrounding structure. But as observational techniques and computer models grow ever more sophisticated, we may eventually succeed in relating these extraordinarily energetic objects, which have puzzled a generation of astronomers, to the formation of galaxies much like those we observe in our immediate cosmic neighborhood.

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# The Human Telomere

*Although this specialized DNA cap at each end of the chromosome carries no genes, it is still valuable. Recent evidence indicates that chromosomes need their telomeres to survive*

by Robert K. Moyzis

The Nobel laureate Hermann J. Muller proposed more than 50 years ago that the segments at the ends of chromosomes play a critical role in the cell. Before anyone knew that the DNA in chromosomes was double stranded and carried genes, he understood that the terminal material caps chromosomes to prevent their decay. Muller also gave the tips a name: telomere, from the Greek (*telos* means end; *meros,* part).

For decades, little more was learned about the telomere. Then, roughly 10 years ago, investigators began to decipher its structure in various species. The composition of the human telomere, however, eluded discovery.

It is a mystery no longer. A few years ago my colleagues and I at Los Alamos National Laboratory developed new research tools that enabled us to clone the human telomere, identify the sequence of its nucleotides (the building blocks of DNA) and learn more about its three-dimensional structure and its function in the cell.

In the course of our experiments, we helped to confirm that the telomere, which carries no genes, is vital to chromosomal survival. This result supports a growing awareness that gene-free regions of chromosomes often play critical roles in the cell, even though they cannot specify the amino acid sequences of the body's proteins. (Proteins are vital to all life processes.) Clearly, investigators who want to understand how chromosomes and individual genes function will have to identify the DNA sequences not only of genes but also of many nongenic regions. They will also have to determine how the various parts of a chromosome interact with one another.

The cloning of the human telomere is already aiding that ambitious effort—by helping to advance the Human Genome Project in the U.S. and similar projects elsewhere. These programs will map the entire human genome (the full complement of chromosomes in the cell), pinpointing the location of every gene. Just as assembling the edges of a jigsaw puzzle simplifies the puzzle's completion, description of the ends of human chromosomes should facilitate completion of chromosomal maps. As the mapping progresses, researchers will undoubtedly uncover the genetic roots of many diseases and further clarify both how chromosomes direct development and how they ensure that cells operate properly.

In attempting to clone the human telomere, we were guided both by knowledge of its probable functions and by a number of hints about its makeup. We were, for instance, well aware of Muller's early work. His own experiments on the fruit fly *Drosophila melanogaster* and similar experiments performed on maize by Barbara McClintock of Cold Spring Harbor Laboratory revealed that broken, or induced, ends of chromosomes are unstable, whereas intact terminals are stable. The broken ends quickly combine with other chromosomes or are degraded. Muller deduced from such data that telomeric regions, unlike other regions, somehow signal cells to maintain chromosomes as intact and distinct entities.

Telomeres are also thought to prevent chromosomes from shortening when they replicate. Such truncation is potentially lethal because it can eliminate genes. This protective role was originally extrapolated from a peculiarity of the machinery that duplicates linear DNA, such as that of humans, before cells divide.

The enzymes that control duplication have a worrisome flaw: they tend to omit a few nucleotides at one end of each new strand whenever DNA is copied. If the cell did not institute countermeasures, the chromosomes in successive generations of cells would become progressively shorter.

Some amount of shortening might be of little consequence in somatic, or nonreproductive, cells if part of the telomere and all the genes were preserved. But progressive shrinkage would ultimately devastate a species if it occurred in germ cells (eggs and sperm), which give rise to new members of the species. The fact that humans and other species have not shortened their DNA out of existence implied that the end segments—the telomeres—on the original strands probably serve as sentries that somehow ward off the enzymatic danger at the tips.

As we sought to clone the human telomere, we assumed that it appeared more than once in every cell, since it would be present at the ends of each chromosome. All somatic human cells contain 46 chromosomes: one set of 22 inherited from the mother and a matching set from the father, as well as a pair

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**TELOMERES, the stretches of DNA that cap chromosomes, can be identified on human chromosomes (*orange*) by a fluorescent probe (*yellow*) that recognizes the nucleotide sequence *TTAGGG*. *T, A* and *G* represent nucleotides (the building blocks of DNA) containing the bases thymine, adenine and guanine, respectively. Such pictures helped to demonstrate that the human telomere consists of hundreds of repeating *TTAGGG* units. The chromosomes shown are in metaphase: each individual chromosome has replicated in preparation for cell division, but the resulting twins have not yet separated from each other.**



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of sex-determining chromosomes (an X from the mother and an X or Y from the father).

We also guessed that telomeric DNA, in addition to being repeated many times in the cell, might consist of or contain repeating nucleotide sequences. Such an arrangement was suggested both by a well-known feature of the human genome and by studies of other organisms.

Some 25 percent of human DNA consists of nucleotide groupings that appear more than once in each cell. Although certain of these repetitive sequences are scattered throughout the DNA, others are reiterated many times in a row, so that they resemble the DNA equivalent of a stutter. These tandem repeats are usually found in critical regions, notably in the centromere, which ensures the proper distribution of chromosomes into daughter cells during cell division. Further, reiterated units or clusters of such units often adopt unusual three-dimensional structures that might serve some purpose for the cell. Together these findings implied that repetitive sequences may well have specialized functions in chromosomes and that the telomere's ability to cap chromosomes and prevent shortening might derive from having such repetitive units within it.

Studies of telomeres in other organisms offered concrete encouragement for this hypothesis. Elizabeth H. Blackburn and Joseph G. Gall, then at Yale University, were the first to isolate a telomere, from the microorganism *Tetrahymena thermophila*. They studied *T. thermophila* mainly because at certain times in its life cycle its telomeric DNA constitutes a major fraction of the genome.

While in those phases, the creature shatters segments of its chromosomes and amplifies them, generating about 10,000 copies of each of the resulting "minichromosomes." These relatively short, amplified units, which carry intact telomeres to assure stability, can be isolated readily from the remaining DNA and their nucleotide sequence determined. Such analysis revealed that the ends of the minichromosomes consist of simple tandem arrays of the sequence *TTGGGG*.

This notation is a kind of shorthand. Nucleotides are made up of a sugar, a phosphate group and one of four distinguishing bases—thymine (*T*), guanine (*G*), adenine (*A*) or cytosine (*C*). Consequently, geneticists often represent the nucleotides solely by the symbols for their bases. Moreover, thymine on one strand of DNA combines with adenine on the complementary strand, and guanine pairs with cytosine. Hence, the designation *TTGGGG* signifies that the thymine nucleotides are attached to adenine nucleotides on the complementary strand and that, likewise, the guanine nucleotides are attached to cytosine units.

Knowing at least one telomeric structure was better than none, but the 100-fold larger amount of DNA in human cells (which contain about six billion nucleotide pairs) and the relative paucity of telomeres (only two on each chromosome) meant that isolation of the human telomere would require other strategies. Predictably, then, the next

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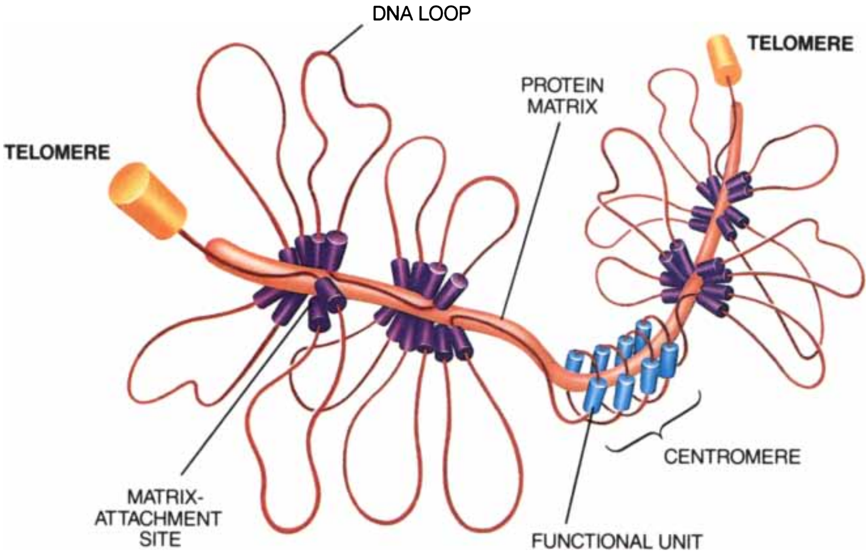


**CRITICAL PARTS OF HUMAN CHROMOSOME are depicted highly schematically. Each loop is thought to contain one or more genes, the protein-specifying segments of chromosomes. The cylinders represent stretches of DNA that contain no protein codes but are nonetheless important to chromosomal stability or activity—notably, the telomeres, matrix-attachment sites (which might also be replication origins, where DNA synthesis begins) and the centromere. Centromeres mediate the proper segregation of duplicated chromosomes during cell division.**

several years saw little direct progress.

Meanwhile, however, elegant work in many laboratories, including Blackburn's after she moved to the University of California at Berkeley, demonstrated that the telomeres of a number of unicellular eukaryotes (organisms other than viruses or bacteria) are similar to that of *T. thermophila.* They all consist of simple, repetitive guanine-rich sequences fitting the general formula $(T/A)_{1-4}\,(G)_{1-8}$. In other words, the repeating unit on one DNA strand includes one to four thymine or adenine nucleotides (or a mixture of the two) and one to eight guanine nucleotides. The most common units include three or four guanine nucleotides.

On the basis of the telomere's importance to the stability and accurate replication of chromosomes, my co-workers and I reasoned that the human version, in addition to including repetitive units, might fit the same formula described in other eukaryotes. After all, it is unlikely such a vital, adaptive structure would change capriciously in the course of evolution. Rather it would tend to be highly conserved, particularly among species belonging to the same order.

If our suspicion that the human telomere included a conserved, repetitive sequence was on target, we thought we might narrow our search for that sequence by exposing a library, or collection, of human DNA clones to probes made from repetitive DNA of another mammal, such as a rodent. When a specific stretch of DNA is included in a library, a probe derived from the same or a similar sequence in another organism will identify it. We hoped, therefore, that telomeric DNA from a rodent would pick out the human telomere and that our knowledge of the terminal's features would enable us to distinguish it from other repetitive DNA selected by our probes.

The standard method for isolating a target segment in a library is usually straightforward. The DNA in the library is treated with a solution that causes the double-helical strands to separate from each other. Then single strands of the probe are introduced. If the probe finds its complementary bases in the library, it will bind to those bases, forming a patch of double-strand DNA—a process known as hybridization. Various techniques can then be applied to purify the probe-bound DNA and identify its nucleotide sequence.

Many studies in other laboratories supported our hope that a probe derived from a rodent could pick out the human telomere. They showed that when cells of rodents are induced to take up human chromosomes, the cells do not destroy the foreign cargo. In fact, the human DNA replicates whenever the cells divide. If the human telomere was very different from that of the host, the molecules directing replication in the rodent cells would not be able to recognize it and would probably be unable to copy the DNA faithfully.

Our basic game plan was reasonable, but we had a problem. Regardless of which probes we might choose, there seemed little hope of isolating the human telomere from existing libraries of human DNA.

Researchers construct most libraries with the help of restriction enzymes, which recognize specific, short nucleotide sequences scattered throughout chromosomes and then cut the DNA at those sites [*see left side of illustration on opposite page*]. Other enzymes then fit the individual fragments into plasmids (circular bits of DNA from bacteria) or other kinds of circular DNA that have been slit open by the same restriction enzyme. Use of the identical restriction enzyme ensures that the free ends of the fragments and the cut circles will mesh readily. The genetically altered circles, or vectors, are then introduced into bacteria, usually *Escherichia coli,* where they replicate freely. Each bacterial cell gives rise to many identical copies, or clones, of the vector and thus of the inserted human DNA. The full set of human DNA clones purified from the bacterial cells constitutes the library.

Unfortunately, when restriction enzymes chop up chromosomes, the end fragments, which contain the complete telomere along with other nucleotides, carry only one cut end, where the DNA was snipped. The far tip consists of the original, intact DNA. The cut section can hook up with a vector, but the other part cannot, and so the entire DNA fragment is lost to the library. Even if the natural end could be made to bind with the vector, the telomeric fragment might be too large for the vector to accommodate.

Clearly, if we wanted to search for telomeric DNA in a human library, we would have to construct a library that would be sure to include such DNA. We solved the problem by abandoning restriction enzymes. Instead we mechanically passed chromosomes through a syringe fitted with a fine-gauge needle. The procedure sheared the DNA into small bits. Those bits would surely include segments of the telomere.

We could then have made a suitable library by inserting the fragments into plasmids (using a standard technique) and introducing the plasmids into bacteria. To simplify the screening process, though, we included another step between the shearing and insertion stages. Because we expected the basic unit of the telomere to be repeated many times in a cell, we eliminated fragments lacking repetitive DNA. We thereby re-


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moved some unnecessary clutter from our final collection.

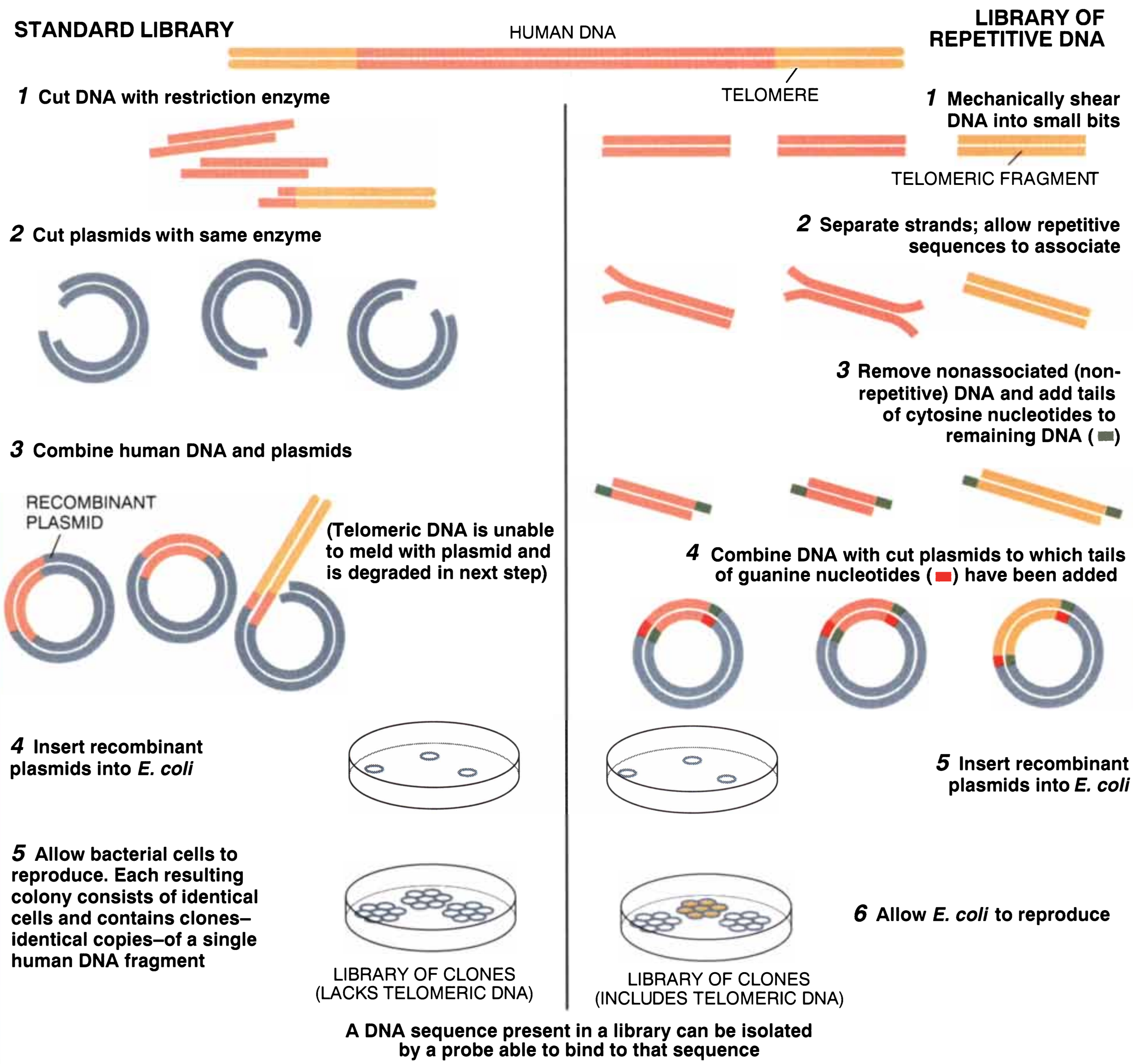
Deleting the nonrepetitive DNA was fairly easy. We separated the strands of the fragments we had created. Then, for a short time, we allowed complementary segments to hybridize. Because only repetitive sequences occurred in multiple copies, they found mates faster than did strands having only a single complement buried somewhere in the entire DNA soup. Finally, we enzymatically removed all the DNA that had failed to hybridize—that is, the nonrepetitive DNA.

With our library complete, we returned to our plan of screening human DNA for conserved repetitive sequences. When we exposed the DNA clones in our new library to radioactively labeled repetitive DNA from hamsters, we found that two clones out of thousands contained a potential telomeric sequence. Both clones consisted of tandem repeats of *TTAGGG*, which was consistent with the general formula for telomeres in other species. Moreover, the exact sequence had been found previously in the telomere of the microscopic parasite *Trypanosoma brucei*.

Had we, in fact, identified the basic unit of the human telomere? Additional studies were encouraging. First we turned to flow cytometery, a technique pioneered at Los Alamos that exploits lasers to identify and isolate individual chromosomes. With this method, we de-

## How a Library Containing Telomeric DNA Is Built

Standard DNA libraries have facilitated the cloning of many genes, but they lack telomeric DNA (*left*). To isolate the telomere from human cells, the author and his colleagues had to construct a library that would include telomeric nucleotide sequences (*right*). Knowing that the telomere probably consisted of many repeats of one fixed sequence, they also eliminated nonrepetitive DNA from the library.



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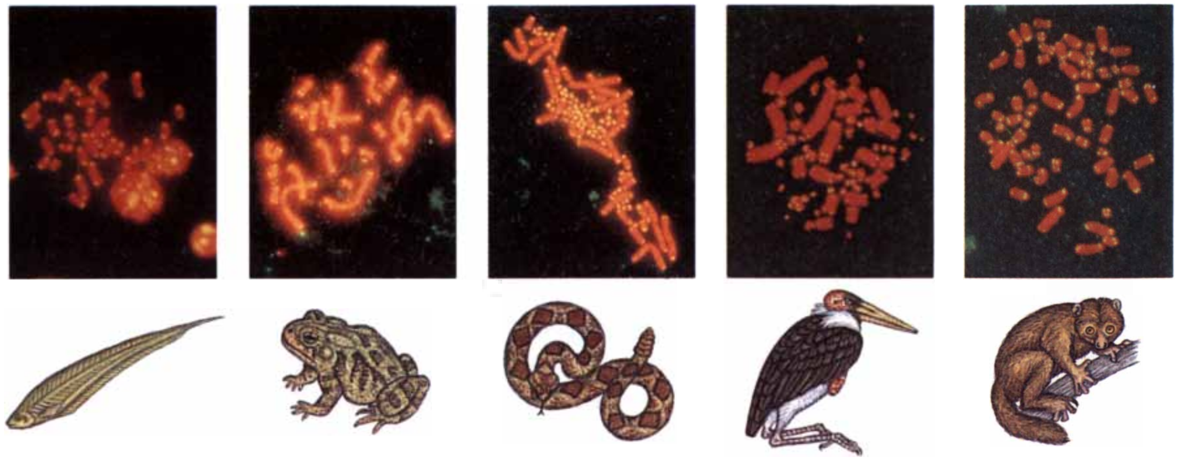


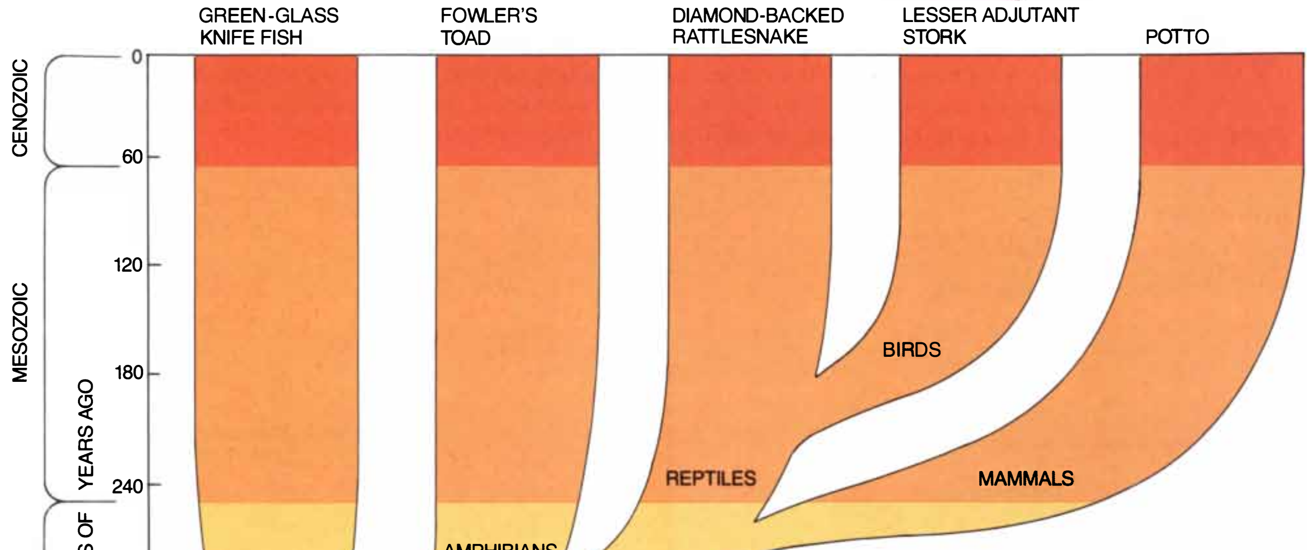


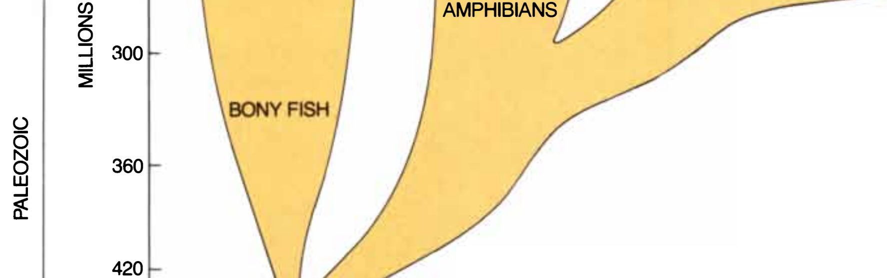

**FLUORESCENT PROBE that recognizes the human telomeric sequence *TTAGGG* (*yellow dots in micrographs*) has bound to the tips of all chromosomes extracted from the animals depicted here. It has also picked out the ends of chromosomes from every other bony fish, amphibian, reptile, bird and mammal studied so far (more than 100 species in all). The findings indicate that the telomeres of all five groups are identical, even though the creatures have not shared a common ancestor for more than 400 million years. Such conservation of a DNA sequence over the ages is remarkable.**

termined that each of the chromosomes carried *TTAGGG* repeats, as would be expected for a telomeric sequence. We could not, however, determine where on the chromosomes the repeating segments occurred.

My colleagues Julianne Meyne, Robert L. Ratliff and I next showed visually, by a technique called in situ hybridization, that long stretches of the repeats appear at both ends of all chromosomes in the human cell. These terminal arrays are often represented as $(TTAGGG)_n$, where *n* indicates some unspecified number of repeats.

We carried out the hybridization by isolating chromosomes from human cells, immobilizing them on slides and separating the strands of the double helix. Next, applying an approach developed by David C. Ward of Yale, we added the chemical biotin to a synthetic probe that was designed to hybridize with *TTAGGG* and put the biotin-tagged probe on the slides. Later, we introduced fluorescently labeled avidin, which binds tightly to biotin. Finally, we amplified the avidin signal by introducing fluorescently labeled antibodies that themselves recognize avidin.

The images we saw with fluorescence microscopy were unequivocal [*see illustration on page 49*]: the probes lit up both ends of every chromosome but did not recognize any other sections. We could not ascertain, however, whether the probe had hybridized to the final few nucleotides of the chromosomes or merely to some point close to the extreme tips.

To reassure ourselves, we briefly exposed chromosomal DNA to an enzyme called *Bal*31. Pacman-like, *Bal*31 progressively shortens DNA molecules from their ends. The *TTAGGG* groupings were the first to disappear, which confirmed that those sequences did reside at the extremities. This experiment, together with others, further revealed that each human telomere consists of 250 to 1,500 *TTAGGG* repeats. Most of the variation occurs between



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different cell types, with sperm chromosomes having the longest telomeres.

We felt confident from these experiments that we had truly identified the human telomere, but we continued to seek confirmation. Firm evidence that the *TTAGGG* repeat was conserved in many species, not just shared with hamsters and a parasite, would help, and so we applied in situ hybridization to DNA from more than 100 vertebrate species. Our sample included mammals, birds, reptiles, amphibians and bony fish—organisms that have not had a common ancestor for more than 400 million years.

We designed the experiments so that hybridization would occur only if the probe encountered *TTAGGG* but not if it encountered a very similar sequence, such as *TAAGGG*. The human sequence was found at the telomeres of all species examined—a remarkable discovery, given that the order of nucleotides in most parts of the genome tends to change rapidly over time. To put this finding in perspective, consider that the $(TTAGGG)_n$ telomere apparently arose long before dinosaurs roamed the earth. It is therefore likely that the telomeres of dinosaur chromosomes, if they could be known, would be identical to those in human chromosomes.

Of course, the ultimate proof that $(TTAGGG)_n$ is the human telomere would be a demonstration that it functions as a telomere in human cells. In the ideal approach, we would insert the sequence into an artificial chromosome containing nothing but the apparent telomere and human DNA segments known to be crucial to chromosomal replication, namely, a replication origin (where DNA synthesis begins) and a centromere. If this stripped-down chromosome remained intact in human cells and replicated without shortening, we could be sure $(TTAGGG)_n$ was responsible for the success and was, therefore, the telomere.

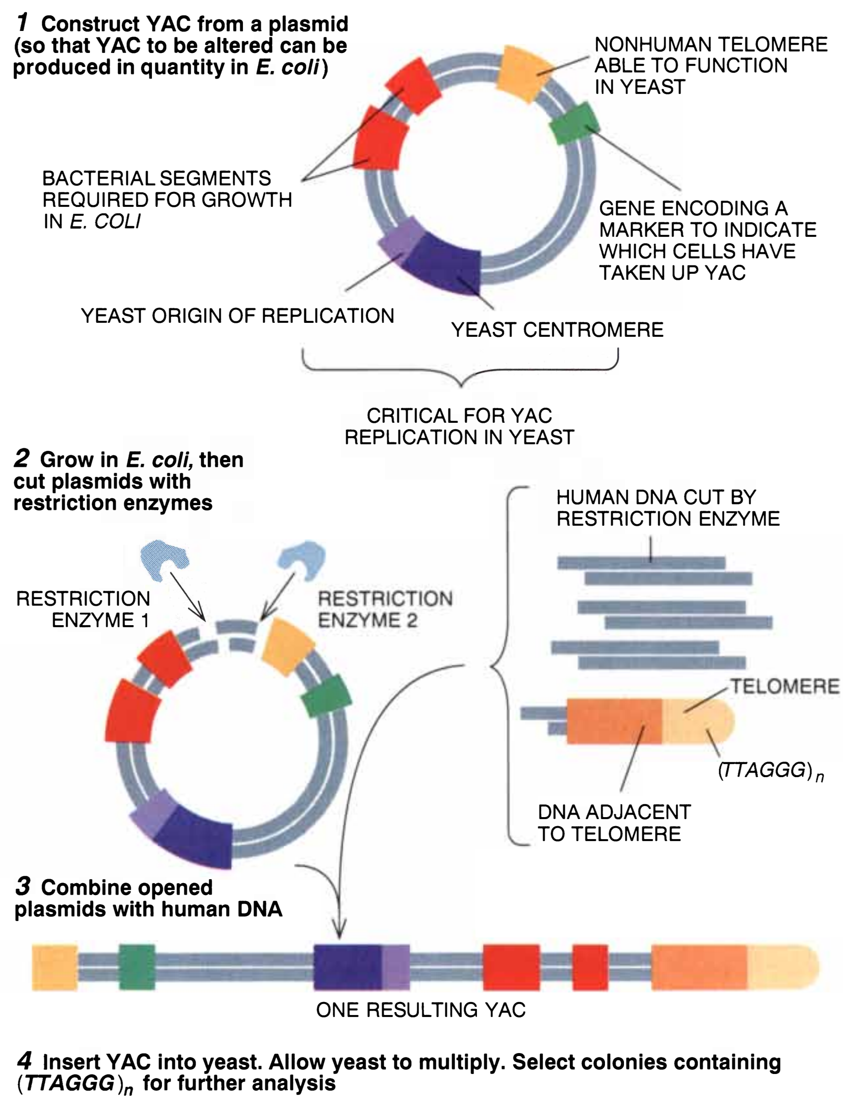
Regrettably, no one has been able to devise an all-human artificial chromosome, because the sequences critical to the functioning of the human centromere have yet to be identified. A similar experiment can be conducted, however, with yeast artificial chromosomes (YACs). Our collaborators Harold C. Riethman, David T. Burke and Maynard V. Olson of Washington University in St. Louis constructed YACs carrying the putative human telomere in place of one yeast telomere. When this "chimeric" DNA was inserted into yeast cells, the chromosome survived and replicated accurately, indicating that the human $(TTAGGG)_n$ sequence did in fact behave as a telomere. The laboratories of William R. Brown at the University of Oxford, Howard J. Cooke at the Medical Research Council in Edinburgh, and Charles R. Cantor, then at Columbia University, have independently reported similar results.

Because yeast and humans had a common ancestor more than a billion years ago—which is to say they are essentially unrelated—failure of the experiment would not necessarily have discounted our earlier conclusions. Nevertheless, the fact that even yeast cells, whose telomeres are more variable, recognize the human sequence as a telomere is added proof that the DNA segment we isolated from our library is indeed the human telomere.

Once the identity of the human telomere was established, our group and others began to exploit the telomere-containing YACs for other purposes. One goal has been to identify the nucleotide sequences adjacent to the telomeres on every chromosome. YACs are invaluable for this task because they can accommodate stretches of 500,000 nucleotides or more. Plasmids, in contrast, can accept only about 40,000 foreign nucleotides.

## The Making of a YAC for Cloning Human DNA

The human telomere, along with DNA adjacent to it on a chromosome, can be spliced into yeast artificial chromosomes (YACs), such as the one resulting from step 3, and replicated in yeast. Researchers can then remove the amplified human DNA and determine its sequence. This approach is helping to reveal the composition of the DNA next to the telomere on a number of chromosomes.



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These efforts are already helping to fill in missing pieces in the maps of human chromosomes. Current maps are similar to 16th-century representations of the world, in that some regions contain great detail but other regions—the New World, for example—contain only hypothetical descriptions of the boundaries of entire continents.

Until recently, investigators determined the locations of genes by estimating how far they were from DNA markers (nucleotide sequences that are often inherited along with a particular gene). The frequency with which a gene and a marker are inherited in tandem can be translated into a loose estimate of the distance between the two; higher frequencies indicate closer positions on the chromosome. Comparison of the inheritance patterns of a number of markers gives their approximate locations and, hence, the approximate positions of the associated genes.

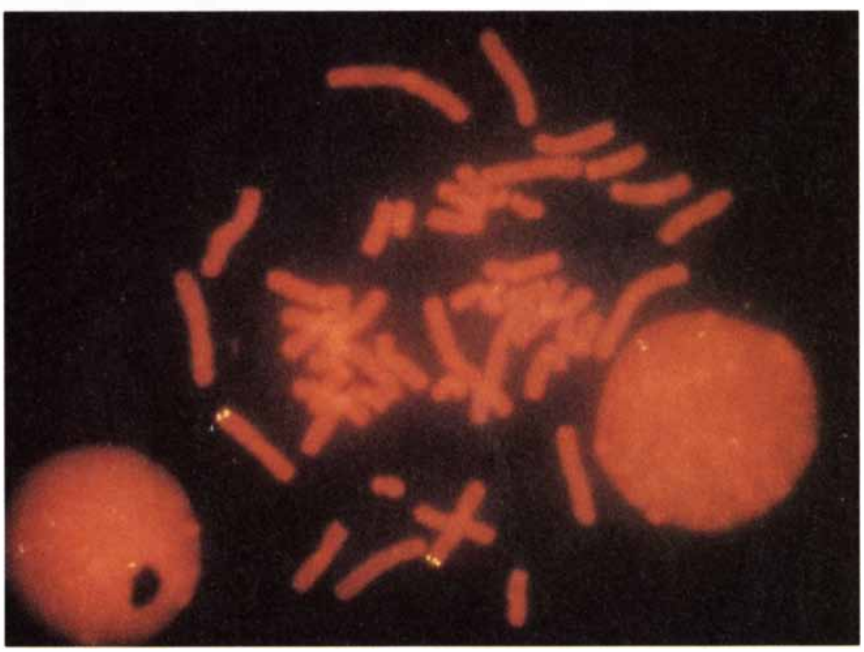
In the past, when a marker was thought to be near the end of a particular chromosome, a new one was often isolated that pushed the end millions of nucleotides farther out. Now researchers can establish whether a marker is in fact near the end—by cloning the telomere and adjacent DNA in YACs and directly measuring the distance between some point in the cloned material and the marker. Eventually one should be able to determine the location of all DNA markers by measuring their precise distance from a telomere.

YAC studies of DNA adjacent to the telomere are also clarifying the function of such sub-telomeric material. One might predict that the regions would be a dangerous place for genes and would therefore contain few of them. After all, if the telomere were somehow excised, the genes in that area would be the next ones to be eliminated. Indeed, most unicellular organisms place noncoding DNA next to their telomeres, presumably to serve as a buffer between the telomere and the protein-coding regions.

Apparently, human chromosomes adopt a similar strategy. Many of the fragments that have been examined in YACs are reminiscent of this "spacer" DNA. Like the sub-telomeric regions of unicellular organisms, they contain many repeats. Moreover, in contrast to telomeric DNA, the number and sequence of the repeated units vary greatly from chromosome to chromosome and even from person to person.

Studies of sub-telomeric DNA may uncover new DNA markers associated with disease-causing genes and may help reveal the identity and location of the few genes lying relatively near the telomere. For instance, the gene responsible for Huntington's disease, a programmed degeneration of specific neurons, has been mapped to somewhere near the end of the short arm of chromosome 4. Researchers had been unable to pinpoint the exact location, because they could not find a DNA marker that bracketed the gene on the telomeric side. Part of the difficulty was that they did not know where the chromosome ended. With identification of the human telomere, the search for the physical basis of this disease now has a defined boundary: the gene must lie in the last two million nucleotides of the chromosome. Those nucleotides can now be examined for markers and, ultimately, for the gene itself.

Finally, the cloning of the telomere is contributing to a rather different line of research: investigations into the causes of cellular aging. One proposal holds that only germ cells contain the machinery for preventing the shortening of chromosomes during replication and that nonreproductive cells actually lose telomeric subunits whenever they divide. When all or most of the telomere is gone, the chromosomes decay and the cells die. Now that the human telomere has been identified, researchers can begin to evaluate this theory in the laboratory.



**HUMAN DNA (*yellow*) that was cloned in a yeast artificial chromosome homed to a spot next to the telomere on the long arm of each copy of chromosome 7 in a human cell at metaphase. Researchers can now pinpoint the location of genetic markers on chromosome 7 by measuring their distance from the highlighted DNA. (The spheres in the photomicrograph are nuclei from other cells.)**

Although isolation of the human telomere is already contributing to many areas of research, questions remain about the behavior of the telomere itself. In particular, how does this segment of DNA stabilize chromosomes and prevent their truncation during replication?

A few surprising findings suggest a partial answer to the replication problem. It is now known, for instance, that the termini of many telomeres do not take the form of a double helix; rather the *G*-rich strand protrudes beyond the complementary *C*-rich strand. Greg B. Morin of Yale has found evidence in human cancer cells that an unusual enzyme called telomerase can add *TTAGGG* units to this protrusion. This activity resembles that of the first-known telomerase, which was discovered in *T. thermophila* by Blackburn and Carol W. Grieder, who is now at Cold Spring Harbor Laboratory.

Unlike the human enzyme, the telomerase of *T. thermophila* has been studied in detail. It contains not only amino acids but also RNA, a close relative of DNA. (RNA is usually single stranded, and the base uracil substitutes for thymine.) The RNA in the enzyme includes the complement of the *G*-rich strand of the *T. thermophila* telomeric subunit: *TTGGGG*. The protein-RNA hybrid is able to line up under the protrusion, so that the RNA segment extends immediately beyond the final *TTGGGG* group. So situated, the RNA attracts complementary nucle-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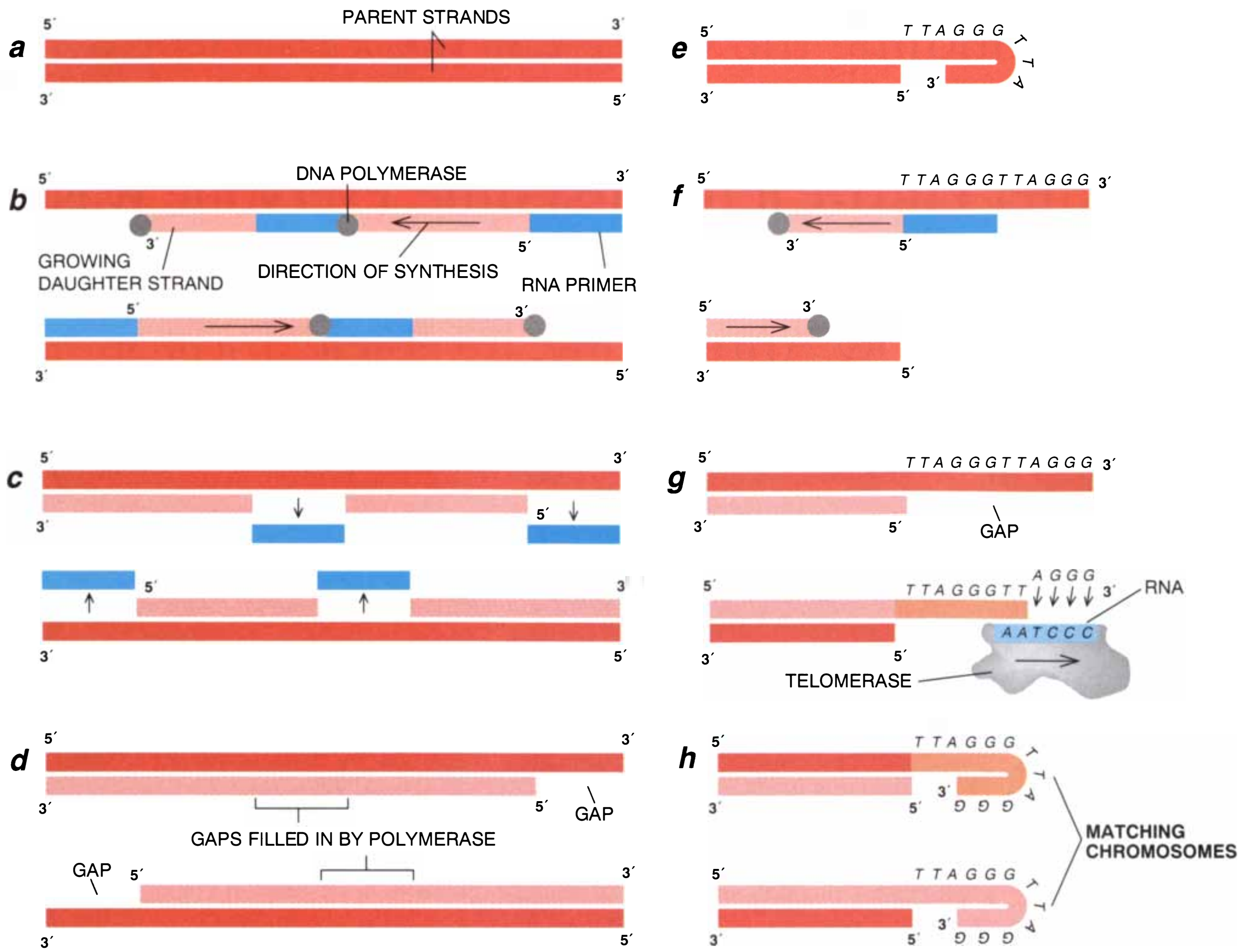


**DNA SHORTENS as it replicates (*left*). When the joined parent strands (*a*) separate (*b*), RNA primers attach to them, enabling polymerase enzymes to synthesize daughter strands. After the primers are removed (*c*), a polymerase merges the new DNA fragments (*d*) but cannot fill the gaps at the far ends (at the telomeres). The enzyme telomerase may counteract such shortening. One hypothesis (*right*) suggests that the 3′ telomeric segment of each parent strand, which actually protrudes beyond the opposite 5′ end and is probably curled (*e*), unfurls during replication (*f*). (Only one 3′ terminal is shown.) Normal RNA-primed synthesis then occurs. The 5′ gaps remain (*g*), but telomerase, which in humans may include RNA complementary to *TTAGGG*, adds telomeric units to the new 3′ ends. The ends then recurl (*h*), capping the DNA.**

otides, which it adds to the end of the overhang, in the form of *TTGGGG* groups.

Human telomerase may add *TTAGGG* units to human DNA in a similar way. Various ideas have been proposed to explain how such extra units would prevent chromosomes from shortening during replication, but none has yet been proved. One possibility is shown in the illustration above.

The answer to the capping question is equally sketchy but may lie with the fact that all known telomeric sequences can form unusual structures. For instance, the guanine bases on one DNA strand seem capable of pairing with guanines on the same DNA strand, even though in genes, guanine always pairs with cytosine, never with itself. This unusual conformation may somehow prevent binding by enzymes that degrade telomere-free DNA.

Regardless of the open questions, the demonstration that $(TTAGGG)_n$ is the human telomere has lent credibility to our original hypothesis—that repetitive sequences not involved directly in protein synthesis may well store information critical to the survival and function of chromosomes. The challenge now is to identify other sequences of equal import and to learn how both they and *TTAGGG* convey their messages to the cell.

FURTHER READING

A HIGHLY CONSERVED REPETITIVE DNA SEQUENCE, $(TTAGGG)_n$, PRESENT AT THE TELOMERES OF HUMAN CHROMOSOMES. Robert K. Moyzis, Judy M. Buckingham, L. Scott Cram, Maria Dani, Larry L. Deaven, Myrna D. Jones, Julianne Meyne, Robert L. Ratliff and Jung-Rung Wu in *Proceedings of the National Academy of Sciences*, Vol. 85, No. 18, pages 6622–6626; September 1988.

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STRUCTURE AND FUNCTION OF TELOMERES. Virginia A. Zakian in *Annual Review of Genetics*, Vol. 23, pages 579–604; 1989.



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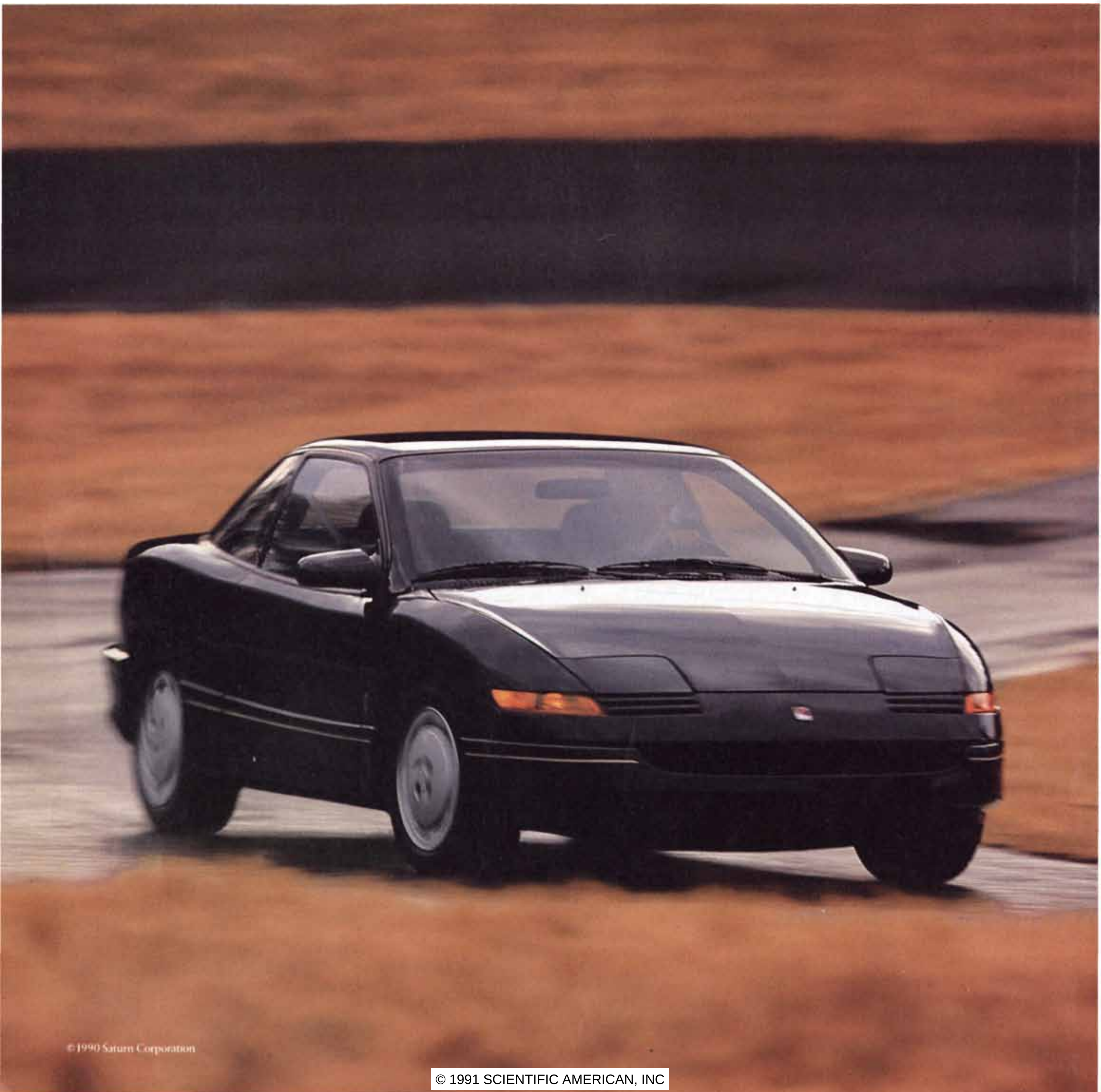


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# Tracking and Imaging Elementary Particles

*How and why 25 billion bits of data produced in a second by the world's largest collider are translated into images of elementary particles*

by Horst Breuker, Hans Drevermann, Christoph Grab, Alphonse A. Rademakers and Howard Stone

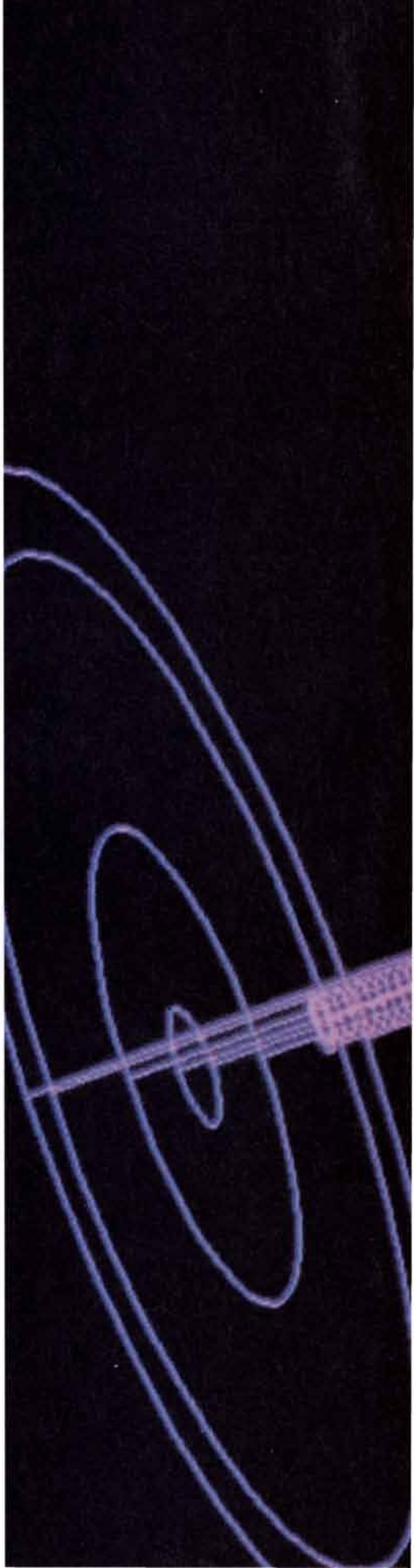
The Large Electron-Positron (LEP) Collider is one of the most powerful particle accelerators ever built. It smashes electrons into their antimatter counterparts, positrons, releasing as much as 100 billion electron volts of energy within each of four enormous detectors. Each burst of energy generates a spray of hundreds of elementary particles that are monitored by hundreds of thousands of sensors. In less than a second, an electronic system must sort through the data from some 50,000 electron-positron encounters, searching for just one or two head-on collisions that might lead to discoveries about the fundamental forces and the elementary particles of nature.

When the electronic systems identify such a promising event, a picture of the data must be transmitted to the most ingenious image processor ever created. This device is undoubtedly the most important resource in all of experimental physics, and it has certainly taken many more years to develop than the LEP Collider. The device is the human brain.

Computers cannot match the brain's capacity to recognize complicated patterns in the data collected by the LEP detectors. The work of understanding subnuclear events begins therefore through the visualization of objects that are trillions of times smaller than the eye can see and that move millions of times faster than the eye can follow.

During the past decade, we and our colleagues at the European laboratory for particle physics (CERN) have attempted to design the perfect interface between the minds of physicists and the barrage of electronic signals from the LEP detectors. Using sophisticated computers, we translate raw data—500,000 numbers from each event—into clear, meaningful images. With shapes, curves and colors, we represent the trajectories of particles, their type, their energy and many other properties.

Our efforts have contributed to several important discoveries since the LEP Collider began operation two years ago. Physicists at LEP have investigated, in unprecedented detail, a particle known as $Z^0$ (pronounced "zee zero"). It conveys one of the four fundamental forces of nature, the weak interaction, just as photons carry the electromagnetic



***EVENT DISPLAY reveals particles produced by the decay of a*** $Z^0$ ***within the L3 detector at LEP. The decay generated three primary particles: an electron* (blue), *a positron* (light blue) *and a photon* (yellow). *The purple lines indicate the structure of part of the detector. The towers in blues and yellows show where the particles hit the detector. The height of a tower reveals how much energy was deposited.***

HORST BREUKER, HANS DREVERMANN, CHRISTOPH GRAB, ALPHONSE A. RADEMAKERS and HOWARD STONE design event-display systems for the LEP detectors at CERN, the European laboratory for particle physics, near Geneva.



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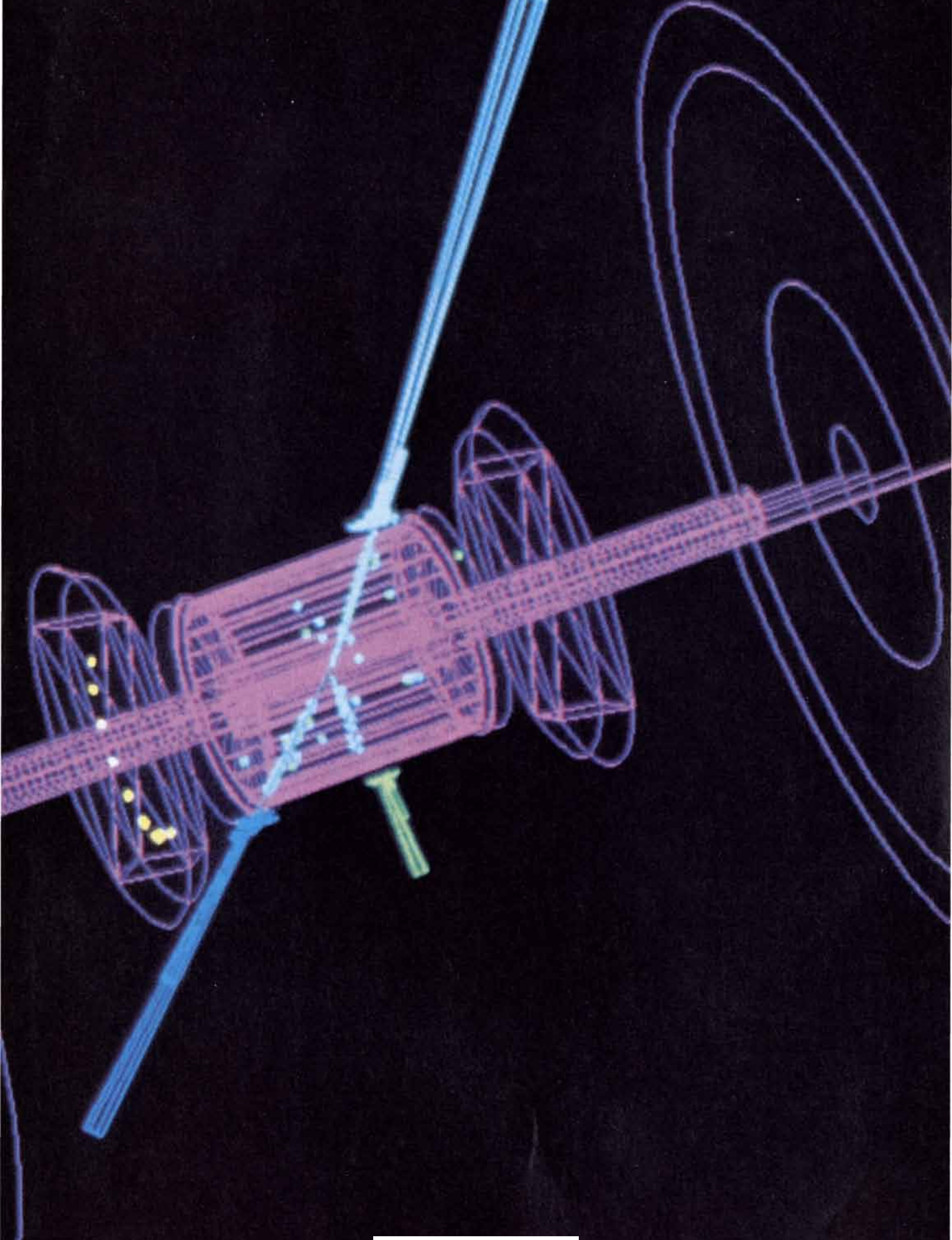

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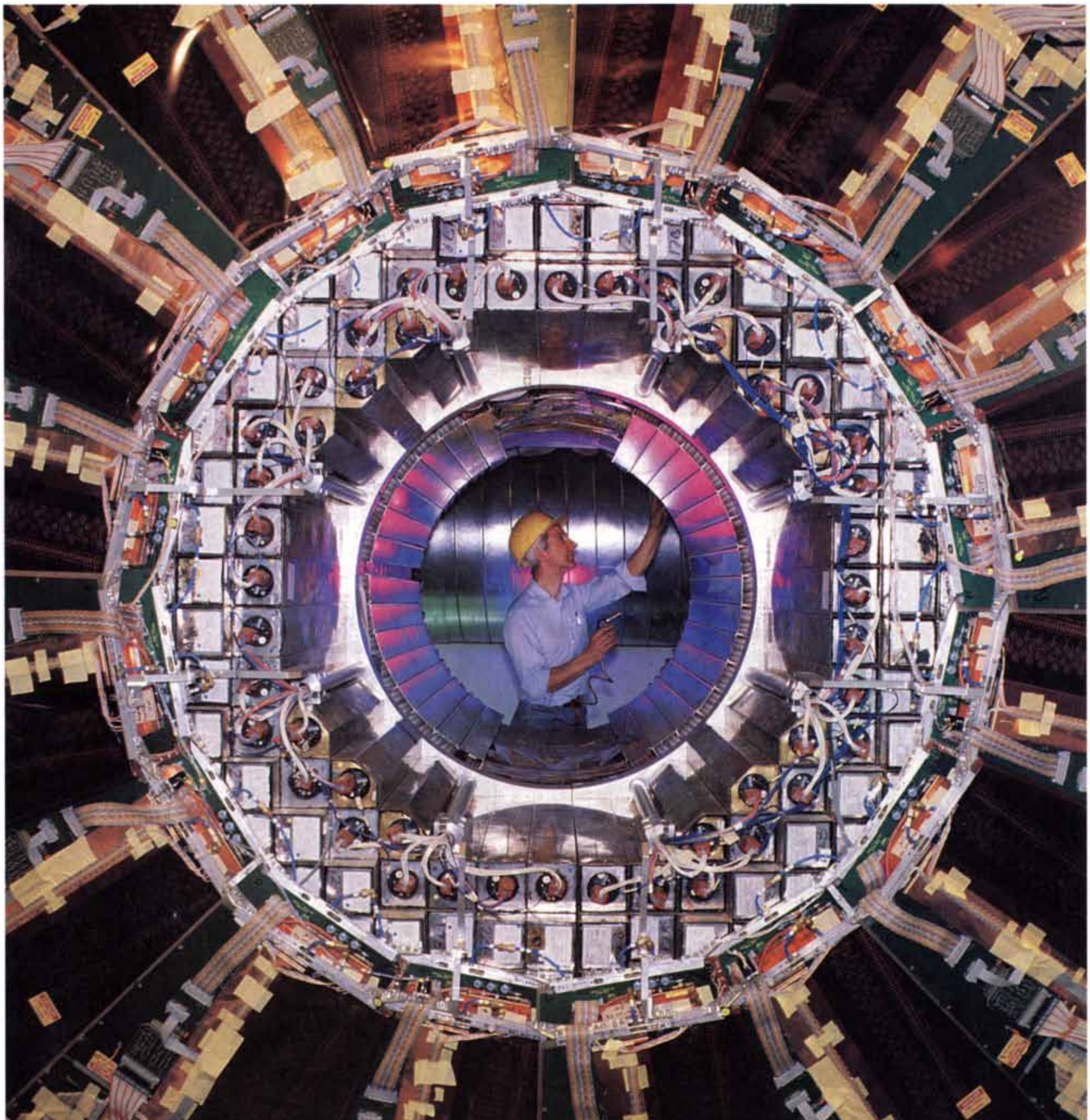
force. To understand the weak interaction, scientists at LEP have precisely determined the mass of the $Z^0$ and have observed how it decays into other particles. These studies have produced convincing evidence that all matter consists of only 12 elementary particles: six kinds of quarks and six leptons. As experiments continue at the LEP Collider, we hope to find new types of matter and study the processes that generate quarks and leptons [see "The Number of Families of Matter," by Gary J. Feldman and Jack Steinberger; SCIENTIFIC AMERICAN, February].

The technologies for tracking and imaging elementary particles have changed dramatically during the past three decades to keep pace with improvements in particle accelerators.

To monitor particle collisions, or "events" as they are often called, physicists once relied on such detectors as cloud chambers, bubble chambers and streamer chambers. In each of these devices, a charged particle is detected as it moves through a medium and leaves a trail of ionized atoms. In cloud chambers the ionized atoms promote the condensation of water droplets. In bubble chambers, ionization initiates the formation of bubbles in a liquid. In streamer chambers the ionized atoms interact with a high-voltage electric field, generating sparks. The trails of water



*OPAL DETECTOR requires a huge number of cables to convey 180,000 channels of information from the sensors to a data acquisition system. Particle beams are directed through the center of the detector.*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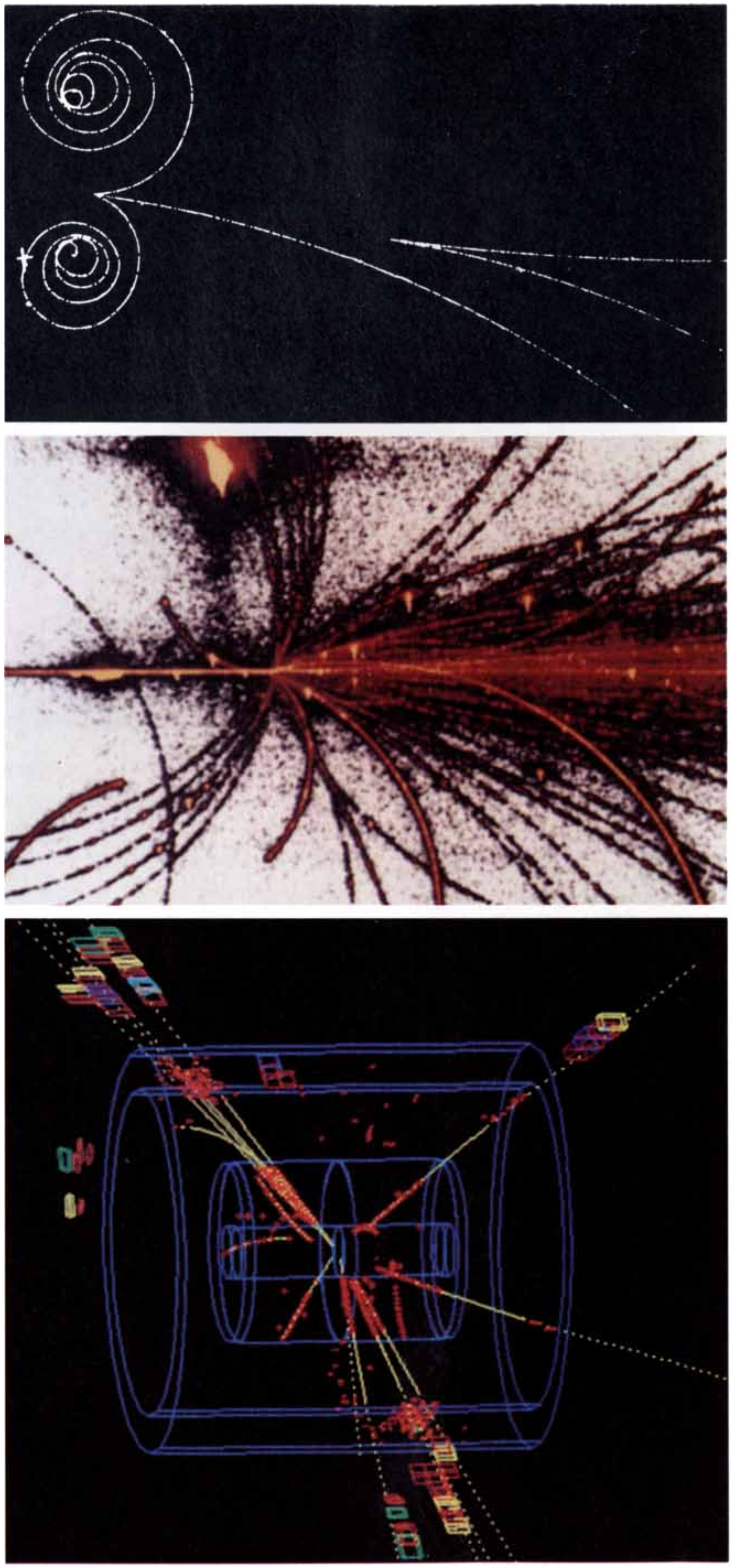
droplets, bubbles or sparks can then be recorded on film.

The photographs provided complete and detailed records of events in a form that experienced physicists can interpret at a glance. In the late 1960s computers were introduced to scan the photographs automatically. Complicated images, however, would often boggle the computer, in which case an operator assisted with the analysis.

Capturing events on film became impossible when accelerators were developed that produced thousands of particles in a second. To record particles at this rate, physicists designed complicated electronic detectors. Because information was gathered in electronic form, computers became an essential tool for making quick decisions during data collection.

Yet physicists still cannot rely exclusively on computers to analyze the data. Computers that automatically inspect events are limited by the expectations of the programmers. Such systems can selectively suppress information or obscure unusual phenomena. Until scientists invent a pattern recognition program that works better than the human brain, it will be necessary to produce images of the most complicated and interesting events so that physicists can scrutinize the data. This strategy was adopted by workers when they began to design the LEP detectors in the early 1980s.

The LEP Collider and its detectors occupy a subterranean tunnel that runs beneath the Jura Mountains across the French-Swiss border. The collider consists of magnets and accelerating cavities that surround a circular track 26.7 kilometers in circumference. The magnets guide electrons and positrons in opposite directions around the track. The cavities impart energy to the particles, accelerating them to 50 billion electron volts. Electrons and positrons collide head-on within the heart of four detectors: Aleph, Delphi, L3 and Opal [see "The



*IMAGES OF PARTICLES evolved as physicists developed an assortment of new detectors. As particles pass through a bubble chamber, they generate trails that can be photographed* (top). *In streamer chambers, particles promote the formation of sparks that can be sensed electronically. The signals are fed to a computer that produces an image* (middle). *The display at the bottom represents data collected by the Delphi detector at LEP. It shows a $Z^0$ decaying into two jets of hadrons and, at the right, two isolated muons.*



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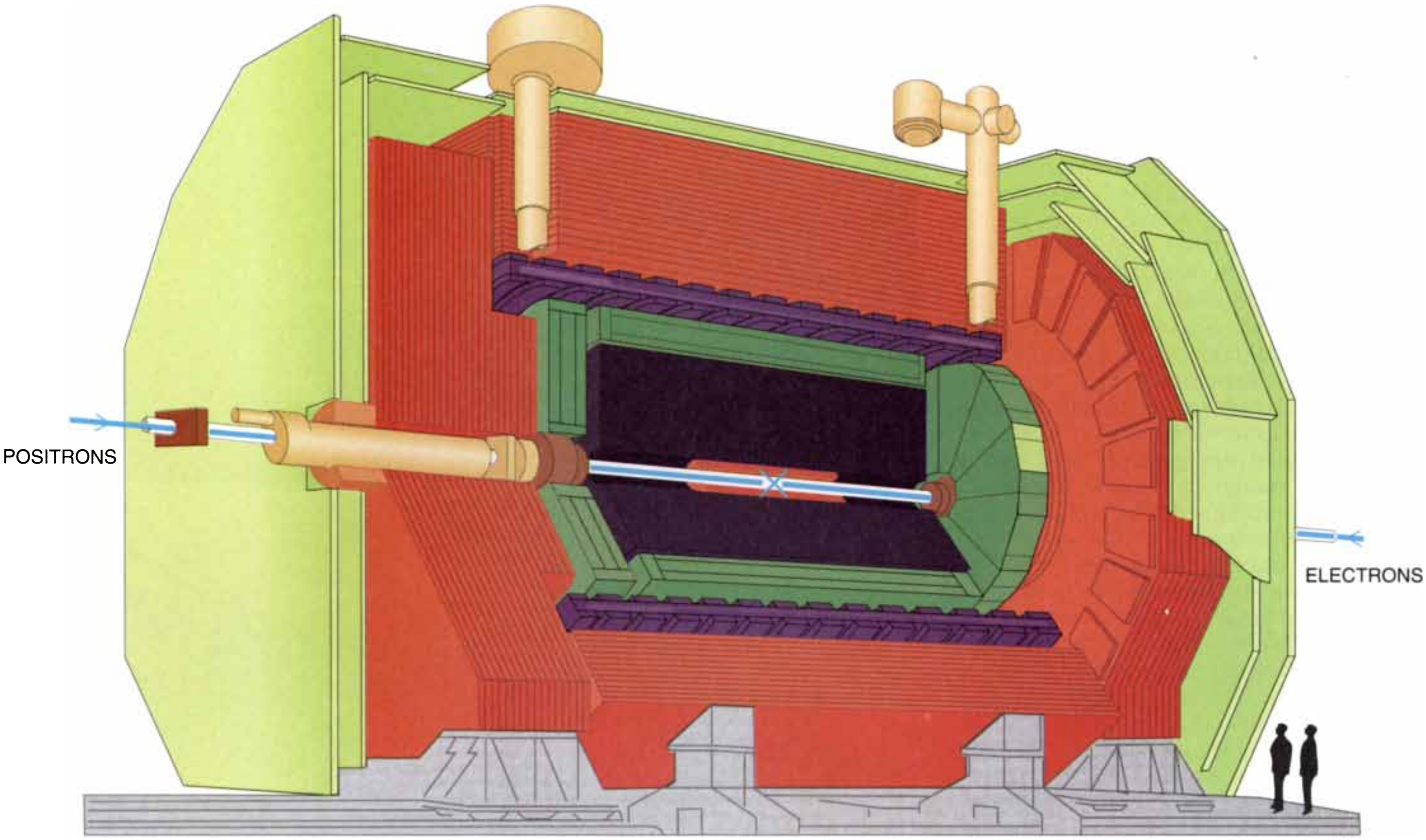


***GRAPHIC PRESENTATION of events allows physicists to visualize the trajectories and energies of particles within the structure of the detector (in this case, the Aleph experiment). The diagram above shows the components of Aleph. Images on the opposite page show three different views of the same event.***

- Muon counter
- Hadron calorimeter
- Magnet
- Electron/photon calorimeter
- Outer tracking chamber
- Inner tracking chamber
- Path of a particle
- Region of the calorimeter that was struck by a particle
- Hadron detection (the length of the bar is proportional to the energy of the hadron)
- Electron or photon detection (the length of the bar is proportional to the energy of the particle)

LEP Collider," by Stephen Myers and Emilio Picasso; SCIENTIFIC AMERICAN, July 1990].

The collisions between electrons and positrons release as much as 100 billion electron volts at a rate unmatched by any other electron-positron accelerator. The energy is turned into a very short-lived particle, almost always a $Z^0$. These particles then decay into many lighter particles.

Measuring as many of these particles as possible is the primary goal of the LEP detectors. To this end, Aleph, Delphi, L3 and Opal use similar methods but rely on somewhat different technologies. The four devices are perhaps the most sensitive and complex detectors ever constructed.

Each detector consists of thousands of tons of sophisticated electronic sensors that nearly enclose the point at which the electrons and positrons collide. A particle produced in the collision first travels into a tracking chamber, which is filled with gas. A charged particle traveling through the gas leaves a trail of electrons. These then pass by sensing wires, producing signals that can later be used to deduce the position of the ionization trail and thereby the trajectory of the particle. The tracking chambers at LEP can typically pinpoint the position of a particle to 50 millionths of a meter.

The next major components of the detectors are the inner and outer calorimeters, which measure the energy of particles. Each calorimeter houses tens of thousands of individual sensors. If a particle hits one of the sensors, it produces a signal that is proportional to the energy of the particle. The location of the sensor within the calorimeter also reveals where the particle traversed the detector.

The inner calorimeter captures only electrons and photons. The outer calorimeter absorbs hadrons—particles, such as neutrons and protons, that are composed of quarks.

Particles known as muons and neutrinos pass through the calorimeters undetected. Muons, which are heavy cousins of the electron, are virtually the only *charged* particles that penetrate the calorimeters, and they are therefore identified in tracking chambers that envelop the calorimeters. Neutrinos, which are neutral, are not detected at all, but their presence can be indirectly deduced from the trajectories and energies of the other particles.

The tracking chambers and most of the calorimeters are surrounded by a magnet whose field influences the behavior of charged particles within the entire detector. Monitoring the effects of the fields helps to identify particles and measure their momentum.

The LEP detectors are designed to cope each second with 50,000 encounters between electrons and positrons. For each encounter, some of the 500,000 components of the detector send an electric signal, which can later be translated into information



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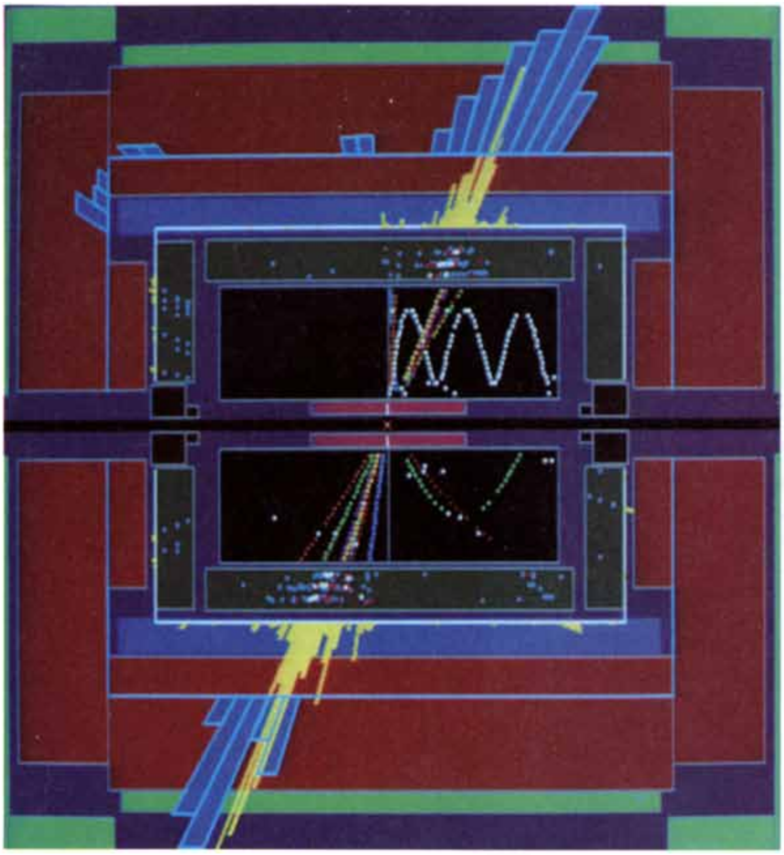
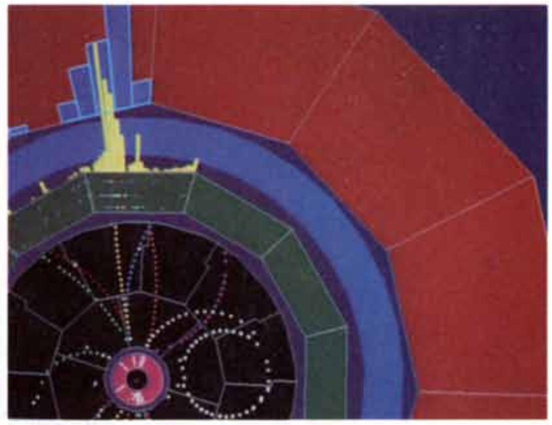
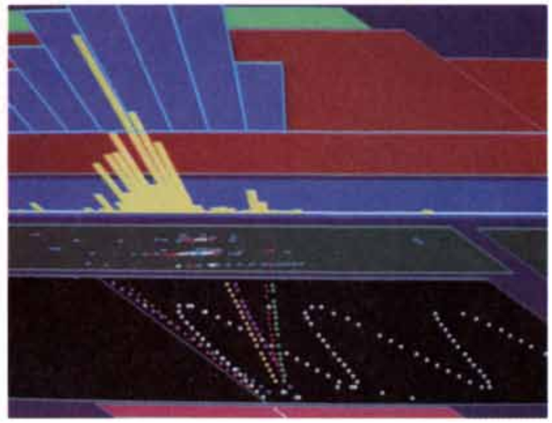

about the position or energy of a particle. The signals are transmitted to an array of electronic data processors. This system searches for key signals that indicate whether an encounter is "interesting." If not, the system discards the data. Only one or two of these 50,000 encounters are eventually stored in the computer system.

To convey the essential information about an event to physicists, we and our co-workers have developed many computer programs that translate data into images. Some programs sort through the data from an event and then attempt to figure out how many particles were produced and how they moved.

Other programs display the trajectories of the particles relative to one another and to the components of the detector. These programs also show where the calorimeters captured the particles and how much energy the calorimeters absorbed. For example, to give an impression of the distribution of energy among the particles, a program can assign colors to the trajectories of particles that fall within a particular range of energy.

Computer programs also allow the user to choose how the data should be presented. By pointing to an object on a computer screen, physicists can call up specific information about that object. Thus, the image on the screen acts as an index to all the information gathered by the detector for an event.

One important feature is the ability to convey three-dimensional spatial information on a flat computer display. If an event is presented from only one point of view, it may be misinterpreted because some tracks that are actually distant can appear to be very close together. To overcome this problem, most programs can display the event from different points of view or shift continuously from one point of view to another as if a three-dimensional model of the event were rotating within the monitor. These techniques make it possible to get a sense of the event in three dimensions and to find, in an efficient way, the clearest perspective.

In the early phases of experiments, event-display programs help physicists identify problems in the detector systems. During initial runs of the detector, the programs occasionally produce images showing inconsistencies between the data and the laws of physics. These inconsistencies can arise because of a malfunction in part of the detector, in the data acquisition system or in data analysis software.

During experiments, physicists routinely scan randomly selected events to ensure that everything is working correctly. This habit also helps them develop a sense of how the detector is operating. The detectors, like all complex mechanisms, have certain quirks. Some regions of the detector can be prone to problems, and others may fail intermittently. Such knowledge is important for an accurate analysis of the data.

Ultimately the event displays serve as a tool for discovering clues to new phenomena. The displays allow physicists to spot unexpected patterns among particles or to find correlations between trajectories and the energy deposited in the calorimeters. By analyzing such patterns and correlations, workers at LEP have contributed greatly to our knowledge about $Z^0$ and the processes that create quarks and leptons.

Because the LEP detectors provide information about structures as small as $10^{-18}$ meter, they may be regarded as extremely high-powered microscopes that reveal the beauty of the smallest components of the universe.


FURTHER READING

GRAPHICAL CONCEPTS FOR THE REPRESENTATION OF EVENTS IN HIGH-ENERGY PHYSICS. H. Drevermann and C. Grab in *International Journal of Modern Physics C*, Vol. 1, No. 1, pages 147–163; 1990.

PARTICLE PHYSICS AFTER A YEAR OF LEP. David J. Miller in *Nature*, Vol. 349, pages 379–387; January 31, 1991.




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# Biosensors

*Sophisticated descendants of the canary in the coal mine are based on molecular components of plants and animals bound to microscopic electrodes or optical fibers*

by Jerome S. Schultz

A 63-year-old man lies in a hospital bed, recovering after a routine hip-replacement operation. Suddenly his heart begins beating irregularly. As physicians and nurses work to restore the heart's normal rhythm, they draw blood samples to analyze the oxygen, potassium and calcium levels, pH, hematocrit and other factors that might provide a clue to the source of the danger.

The laboratory results will typically come back in an hour or more, perhaps too late to be useful. Moreover, information about the patient's blood chemistry 10 or 15 minutes after the arrhythmia has started is not all the physicians want to know; how the blood chemistry changed before the heart began beating irregularly would be even more helpful.

Biosensors—detectors based on selective molecular components of plants or animals—are already making analytical results available at some patients' bedsides within a few minutes. Systems now being developed may be able to provide not merely a snapshot of a patient's condition but a continuous "biochemical videotape."

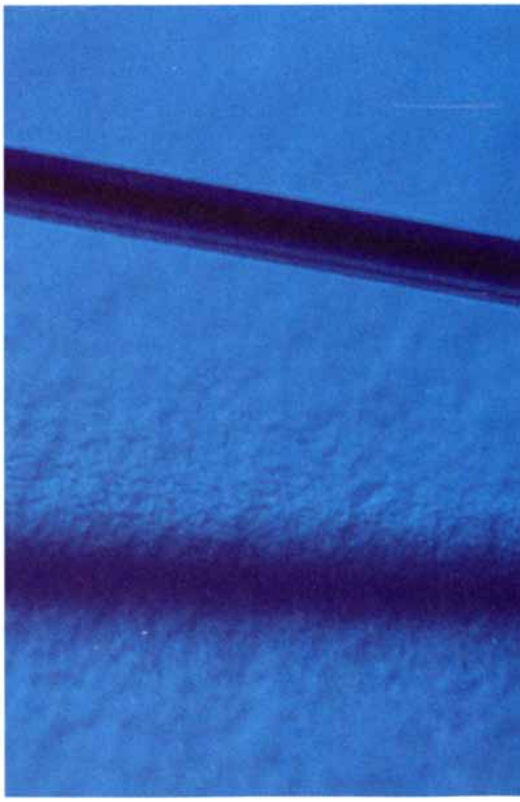
Modern biosensors evolved from the marriage of two disparate disciplines: information technology, exemplified by microcircuits and optical fibers, and molecular biology. The former provides minuscule electrodes or optical sensors; the latter, biomolecules that can recognize a target substance.

The potential applications of these devices are as varied as the molecules that they may incorporate. Medical care stands to benefit most clearly and immediately from biosensors, not only in clinical testing but also in the manufacture of pharmaceuticals and the development of such replacement organs as an artificial pancreas for diabetics. Biosensors are also being used to determine food quality and safety and to detect environmental pollutants.

The evolution of the first biosensor began in the mid-1950s, when Leland C. Clark, Jr., of the Children's Hospital Research Foundation in Cincinnati invented an electrode designed to measure dissolved oxygen in the blood of patients undergoing surgery. He surrounded a standard platinum electrode and reference electrode with a plastic membrane permeable to gases. The voltage bias of the platinum electrode was set so that the rate of current flow through the circuit depended on the rate at which oxygen diffused through the membrane, which in turn was directly proportional to the external oxygen concentration.

By 1962 Clark had extended the "oxygen electrode" to sense blood glucose levels. He coated the oxygen sensor with a layer of gel containing a biocatalyst, the enzyme glucose oxidase, followed by a semipermeable dialysis membrane that allowed glucose to diffuse into the sensor but prevented the enzyme from diffusing out. (The membrane also prevented the entry of enzymes that could degrade the biocatalyst.) The more glucose entered the sensor, the more oxygen was consumed by the enzyme. Lower oxygen readings translated directly to higher glucose levels.

Clark's device never found its way into routine patient care. Its accuracy depended critically on the rate at which oxygen and glucose diffused into the sensor, and that rate could change either as the patient's blood oxygen level varied or as clots formed on the sensor's surface. Nevertheless, the device provided a conceptual base for subsequent work by Clark and others: a biological system sensitive to a particular compound, a physical transducer to convert the chemical change into a meter reading and membranes to separate



**HYPODERMIC NEEDLE holds a glucose-measuring biosensor developed by the author. Glucose diffusing into the sensor displaces fluorescein-labeled dextran molecules from binding sites on the interior wall of the sensor. An optical fiber directs laser light into the sensor to excite the freed dextran; it also carries the resulting signal to a detector.**

JEROME S. SCHULTZ is director of the Center for Biotechnology and Bioengineering at the University of Pittsburgh, where he conducts research on biosensors and immunotechnology. Previously he was chairman of the chemical engineering department at the University of Michigan; between 1985 and 1987 he also served as deputy director for cross-disciplinary research at the National Science Foundation, where he contributed to the development of the Engineering Research Center program. Schultz received his B.S. and M.S. in chemical engineering from Columbia University and his doctorate in biochemistry from the University of Wisconsin.



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sensor elements and protect them from the outside world.

The next major innovation came in 1969, when George G. Guilbault of Louisiana State University at New Orleans built a system to measure urea in body fluids. His device used urease, the enzyme that converts urea into carbon dioxide and ammonia. An electrode sensed the resulting changes in ammonium-ion concentration. Guilbault's sensor marked a significant advance because it relied on potentiometric detection, a technique that has since become widely used.

Whereas Clark's sensor measured the current flowing through the electrode, a potentiometric sensor measures the voltage bias required to maintain current flow at zero. The electrode does not consume any of the reactants and thus is less susceptible to errors caused by changes in external conditions. In addition, potentiometric systems have a logarithmic response curve and so can track concentrations over a 100-fold range.

In the decades following the development of these electrochemical methods, roughly 100 different enzymes have been used in biosensors. Workers have realized, however, that individual enzymes are not the only useful biocatalysts. Recently Garry A. Rechnitz of the University of Hawaii has shown that tissue preparations can carry out a complex sequence of reactions that yield a response to amino acids and other biologically important molecules. Among those used are banana pulp for measuring dopamine, corn kernels for pyruvate, cucumber leaf for cysteine, sugar beets for tyrosine, rabbit liver for guanine and powdered rabbit muscle for adenosine monophosphate.

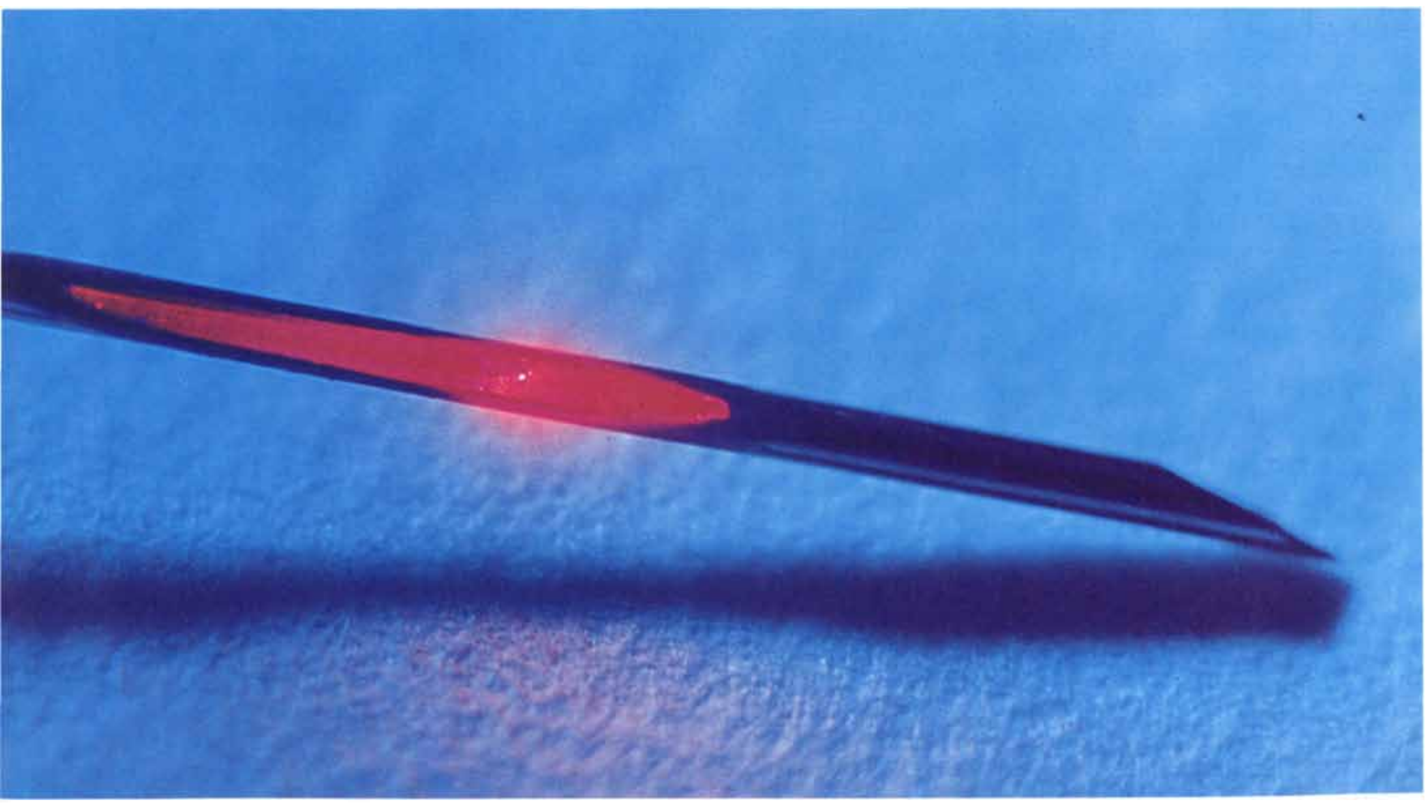
Rechnitz has gone even further in co-opting parts of biological systems: one of his sensors contains an antennule, or small sensing organ, from a Maryland blue crab, dissected to expose its nerve fibers to an electrode. The antennule-based system can measure the concentrations of a number of drugs and environmental toxins.

The crab sensor and devices like it offer the opportunity to unravel their information-transmitting structure and build simpler sensors that incorporate the same molecules. Such sensors also point out the advantages of generality: although enzymes and antibodies provide admirable power to detect a single compound, other biomolecules may be more useful in detecting the presence of any member of a broad class of chemicals. Richard F. Taylor of Arthur D. Little, Inc., for example, has built a sensor incorporating the membrane receptor for acetylcholine, which transmits messages from nerve fibers to muscles. The device can detect several different nerve gases.

One key factor in moving biosensors out of the laboratory and into common use is the development—generally unrelated to biosensor research—of techniques for stabilizing biomolecules and tethering them to surfaces so that they retain their activity. Chopping up bananas to measure dopamine at a patient's bedside is clearly impractical. Many of the same techniques used to affix enzymes or antibodies to a surface so that they can be used in laboratory assays or biochemical manufacturing, however, can also be used to attach molecules to a biosensor.

Although removing proteins from their cellular environment can disrupt their structure and expose them to chemical attack, the same techniques that affix proteins to a substrate also tend to stabilize them. The chemical bonds that hold a protein molecule to a polymer bead, for example, may cross-link parts of the protein so that it is less likely to unfold and becomes more resistant to enzymatic degradation. As a result, biosensors can be stored in either moist or dry conditions for a week, a month or, in some cases, as long as a year without losing sensitivity.

Advances in membrane technology have also given biosensor workers a free ride in improving their systems. Membranes can now be tailored to separate solutes based on molecular size, charge or solubility. One widely used laboratory assay system has as many as a half dozen membrane layers, each





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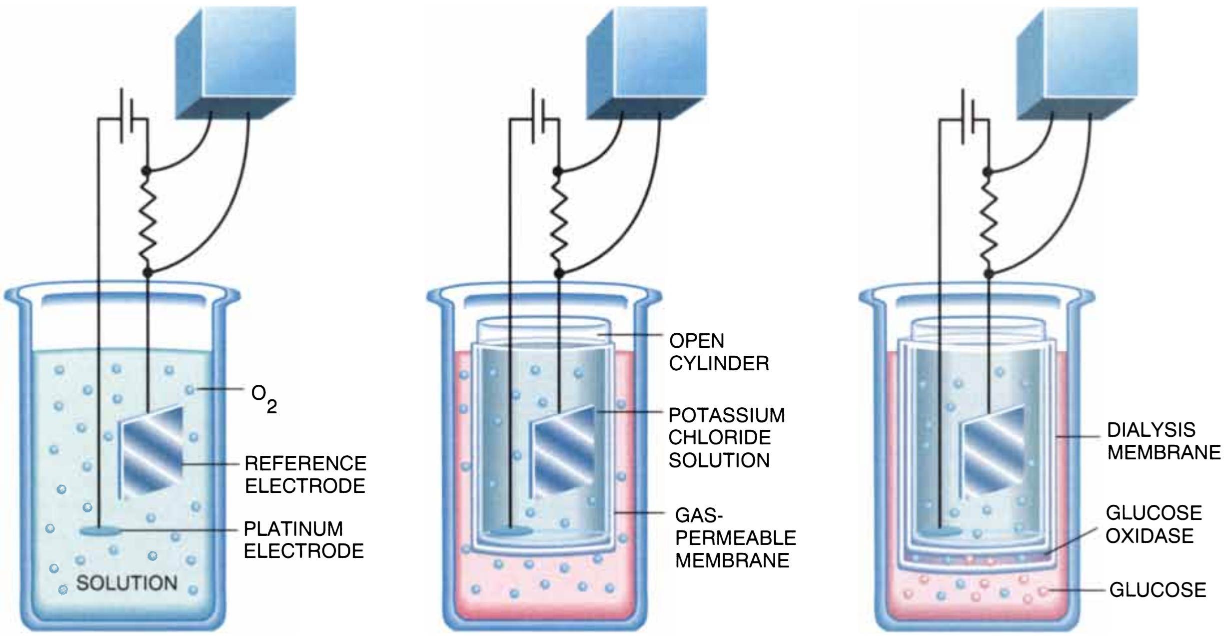
## Evolution of the Glucose Biosensor




CURRENT FLOW between a biased platinum electrode and a reference electrode measures the amount of oxygen in a solution.

GAS-PERMEABLE MEMBRANE isolates electrodes from blood or other biological fluids but allows oxygen to diffuse into the potassium chloride solution surrounding the electrodes.

DIALYSIS MEMBRANE–permeable to ions and small molecules–encloses gel containing glucose oxidase enzyme, which converts glucose to gluconic acid and consumes oxygen. The rate at which oxygen reaches the inner solution depends inversely on the level of glucose in the blood.

with different properties and incorporating different reagents. Recent progress in understanding lipid bilayers, which are similar to the bilayers in the walls of living cells, may make it possible to incorporate receptor proteins from cell membranes (such as the acetylcholine receptor) into a biosensor, under conditions that mimic the receptors' natural environment.

Although biotechnical innovations have certainly improved biosensors, it is the semiconductor industry that has made them cheap and readily available. In the early 1970s James B. Angell of Stanford University and Kensall D. Wise of the University of Michigan built multiple miniature electrodes on a silicon chip that could make electrochemical measurements on neural tissue. And Jiří Janata of the University of Utah coated the gate of a field-effect transistor with the antibody surrogate concanavalin A (ConA), spawning the CHEMFET detector. Research on these devices has led to general techniques for combining chemical components and integrated circuits in a single system.

Clark's first glucose sensor was roughly a centimeter in diameter; during the past decade, manufacturing techniques initially developed for integrated circuits have made possible the production of miniaturized sensor electrodes only a few hundredths of a millimeter across. Machines essentially equivalent to computer ink-jet printers lay down reagents and membranes on top of the electrodes in precisely registered patterns. These manufacturing methods can stamp out thousands or even millions of identical sensors at a very low unit cost. As a result, a medical worker can discard a sensor after making a single patient measurement, avoiding the risk of contamination.

Such low-cost sensors are also a boon to diabetics, who must test their blood sugar levels several times a day. One system, based on the work of Anthony P. F. Turner of the Cranfield Institute of Technology in England, combines a sensor, integrated-circuit amplifiers and a liquid-crystal display in a package the size of a fountain pen. Its enzyme converts glucose to gluconic acid, as in Clark's original sensor, but then a mediator called ferrocene returns the enzyme to an oxidizing state and is itself reactivated by current from the electrode. The monitor does not consume any reagents and has the potential to function for long periods.

Meanwhile the range of chemically sensitive electrodes available has broadened, so that workers can exploit enzymatic reactions that produce changes in quantities other than just oxygen concentration or pH. Biosensors for several different substances can be placed on a single chip. A physician could thread a catheter containing such a chip into a patient's vein and make continuous measurements of blood chemistry or other factors in much the same way that instruments now monitor heart rate, blood pressure or brain function.

Whereas some researchers have miniaturized electronic biosensors, others have developed entirely new systems based on optical sensing. Rapid innovations in the communications and semiconductor industries have made available low-loss fibers, circuitry for processing optical signals, integrated beam splitters and wavelength filters, and miniaturized,



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spectrally pure light sources, such as light-emitting diodes and solid state lasers. In 1969, at the National Institutes of Health, Gerald G. Vurek and Robert Bowman demonstrated one of the first fiber-optic sensors for clinical analysis, a colorimeter that measured the binding of dyes to kidney tubules. Optical fibers can serve as remote spectrophotometers to measure the reflection or transmission spectrum of a fluid; fluorimeters to sense reemission of particular wavelengths of light; or turbidimeters to measure light scattering.

There are three broad categories of fiber-optic biosensors. The first, a straightforward extension of electronic biosensor techniques, simply detects changes in a target substance's optical properties rather than in its electrical ones. The other two, evanescent-wave and surface plasmon devices, make use of the particular way that optical fibers transmit light.

The first kind of optical biosensor consists of a cell bounded by a semipermeable membrane, reagents inside the membrane or bound to its inner surface, a fiber to illuminate the cell and detectors to measure the change in optical properties. In most cases, a single fiber both carries light into the cell and collects transmitted or reflected light for analysis.

My own work as a biochemical engineer on various artificial-organ projects led me to apply these optical techniques to build yet another glucose sensor, one that might eventually be suitable for an artificial pancreas. The physicians I worked with pointed out that there were many excellent insulin pumps, but all the devices still had to be programmed by hand based on the results of pinprick blood tests. The ideal sensor from a clinical point of view would make continuous readings; it would consume neither glucose (thus yielding a true equilibrium measurement) nor reagents; it would have no electric connections to the body; and, if at all possible, it would be noninvasive, so that long-term inflammation or other reactions could be avoided.

The device I built fulfills most, but not all, of the clinical requirements. In addition, it serves as an archetype for optical biosensors that can detect a virtually unlimited range of molecules. It is based on the fluorescent immunoassay technique used in clinical analyses. In this case, ConA, which binds both glucose and dextran (a glucose polymer), is bound to the interior of a hollow dialysis fiber, a membrane originally developed for an artificial kidney. The fiber is filled with a dilute solution of fluorescein-labeled dextran. The dextran complex cannot diffuse out, but glucose can diffuse in. As glucose enters the sensor, it displaces dextran from some ConA binding sites; the higher the glucose concentration, the more dextran is forced into solution. Meanwhile light transmitted through an optical fiber causes the dextran complex in solution to fluoresce, thereby producing a signal; dextran bound to ConA on the walls of the dialysis fiber is not in the path of the light and so produces no signal.

The dialysis fiber does not merely provide an isolated volume in which the reaction can take place; it also conserves the reagents. In a typical laboratory assay, the fluorescein-labeled dextran (or other marker) forced into solution would be lost. For that matter, the ConA (or an antibody) could not be reused after direct exposure to body fluids. Packaging the entire system in a biosensor permits continuous, long-term measurements. The one remaining Achilles heel of the device is that it is invasive—it must be placed inside tissue to maintain contact with the blood. Eventually infection or inflammation will ensue; no one has yet figured out how to make the body accept probes of this kind for long periods.

The second type of optical sensor, which is based on the evanescent-wave approach, does not have to infer the number of labeled biomolecules displaced from a receptor from the number in solution. It senses competitive binding directly. Evanescent-wave detectors rely on the fact that the energy of a light wave transmitted through an optical fiber does not travel only through the core of the fiber; instead part of it travels through a region that extends outward roughly 1,000 angstroms into the medium surrounding the core. If a fiber's protective cladding is removed, any material adhering to the core can absorb this evanescent wave and fluoresce.

The late Tomas B. Hirschfeld of Lawrence Livermore National Laboratory attached antibodies to the surface of a decladded fiber and measured the natural fluorescence of antigens that bound to them. Evanescent-wave sensors can also measure competitive binding of the kind employed in my glucose sensor. If one binds antibodies to the fiber and then adds a known quantity of fluorescently labeled antigen and an unknown analyte, the amount of fluorescence caused by the evanescent wave indicates the ratio of labeled antigens to the unlabeled ones in the sample being tested.

An alternative to the evanescent-wave method, a so-called surface plasmon device works by means of a film of metal, such as silver, deposited on the surface of a thin piece of glass that acts as a light guide. The conductive film provides a pathway (the plasmon) for light energy and so changes the critical angle of incidence at which light is trapped within the glass. The new critical angle depends very sensitively on the amount of material adsorbed on the metal film. The surface plasmon signal does not require labeled molecules and competitive assays; if antibodies or other bioreceptors are attached to the de-

## Biosensors and Their Applications

| Substance Measured | Biological Sensor | Physical Sensor |
|---|---|---|
| Benzo(a)pyrene | Antibody to benzo(a)pyrene | Optical-fiber fluorimeter |
| Creatinine | Creatinine iminohydrolase | Ammonia field-effect transistor |
| Ethanol | NADH and dehydrogenase | Oxidation-reduction electrode |
| Gamma globulin | Antibody to gamma globulin | Polarized light |
| Lidocaine | Antibody to lidocaine and ferrocene-lidocaine complex | Oxygen electrode |
| Nerve gas | Acetylcholine receptor | Conductivity measurement |
| Parathion | Antibody to parathion | Piezoelectric crystal |
| Penicillin | Beta-lactamase | Thermistor |
| Testosterone | Bioluminescence enzymes: dehydrogenase and luciferase | Optical-fiber fluorimeter |
| Theophylline | Antibody to theophylline | Surface plasmon resonance |
| Vitamin $B_{12}$ | Bacteria (*Escherichia coli*) | Oxygen electrode |



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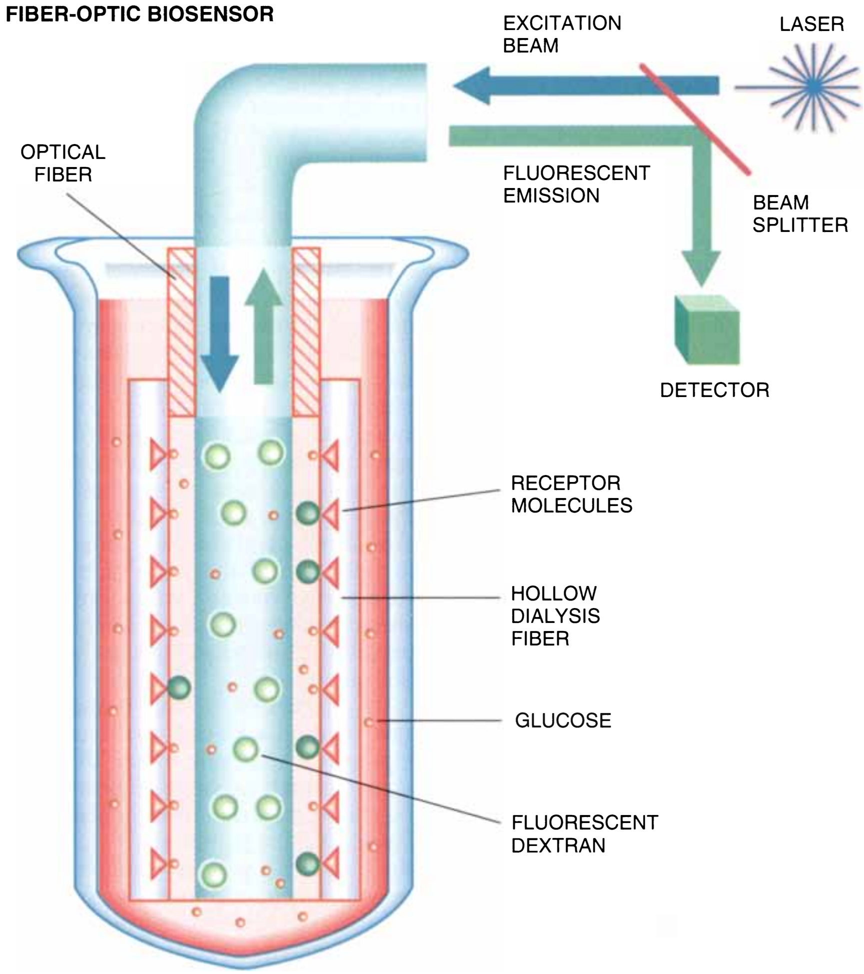


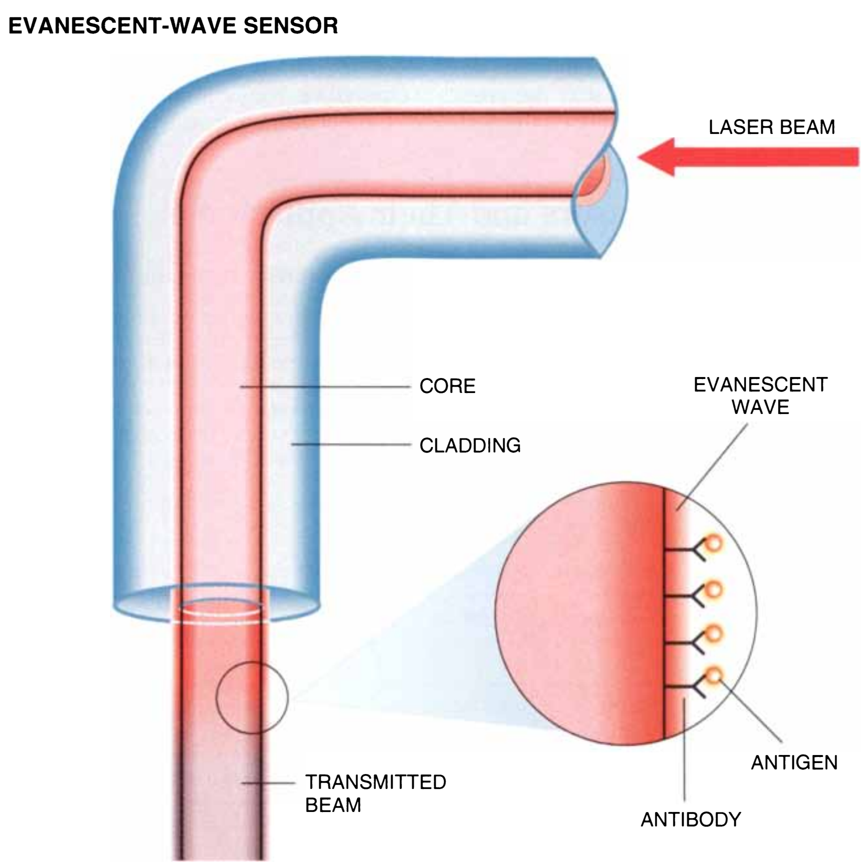


vice, it is possible to measure precisely how much material in a fluid sample binds to those receptors.

Because the surface plasmon method does not require labeled molecules, it can be used in biosensors for a wide range of substances. Indeed, one company, Pharmacia, has created a system, intended for research laboratories, that contains generic surface plasmon sensors. Workers deposit whatever biomolecule they want to investigate on these sensors.

Although biosensors are currently most prevalent in medical uses, other applications may prove at least as important in the long run. For example, a sensor developed by Isao Karube and Shuichi Suzuki of the Tokyo Institute of Technology measures biochemical demand for oxygen, an index of the level of organic materials in polluted water. The sensor, based on a yeast, produces readings in 30 minutes as opposed to the five days required by conventional methods.

Other sensors could be used to monitor such toxic chemicals as polychlorinated biphenyls (PCBs), chlorinated hydrocarbons or aromatic compounds. In the event of an accident, the sensors trigger an automatic, immediate response and inform emergency teams of exactly what compounds they are about to confront.

Unpleasant and potentially dangerous compounds enter the environment not only as a result of accidents. In the case of food, they accumulate as a part of the normal process of spoilage. Both Canadian and Japanese companies are marketing biosensors that measure the level of xanthine and other compounds in fish to determine its freshness. (In

**FIBER-OPTIC BIOSENSOR (*top*) contains receptor molecules fixed to the inner wall of a semipermeable dialysis membrane and large fluorescently labeled molecules (dextran) that bind to the receptors. When glucose molecules diffuse through the membrane, they displace labeled molecules. The displaced molecules are trapped in solution within the membrane. They absorb focused laser light entering the sensor and produce a signal proportional to the number of unlabeled molecules that have displaced them. An evanescent-wave sensor (*bottom*) exploits the fact that some of the energy passing through an optical fiber penetrates the boundaries of the light-guiding core. Antibodies or other biomolecules attached to the surface of a decladded fiber can bind the compound to be sensed, which then absorbs part of the evanescent wave and thereby produces a signal.**



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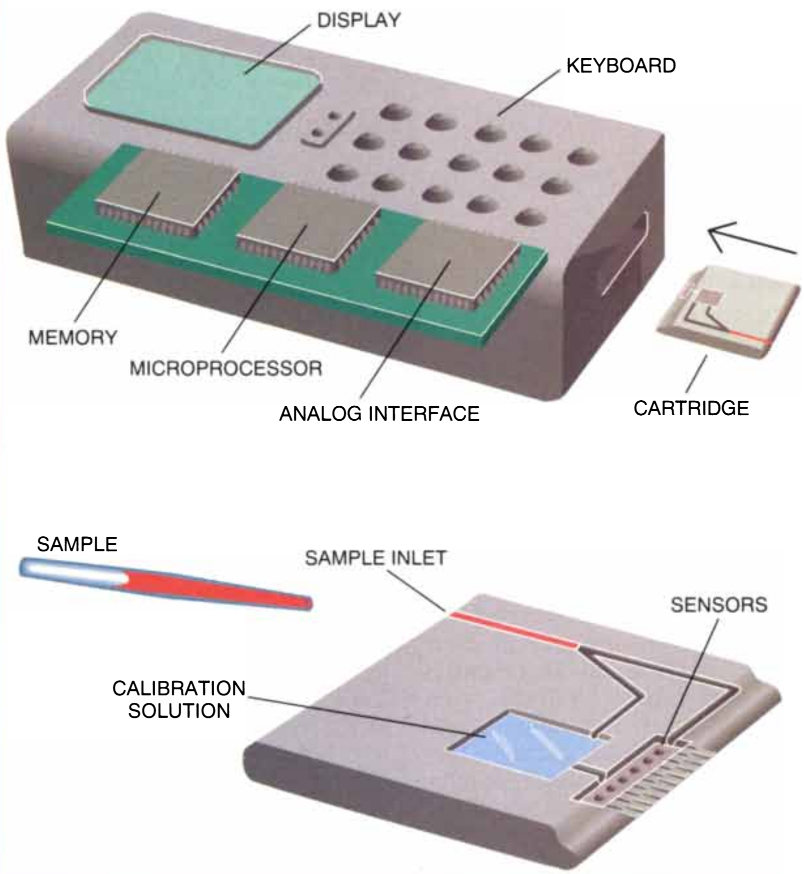
## Bedside Analysis




A hand-held analyzer currently under evaluation at the Hospital of the University of Pennsylvania demonstrates how biosensors might find their way into clinical use. The I-STAT PCA is one of several bedside biosensor systems now being readied for what could be a substantial market. It simultaneously makes six commonly requested chemical measurements on a patient's blood—sodium, potassium, chloride, urea nitrogen, glucose and hematocrit—producing results in less than two minutes. The bedside tests cost more than ones performed in a central laboratory, but their immediacy may make them more effective.

The PCA achieves accuracy comparable to that of laboratory equipment by using a disposable cartridge containing six biosensors and a calibration sample. A medical worker places 60 microliters of blood in the cartridge; the analyzer then measures both the calibration sample and the patient sample. It displays test results and also stores them, keyed to time and the patient's identification number, for later analysis. The cartridge-based design adopted by manufacturers will make it possible to perform a different set of tests once the appropriate sensors have been developed.

Japan the freshness index of fish is typically printed on the package.) Sensors to measure the quality of beef and other foods are also being developed.

Industrial process control is a final area in which biosensors could make a substantial difference. Although detectors in automated chemical process plants can already measure pressure, temperature and acidity in real time, biosensors will be able to determine the chemical composition of materials in the process flow as well. Such measurements are especially important in the biotechnology industry, which currently has no way to monitor precisely the culturing of microorganisms in fermenters that produce such drugs or active proteins as interferon or insulin. Indeed, biosensor development could feed back synergistically so that improved manufacturing techniques could allow the cheaper production of a wider range of sensing molecules.

Even as the range of biosensor applications expands dramatically, investigators are exploring the possibility of a generation of sensors that would eliminate the distinction between the biomolecule that senses a compound and the electrode that senses the molecule's response. Adam Heller of the University of Texas at Austin, for example, has introduced electron "relays" into a protein so that chemical binding would be telegraphed directly to an electrode instead of being measured indirectly by mediators or by changes in quantities such as pH or oxygen consumption. Such an approach would enable biosensors to attain much higher sensitivities. If researchers can tailor the chemical properties of such electroactive molecules as well, they could also build more selective biosensors.

Biosensors will always be less sensitive and specific than laboratory assays because of the trade-offs required to make an instrument that works rapidly and reliably in the field. The ultimate rival of the biosensor, however, is nature itself, and in some cases it is clear that researchers will soon be able to build detectors that are more sensitive and specific—and faster to respond—than the organisms from which their molecular mechanisms are derived.

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# Beewolves

*The females of these insects are voracious predators, each year capturing many bees to feed to their young. The males are highly aggressive and fight among themselves for access to females*

by Howard E. Evans and Kevin M. O'Neill

Winging her way rapidly through the air, a beewolf suddenly changes course. Turning, she dives toward a cluster of flowers, where she homes in on a honeybee sipping nectar. Once her target is within range, no time is lost: the beewolf swoops down—legs extended—and in less than three seconds has grabbed her victim and stung it with a powerful, paralyzing toxin. She then tucks the bee under her abdomen and flies off to an underground nest, where the newly captured prey becomes food for her offspring.

Dramatic encounters like this one take place many times during the summer months, when beewolves are active. Indeed, aggregations of beewolves present scenes of high drama to an observer, with their constant comings and goings and the diverse interactions that take place among themselves and their prey, parasites and predators. Having observed beewolves for a number of years, we find they have much to recommend them as objects of biological study.

These voracious insects are neither bees nor wolves but wasps in the family Sphecidae; the name simply reflects their penchant for bees. Although the females are adept hunters, males do not hunt, and only the larvae partake of other insects. Adults feed exclusively on nectar and for that reason have been given the generic name *Philanthus,* which means lover of flowers in Greek; a stark contrast, indeed, to their more ominous-sounding common name.

HOWARD E. EVANS and KEVIN M. O'NEILL have collaborated on studies of beewolf behavior for more than 15 years. Evans is professor of entomology emeritus at Colorado State University, where he has been since 1973. Before then, he was curator of Hymenoptera at Harvard University's Museum of Comparative Zoology. Evans has a Ph.D. in entomology from Cornell University and is author of 12 books and more than 200 articles on insects and their behavior. O'Neill received his Ph.D. in entomology from Colorado State, where he studied under Evans, and is now assistant professor of entomology at Montana State University. O'Neill has written one book (with Evans) and 35 papers on insect behavior and ecology.

The Nobel Prize–winning ethologist Niko Tinbergen popularized the term "beewolf" and began the first rigorous studies of their behavior in the 1930s; since then, much has been learned about these fascinating animals. They are among the most commonly encountered wasps, and although some species are quite small—from seven to eight millimeters long—others are as long as 22 millimeters. In addition, many are brightly colored, marked with bands of yellow across the abdomen, which makes them easy to spot in the field and a pleasure to watch. Of the 136 species of *Philanthus* known to exist in the world, 34 live in North America.

To our great fortune, several of those species thrive in such appealing natural areas as Grand Teton National Park and Yellowstone National Park, as well as in the Great Sand Dunes of southern Colorado, where many of our observations have been carried out. But they are frequently found in more mundane places, too, including urban areas, where the soil is bare and crumbles easily. Any spot where the soil lends itself to digging—forest clearings, eroded hillsides, dirt paths, sandy pits—is often carpeted with the nests of beewolves.

Over the past 15 years, we have spent summers studying more than 20 different species and observing their varied behaviors under natural field conditions. In pursuing our research, we wanted to determine qualitative differences between species. How, for example, do they differ in terms of prey preferences, nesting behaviors, mating strategies and other activities?

Because females build the nests, lay the eggs and hunt, much of our time in the field has been spent watching them. More recently, however, we have focused our attention on the males, which are now known to have a behavioral repertoire as rich and complex as that of the females. In both cases, interpreting the behavior of these insects in terms of its evolutionary adaptiveness has at once given us great pleasure and provided us with a long-lasting intellectual challenge.

Before we describe behaviors unique to various species with which we are familiar, a look at the basic life cycle common to all beewolves is warranted. Like other wasps in the family Sphecidae, beewolves dig nests in the soil and deposit their eggs in subterranean cells provisioned with insect prey. Adults emerge from their nests anytime from late spring to late summer (depending on the species) and generally live no longer than three or four weeks. Males emerge a few days before the females and seek out a small patch of ground, or territory, which they then zealously guard against intruders. When the females emerge, they are attracted to the territories, and mating follows. Once females have mated, they begin to construct their nest or burrow—a necessary prelude to egg laying.

In all *Philanthus* species the burrow consists of a single entrance, a main tunnel and a series of individual cells, ranging in number from as few as two or three to as many as 17 or 18, depending on the species. Initially the female excavates only the main tunnel; she subsequently digs the cells one by one, as prey are gathered to fill each of them.

When the main tunnel is completed, the female embarks on her first prey-capturing mission. On returning to the nest, she deposits a paralyzed bee on the tunnel floor and then leaves to collect additional prey. After several such



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trips (each one lasts anywhere from five to 45 minutes) and after the beewolf has enough prey to fill a cell (from four to 20 insects, depending on their size), she digs the first cell, drags her paralyzed cache into it and then lays an egg on the bee nearest the cell entrance. She immediately closes off the cell with dirt, thus creating a barrier to intruders, and then moves on to start another cell.

Mass provisioning the cell in this way (rather than bringing prey to her offspring on a progressive basis) would be impossible were it not for a remarkable quality of the beewolf's venom. The venom induces deep and permanent paralysis in insects, which effectively preserves them in a state of suspended animation and so provides the larva with a fresh supply of food to see it through development. No further contact is made between mother and offspring; when the egg hatches—in about two days—the larva begins to devour the prey in its cell. Eating rapidly, it reaches full size in a week to 10 days and then spins a cocoon, overwintering underground in its cell. When the adult emerges the following spring or summer, the cycle begins anew.

Females tend to aggregate, often forming densely populated nesting sites, because of the limited availability of good burrowing soil. Consequently, two or more species are often seen occupying the same site. The most diverse locality known to us lies in the San Rafael Desert of Utah. There in a three-day period we collected 10 species along a 15-kilometer stretch of road. Overlap to such a degree suggests that competition for resources might be intense, but in general we observed that species occupying the same site have evolved different activity periods, prey preferences or body sizes (the last being accompanied by a corresponding difference in prey size).

For example, of four species we found nesting together in north central Colorado, two were highly specific in their choice of prey, whereas two were generalists. One, *Philanthus inversus,* captured only male sweat bees (so called because they are attracted to human and animal sweat), whereas the other, *P. bicinctus,* preyed only on bumblebees (and so has come to be called the bumblebeewolf). In contrast, *P. barbiger* and *P. basilaris* preyed on almost any type of bee or wasp. But because the two beewolves differ considerably in body size, they were only occasionally observed exploiting the same prey. Thus, even though four

**MATING BEEWOLVES, such as the *Philanthus bicinctus* pair shown, perch on vegetation (in this case, snakeweed) that grows in or near the male's territory. The male, having linked his genitalia to the female's, typically remains coupled to her, facing downward, for about five minutes before disengaging.**



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species shared the same habitat, not one competed to any significant degree with another.

A second feature of beewolf nesting sites (related, we think, to their overall scarcity) is longevity. Although individuals live for three to four weeks at most, the same sites tend to be occupied by generation after generation. We know, for instance, that beewolves have colonized one site in Yellowstone for at least 30 years and another in Grand Teton for more than 23 years. Yet only in *P. gibbosus* have the burrows themselves been reused by subsequent generations.

Site specificity, however, has its price. Over the course of many generations, predators and parasites also become entrenched at the nesting sites. In fact, those of us who study beewolves in the field are immediately impressed by two phenomena: the ubiquity of their parasites and the various strategies that are employed to evade them.

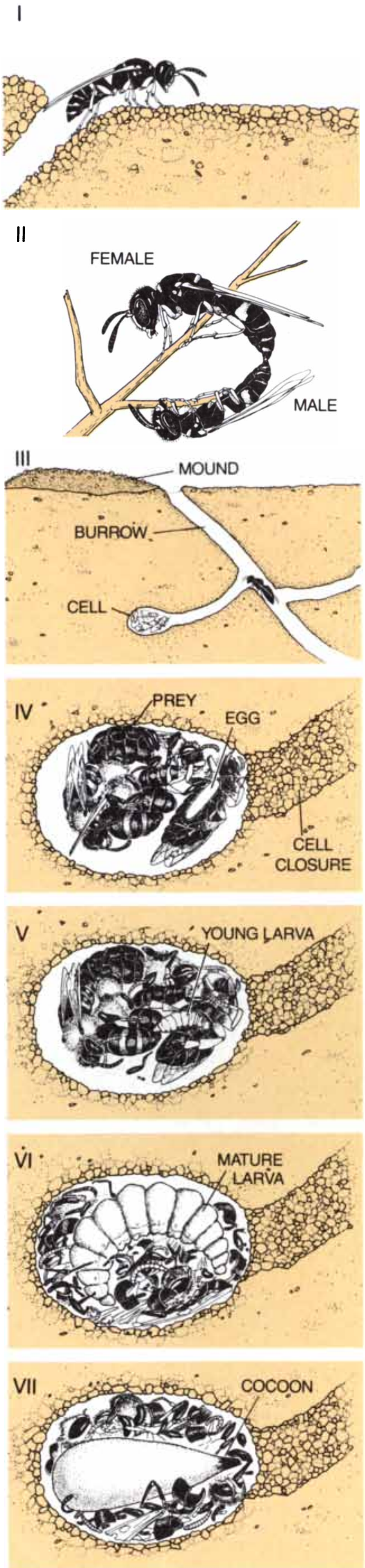
Anyone observing beewolves cannot help but notice the presence of certain types of flies and parasitic wasps that abound at the nesting sites. Rates of parasitism are high, reaching as much as 40 percent in some places, and we think that fact may explain much of the behavioral diversity observed in *Philanthus.* Without question, the most abundant natural enemies of beewolves are the cleptoparasites, so called because they deposit their newly hatched larvae on the beewolf's paralyzed prey, thus effectively stealing it (only later do they incidentally devour the beewolf egg). The efficiency with which cleptoparasites attack the prey can be attributed in part to their rather unusual mode of development. They are larviparous, that is, the females give birth to larvae (maggots), which hatch from eggs inside their mother's genital tract and are then deposited on a beewolf's prey ready to start eating.

Probably the most abundant North American cleptoparasite is the satellite fly *Senotainia,* which hovers around *Philanthus* females as they return to the nest. The fly's strategy is simple: as a beewolf pauses at the nest opening, the satellite fly dashes toward her and in a matter of milliseconds deposits a small maggot on the paralyzed prey. Other cleptoparasitic flies are hole searchers: they look for nest openings in the soil and then either enter the tunnel directly (*Metopia*) or scratch their way through the nest closure (*Phrosinella*), laying their maggots on prey already inside the nest. Two groups of wasps also parasitize the nests of beewolves: velvet "ants" (wingless wasps) belonging to the family Mutillidae and cuckoo wasps in the family Chrysididae. They, too, are hole searchers.

We believe that as a consequence of such selection pressure, beewolves have evolved a number of interesting strategies for thwarting their enemies. Some species, for example, consistently level the mound of excavated dirt at the nest entrance and by doing so may render the site less visible to attackers. Others close the nest opening when they leave, blocking the entry of *Metopia* flies. Unfortunately, the latter tactic has its costs: because a female must pause to remove the closure when she returns to the nest, a *Senotainia* fly has just enough time to lay a maggot on the beewolf's prey.

One activity practiced by several species seems to deter both *Senotainia* and *Metopia* flies. By excavating an accessory or false burrow entrance not far from the real one, a female confuses her attackers, causing them to lay eggs or larvae at the wrong spot. Although we have not tested the hypothesis that these accessory burrows actually lower rates of parasitism, we do know that *Metopia* flies are readily attracted to holes we make in the ground with a pencil or nail. We also know from research carried out on other species of ground-nesting wasps by Katsuji Tsuneki (recently retired from Fukui University in Japan) that rates of parasitism vary according to the presence or absence of accessory burrows. At a field locality in Japan, where two species occur together, the one that consistently dug false burrows had only 9 percent parasitism, whereas the one that did not suffered from 44 percent parasitism.

Another strategy that apparently deters parasites is evasive flight behavior. Most females fly erratically as they approach their nest, a tactic that seems to shake off pursuers. Flight maneuvers differ depending on the species and may include freeze stops in midair,




**LIFE CYCLE OF BEEWOLVES begins from late spring to late summer, depending on the species. Males emerge first (*I*) and mate several days later when the females appear (*II*). After mating, a female constructs the underground burrow (*III*) in which she will deposit her prey and lay her eggs, sealing off the entrance after she leaves (*IV*). A day or two after an egg is laid, the larva hatches and begins devouring its prey (*V*). About a week later, when the larva reaches full size (*VI*), it spins the cocoon (*VII*) in which it will overwinter and metamorphose into an adult.**



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aborted landings, stepped descents and flying in irregular patterns. David McCorquodale, then at the Unversity of Alberta, studied the approach flights of six species of digger wasps (two of them beewolves) and found that those with the more elaborate flight maneuvers were most successful at eluding their attackers.

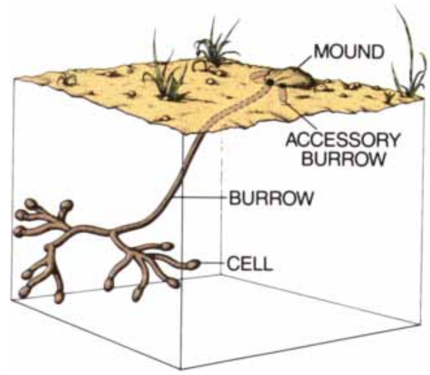
Although aggregate nesting encourages the buildup of parasite populations, it may also provide the beewolves with a defensive advantage by lowering the probability that any one individual will be parasitized. Such was the finding of William T. Wcislo of the University of Kansas, who studied rates of parasitism in an aggregation of ground-nesting wasps in Michigan. He inferred that individuals benefit by seeking safety in numbers, following the "selfish herd" hypothesis of William D. Hamilton of the University of Oxford.

Admittedly, most of the evidence linking different nesting behaviors to selection pressure provided by parasites is circumstantial. To show conclusively that such a correlation exists, we must collect more data on the percentage of cells parasitized in a population as compared with the preponderance of antiparasitic behavior exhibited by wasps in that population. Although the behaviors themselves are easy to record, we can tabulate parasitism accurately only by excavating each burrow and rearing its cells' contents to determine the number of surviving offspring.

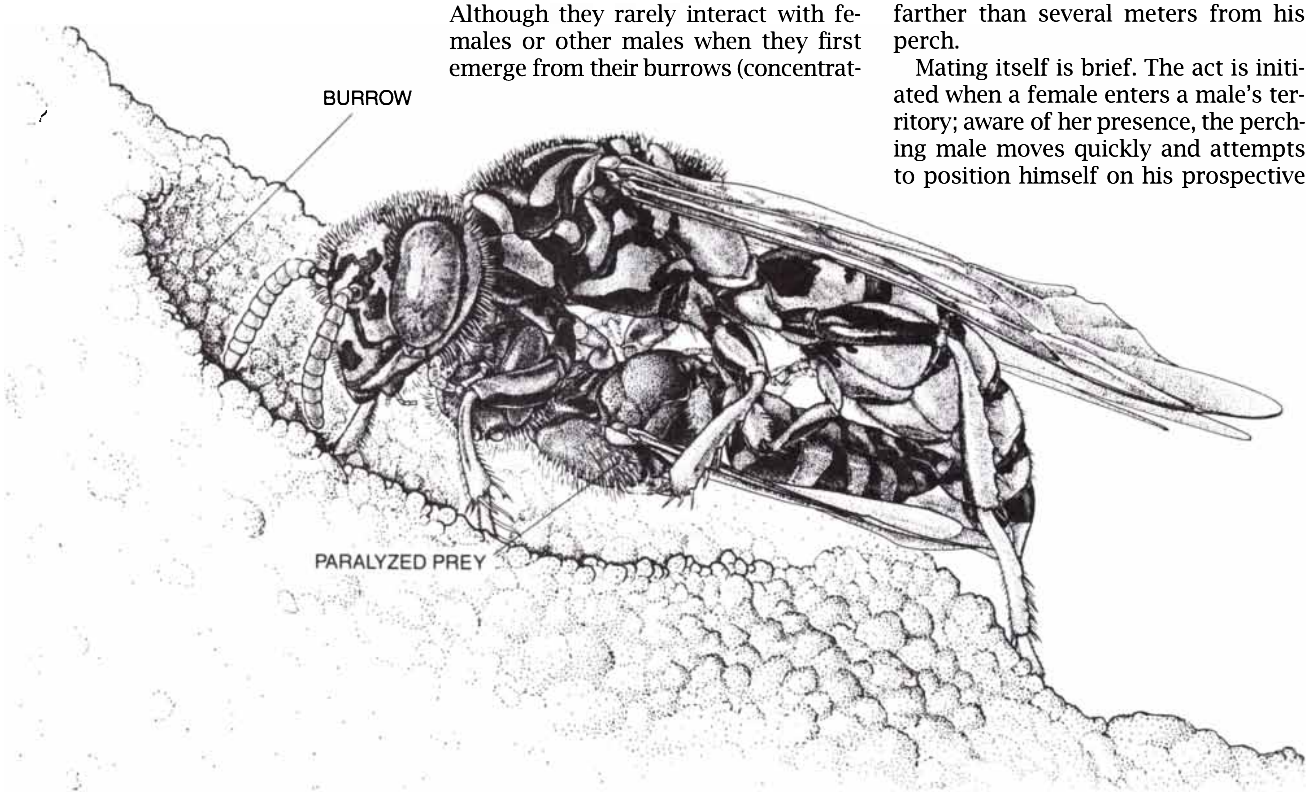
At present, most of our attention has turned to the behavioral diversity of male beewolves, who have repertoires that are far greater and more complex than previously imagined. Yet for many years the males were thought capable of doing little besides copulating with females, and they generated minimal interest among ethologists. Even the great Harvard entomologist William Morton Wheeler, a pioneer in the field of insect behavior, wrote in 1919 that a male wasp was "an ethological nonentity." Today, however, interest in the long-neglected male is flourishing, a tribute to the animal's surprisingly broad array of activities.

In contrast to females, who invest heavily in their offspring and spend most of their lives searching for prey with which to provision their nests, males contribute little but genes to their offspring, instead expending much of their energy seeking mates. When not so occupied, they forage for nectar; at night and during inclement weather, they sleep in shallow burrows. Although they rarely interact with females or other males when they first emerge from their burrows (concentrating instead on feeding), they change their behavior dramatically by mid- to late morning, when they begin to search for specific perches on the ground or on low-lying vegetation from which to tempt females. Having found a perch and thus established a territory, a male then spends anywhere from two to six hours waiting for a female to arrive. During this time, he rarely strays farther than several meters from his perch.

Mating itself is brief. The act is initiated when a female enters a male's territory; aware of her presence, the perching male moves quickly and attempts to position himself on his prospective




**UNDERGROUND BURROWS vary from species to species but generally consist of a single opening, a main tunnel and a cluster of cells, which differ in number and arrangement. A mound and one or more accessory burrows (which may serve to deter parasites) may be present at the nest opening.**




**PARALYZED BEE, *Agapostemon texanus,* is carried by a *Philanthus inversus* female. The beewolf (seen about to enter her underground nest) holds the prey, which measures nine millimeters long, close to her body and so shields it from possible predators. Measuring 12 millimeters in length, the beewolf is only slightly longer than her victim.**



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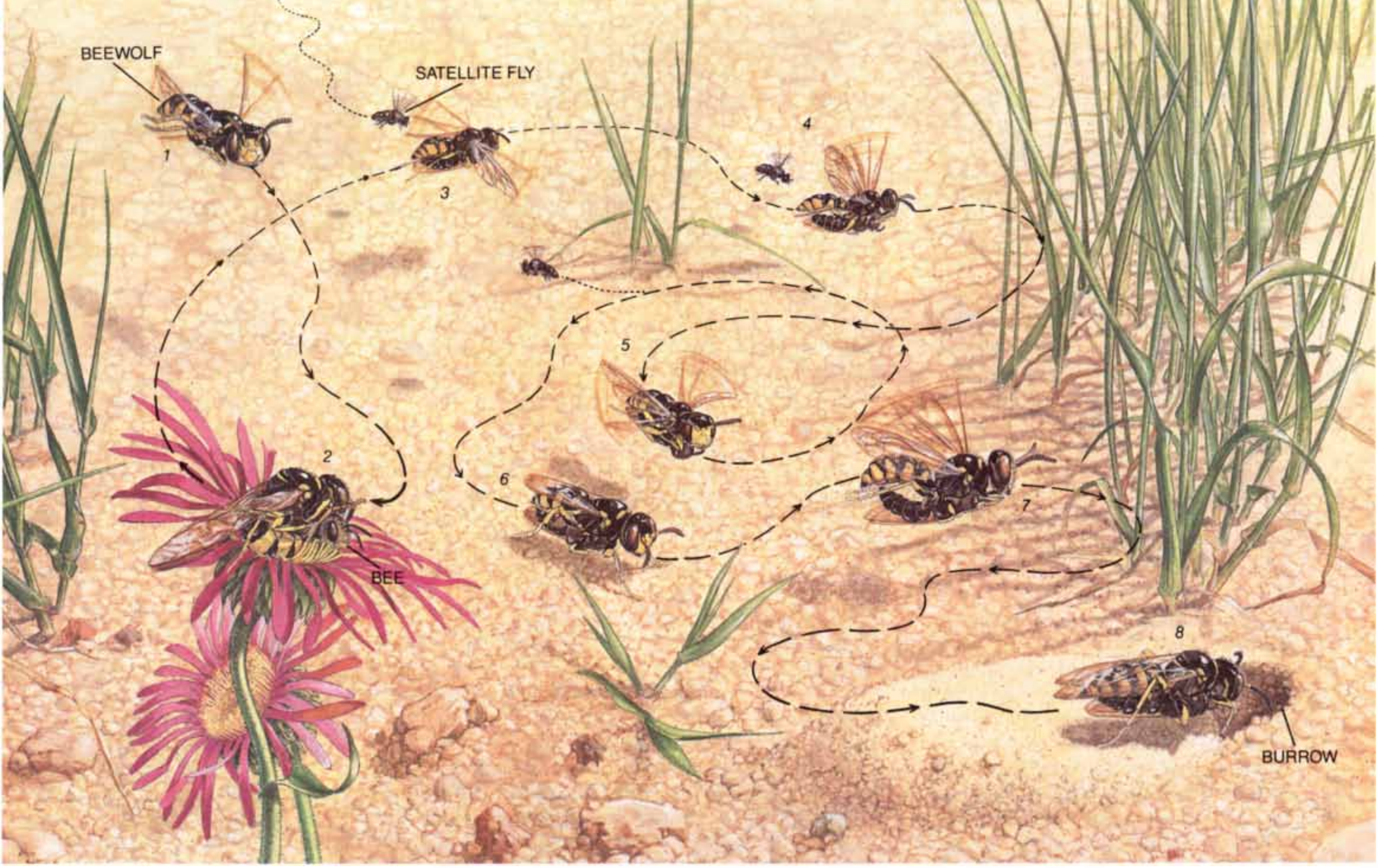


**FLIGHT PATTERNS OF FEMALES help them ward off predators and parasites, such as the ubiquitous satellite flies, which aggressively pursue prey-laden beewolves. After a female beewolf spots a bee (*1*) and paralyzes it (*2*), she heads back to the nest (*3*), maneuvering to evade her enemies (*4*). The tactics, which may include circling (*5*), stopping (*6*) and sudden acceleration (*7*), vary from species to species. If successful, the female arrives at her nest (*8*), having lost her pursuer.**

mate's back. If she is receptive, they couple their genitalia and pivot until they face opposite directions. Such encounters last from five to 10 minutes, during which time the pair will occasionally fly a short distance in tandem before landing and disengaging. After mating, the male returns to his perch, where he continues to pursue other females.

During this period, males are highly territorial and react negatively to any intruder, especially males of the same species. Those that come within a meter or so of the perch are chased and often flee. Sometimes, however, an intruding male will attempt to take possession of an occupied territory. A fierce contest then ensues, with males wrestling on the ground or audibly butting heads while flying. The males also engage in noncontact contests in which they loop and circle about one another at dizzying speeds.

To determine what factors influence the outcome of a territorial dispute, we captured males from various study sites in the mountains of Colorado, measured their body length and gave each a distinctive mark on the thorax, or midsection. In subsequent monitoring of their movements, we found, not unexpectedly, that a battle's outcome was closely related to the difference in size between resident and intruder. From 97 to 100 percent of contest winners (in the four species we studied: *P. inversus, bicinctus, barbiger* and *basilaris*) were larger than or equal to their opponents. The largest males typically fend off numerous intruders each day and are able to maintain the same territory for two or three weeks, which is a substantial portion of their lives.

The ability to establish and maintain control over a territory clearly contributes to a male's reproductive success. Nevertheless, at any given time, large numbers of males, called floaters, fly from territory to territory attempting to displace their occupants. Because our previous studies indicate that success in battle generally depends on size, we postulated that floaters must be smaller on average than the males that occupy territories. To test our hypothesis, we removed males from their perches and measured them. We then did the same for the floaters that replaced them (often within minutes). In 94 percent of the cases the replacement male was smaller than the original resident, providing strong evidence that size does indeed determine whether or not a male establishes a territory.

Not surprisingly, males are highly alert when perching. They pursued, for a meter or more, floaters, butterflies, birds—even pebbles we would throw. Such vigilance, however, has its costs: active males sometimes attract the attention of predators. Predaceous robber flies, for example, occupy the same habitats as beewolves and are often seen attacking the males. In addition, we have occasionally seen female beewolves prey on males of their own species, although the reason for such behavior is unclear.

One beewolf species deviates from the basic pattern of male behavior just described. In the summer of 1977 we began a four-year study of a population of *P. zebratus* in Jackson Hole, Wyo. We found that the smaller males establish


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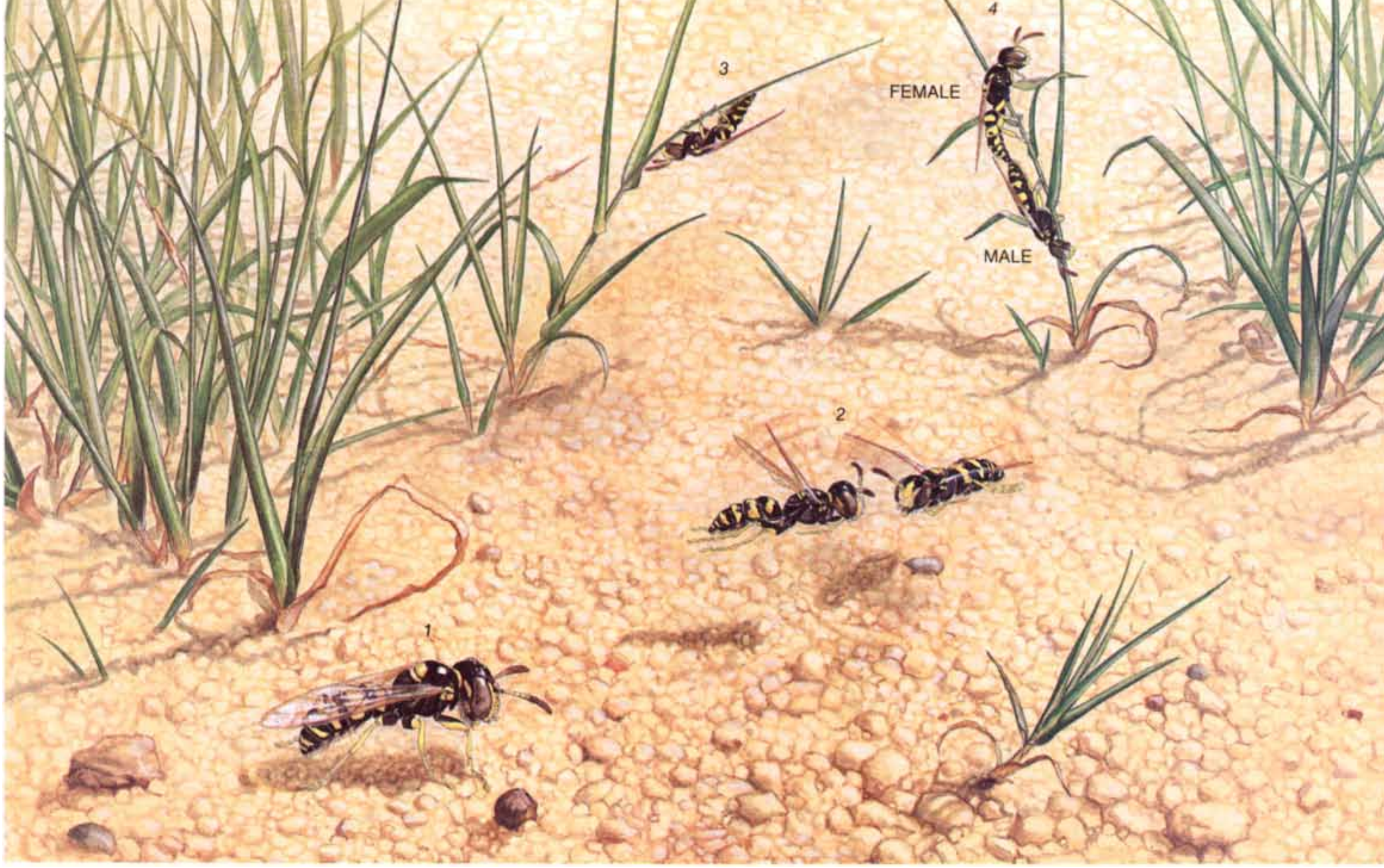


**MALES AGGRESSIVELY DEFEND TERRITORIES. They spend much of their time perching (*1*) but will react immediately to all intruders, especially females and males of the same species. The encounters between males are fierce: they audibly butt heads in midair (*2*) and wrestle on the ground. Males mark vegetation (*3*) with a scent that is thought to attract females to the territory and thus to make it worth defending. Mating frequently occurs on nearby vegetation (*4*).**

perches peripheral to the dense aggregation of nests. The larger males, on the other hand, forgo territoriality for an alternative tactic: they make long, sweeping patrols at a height of three to five meters directly above the nesting sites. It is not understood why this novel behavior occurs only in this one species and not in the others we have studied.

For most species, maintaining one's territory is essential to reproductive success. Still, we wondered why the males defended their small plots of ground so vigorously. What attributes could the sites possess that would make them worth defending or, conversely, worth stealing? In species such as *P. psyche* and *P. bicinctus,* males defend territories within nesting areas where receptive females should be most abundant, but the pattern is not universal. In other species, males defend sites that either are not in the nesting area or are located in a region where the nests are widely dispersed. Moreover, male territories contain no special concentration of resources (food, for instance) that females require, nor do they appear to be corridors through which females travel.

The value of the plot defended by the male may arise primarily from one of his most conspicuous activities. Perching males engage in an unusual and highly ritualized behavior: immediately after selecting a perch, each male makes forays to nearby plant stems. After landing on a stem, he climbs a short distance, then retraces his steps, pressing his head and abdomen against the stem. The frequency with which males undertake this behavior varied from about once every 20 seconds in the smaller species, such as *P. barbiger,* to once every five minutes in the larger species, such as *P. basilaris.* Such activity is reminiscent of scent-marking behavior in other insects. Thus, we wondered if the males were applying some kind of chemical substance to the vegetation.

With the help of several chemists (Justin O. Schmidt, Henry M. Fales, Chris A. McDaniel and Ralph W. Howard), we determined that the males were in fact marking the plant stems with chemicals. We based our conclusion on several key findings. To begin with, we were able to show that volatile substances secreted from the males' enlarged mandibular glands were present on stems visited by patrolling males. In addition, we found no trace of these substances on plants that had not been visited by males. Moreover, we guessed that the longitudinally grooved hairs, called hair brushes, located near the base of a male's mandibles could provide the mechanism by which the scent is applied. We also surmised that the abundant and diffuse hairs on a male's abdomen could help spread the scent as he presses his body against the stem.

Circumstantial evidence provides additional support for our theory that chemicals play a prominent role in male behavior. Not only are enlarged mandibular glands and hair brushes on the head and abdomen of *Philanthus* males absent in female beewolves, but they are also lacking in the one species (*P. albopilosus*) in which males are not known to drag their abdomens on vegetation.



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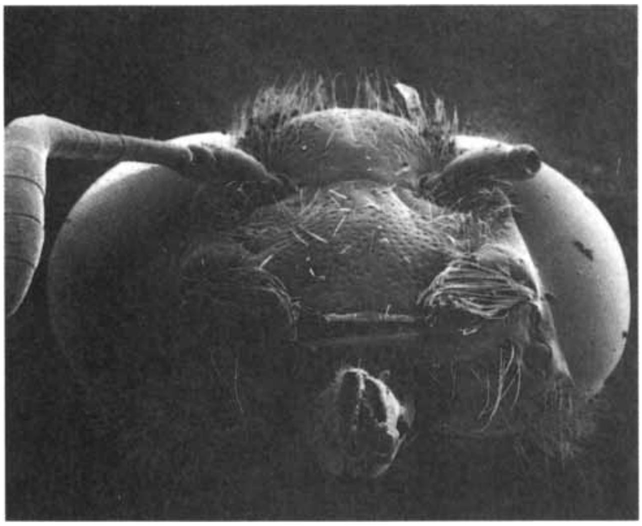
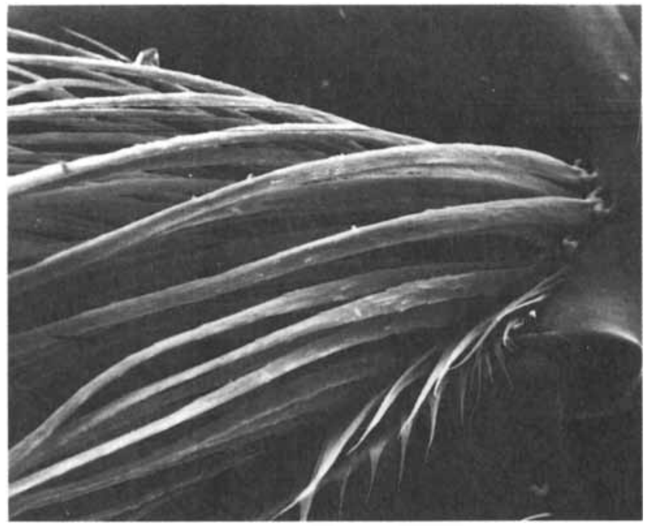

**HEAD OF A MALE *Philanthus gibbosus* is shown in the micrograph (*left*), magnified approximately 30 times. Located above the mouth, between the two compound eyes, are the clypeal brushes, which are used to apply sex pheromones to vegetation. When magnified 130 times, the brushes (*right*) are seen to be clusters of individual hairs.**

In addition, the molecular composition of the mandibular gland secretions suggests the chemicals could be sex pheromones: substances that attract members of the opposite sex and serve as critical components of the mating process in many animals. Mandibular gland extracts of two species we studied in this context, *P. basilaris* and *P. bicinctus,* reveal a species-specific mixture of ketones, fatty acids, ethyl esters and aldehydes, all of which had molecular weights typical for insect sex pheromones.

Although we have yet to confirm experimentally that females react to the males' scent, we have observed their flight behavior as they approach perching males just before mating. In all cases, they fly directly upwind, often zigzagging as they go. Such a flight pattern is typical of insects orienting to wind-borne odors from a single point source. Still, to prove conclusively that females respond to the males' mandibular extract will require controlled experiments in which females are exposed to different scents and then monitored for their reactions.

Yet we believe that the pheromones offer an important clue to the evolution of territoriality in beewolves. Our hypothesis is that males benefit by defending sites to which they have applied pheromones, because in so doing they transform the area from a nondescript plot of ground to one attractive to females. Conversely, a male that usurps a scent-marked territory gains possession of scent-marked plants without having to accrue the costs of manufacturing the pheromone. This might explain why many males attempt to steal territories at the beginning of the day, even when many nearby territories are still unoccupied.

To those of us who spend warm summer afternoons enraptured by the comings and goings of beewolves, they are fascinating and endearing animals. For many others, alas, they are unwanted pests. Not only do they capture bees that pollinate wildflowers and crop plants, they also kill wasps that prey on such agricultural pests as caterpillars and grasshoppers. In addition, beewolves create occasional problems in apiaries. R. T. Simonthomas, recently retired from the University of Amsterdam, estimates that 3,000 female beewolves (a population size that is not uncommon) might capture some 30,000 honeybees a day. He reports that the density of beewolves in the Dakhla Oasis of Egypt is so great that beekeeping there is impossible.

Because beewolves are such voracious predators, we have sometimes been asked whether they could effectively control populations of the Africanized "killer" bees that threaten the southern U.S. To begin with, ground-nesting wasps require soil that is bare and friable, yet well consolidated, to dig their nests. Preparing such large tracts of soil for control purposes would be a formidable task, indeed. Even if some of the larger beewolf species were introduced into such artificially created habitats, it might take years to build a stable population. Moreover, there is no way of knowing whether they could handle the aggressive Africanized bees under such conditions.

Regardless of the economic role of beewolves, much can be said for them as exemplars of adaptive behavior. Each species has evolved features that enable it to thrive despite limited nesting sites and the need not only to share these sites with other insects but to overcome constant harassment by a variety of parasites.

Yet in unraveling the complexities of beewolf biology, we find that much remains unknown. We have still to prove, for example, that males secrete species-specific pheromones; we also have much to learn about the interactions between males and females and between females and their parasites. Somewhat sobering, too, is the fact that of the 34 species in North America, only 20 have been studied to any degree. Thus, it is clear to those of us who have devoted our lives to insect study that beewolves will present an intellectual challenge for many years to come.

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# Antichaos and Adaptation

*Biological evolution may have been shaped by more than just natural selection. Computer models suggest that certain complex systems tend toward self-organization*

by Stuart A. Kauffman

Mathematical discoveries are inviting changes in biologists' thinking about the origins of order in evolution. All living things are highly ordered systems: they have intricate structures that are maintained and even duplicated through a precise ballet of chemical and behavioral activities. Since Darwin, biologists have seen natural selection as virtually the sole source of that order.

But Darwin could not have suspected the existence of self-organization, a recently discovered, innate property of some complex systems. It is possible that biological order reflects in part a spontaneous order on which selection has acted. Selection has molded, but was not compelled to invent, the native coherence of ontogeny, or biological development. Indeed, the capacity to evolve and adapt may itself be an achievement of evolution.

The studies supporting these conclusions remain tentative and incomplete. Nevertheless, on the basis of mathematical models for biological systems that exhibit self-organization, one can make predictions that are consistent with the observed properties of organisms. We may have begun to understand evolution as the marriage of selection and self-organization.

To understand how self-organization can be a force in evolution, a brief overview of complex systems is necessary. During the past two decades, there has been an explosion of interest in such systems throughout the natural and social sciences. The efforts are still so new that there is not yet even a generally accepted, comprehensive definition of complexity.

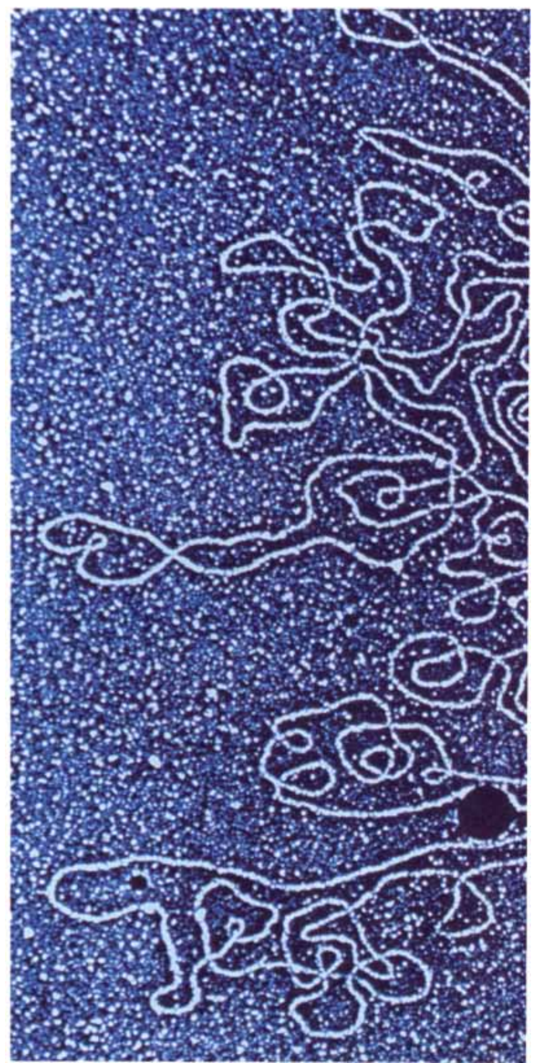
Yet certain properties of complex systems are becoming clear. One phenomenon found in some cases has already caught the popular imagination: the randomizing force of deterministic "chaos." Because of chaos, dynamic, nonlinear systems that are orderly at first may become completely disorganized over time. Initial conditions that are very much alike may have markedly different outcomes. Chaos in the weather is exemplified by the so-called butterfly effect: the idea that a butterfly fluttering in Rio de Janeiro can change the weather in Chicago.

Chaos, fascinating as it is, is only part of the behavior of complex systems. There is also a counterintuitive phenomenon that might be called antichaos: some very disordered systems spontaneously "crystallize" into a high degree of order. Antichaos, I believe, plays an important part in biological development and evolution.

The discovery of antichaos in biology began more than 20 years ago with my efforts to understand mathematically how a fertilized egg differentiates into multitudes of cell types. Since then, mathematicians, computer scientists and solid state physicists, among them my many colleagues at the Santa Fe Institute in New Mexico, have made substantial progress.

Biology is filled with complex systems: the thousands of genes regulating one another within a cell; the network of cells and molecules mediating the immune response; the billions of neurons in the neural networks underlying behavior and learning; the ecosystem webs replete with coevolving species. Of these, the self-regulating network of a genome (the complete set of genes in an organism)

STUART A. KAUFFMAN has been thinking about self-organization in living things since 1965. After studying at Dartmouth College and at the University of Oxford, he went on to receive his medical degree from the University of California, San Francisco, in 1968. Since then, he has held positions at the Massachusetts Institute of Technology, the University of Chicago and the National Cancer Institute. Kauffman is currently professor of biochemistry and biophysics at the University of Pennsylvania School of Medicine and external professor at the Santa Fe Institute in New Mexico. In 1987 he received a John D. and Catherine T. MacArthur Fellowship.



**LOOPS OF DNA extruded by this bacterium contain thousands of genes. The genes act as a self-regulating network, turning one another on and off. Even more complex genetic circuits occur in higher cells. Computational models are now hinting at how such complex systems can spontaneously organize themselves to exhibit stable cycles of gene activity—an essential feature of all life.**



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offers a good example of how antichaos may govern development.

The genome of a higher organism such as a human being encodes the information for making about 100,000 different proteins. One of the central dogmas of developmental biology is that liver cells, neurons and other cell types differ because varied genes are active in them. Yet it is now also clear that all the cells in an organism contain roughly the same genetic instructions. Cell types differ because they have dissimilar patterns of genetic activity, not because they have different genes.

A genome acts like a complex parallel-processing computer, or network, in which genes regulate one another's activity either directly or through their products. The coordinated behavior of this system underlies cellular differentiation. Understanding the logic and structure of the genomic regulatory system has therefore become a central task of molecular biology.

Mathematical models can help researchers understand the features of such complex parallel-processing systems. Every complex system has what can be called local features: these characteristics describe how individual elements in the system are connected and how they may influence one another. For example, in a genome the elements are genes. The activity of any one gene is directly regulated by fairly few other genes or gene products, and certain rules govern their interactions.

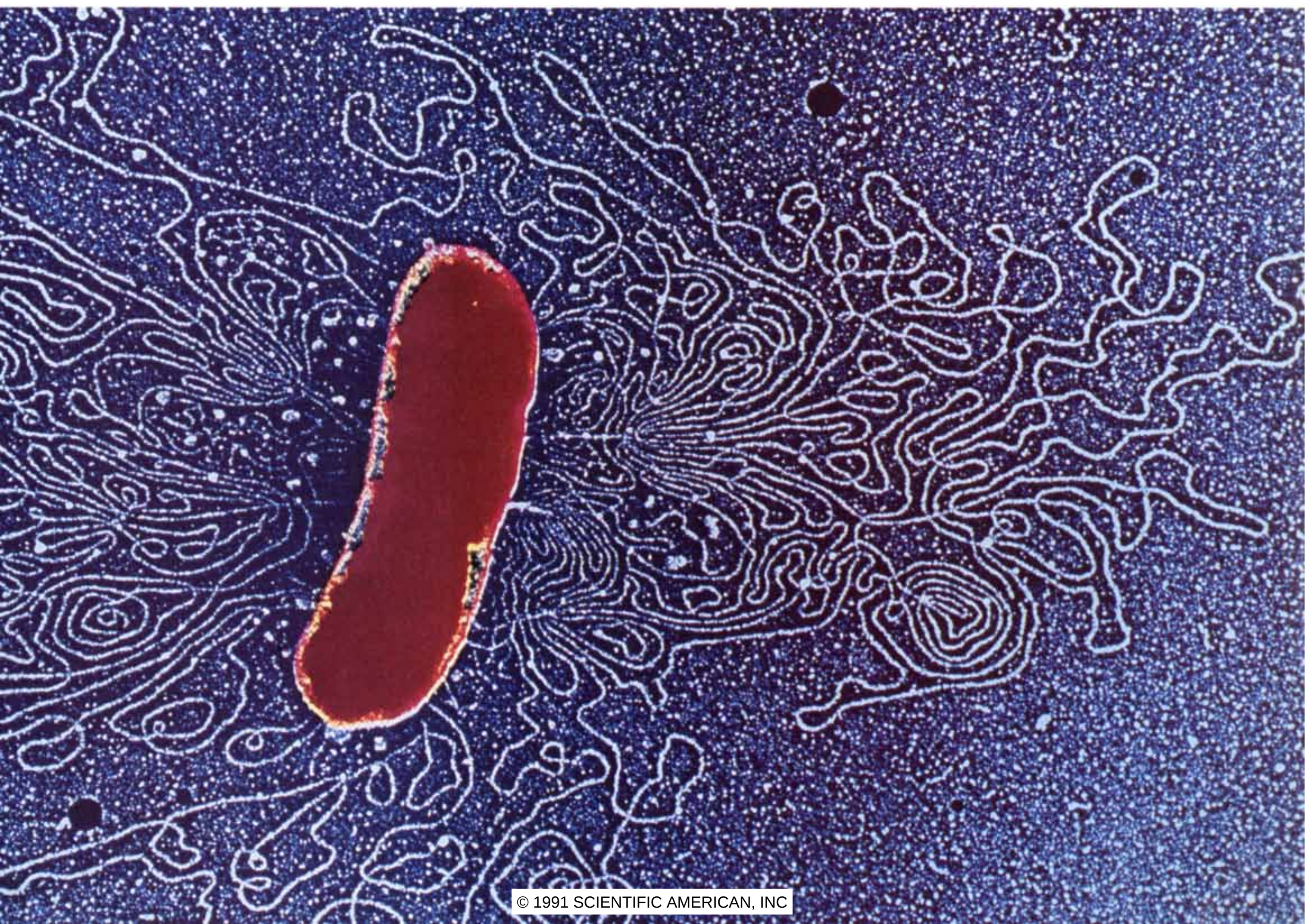
Given any set of local features, one may construct a large ensemble, or class, of all the different complex systems consistent with them. A new kind of statistical mechanics can identify the average features of all the different systems in the ensemble. (Traditional statistical mechanics, in contrast, averages over all the possible states of a single system.) Individual systems in the ensemble might be very different; nonetheless, the statistically typical behaviors and structures are the best hypothesis for predicting the properties of any one system.

The approach begins by idealizing the behavior of each element in the system—each gene, in the case of the genome—as a simple binary (on or off) variable. To study the behavior of thousands of elements when they are coupled together, I used a class of systems called random Boolean networks. These systems are named after George Boole, the English inventor of an algebraic approach to mathematical logic.

In a Boolean network, each variable is regulated by others that serve as inputs. The dynamic behavior of each variable—that is, whether it will be on or off at the next moment—is governed by a logical switching rule called a Boolean function. The function specifies the activity of a variable in response to all the possible combinations of activities in the input variables. One such rule is the Boolean OR function, which says that a variable will be active if any of its input variables is active. Alternatively, the AND function declares that a variable will become active only if all its inputs are currently active.

One can calculate how many Boolean functions could conceivably apply to any binary element in a network. If a binary element has $K$ inputs, then there are $2^K$ possible combinations of inputs it could receive. For each combination, either an active or inactive result must be specified. Therefore, there are 2 to the $2^K$ power possible Boolean switching rules for that element.

The mathematically idealized ver-



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sions of biological systems I shall discuss are called autonomous random Boolean *NK* networks. They consist of *N* elements linked by *K* inputs per element; they are autonomous because none of the inputs comes from outside the system. Inputs and one of the possible Boolean functions are assigned at random to each element. By assigning values to *N* and *K*, one can define an ensemble of networks with the same local features. A random network is one sampled at random from this ensemble.

Each combination of binary element activities constitutes one network "state." In each state, all the elements assess the values of their regulatory inputs at that moment. At the next clocked moment, the elements turn on or off in accordance with their individual functions. (Because all the elements act simultaneously, the system is also said to be synchronous.) A system passes from one unique state to another. The succession of states is called the trajectory of the network.

A critical feature of random Boolean networks is that they have a finite number of states. A system must therefore eventually reenter a state that it has previously encountered. Because its behavior is determined precisely, the system proceeds to the same successor state as it did before. It will consequently cycle repeatedly through the same states.

Such state cycles are called the dynamic attractors of the network: once a network's trajectory carries it onto a state cycle, it stays there. The set of states that flow into a cycle or that lie on it constitutes the "basin of attraction" of the state cycle. Every network must have at least one state cycle; it may have more.

Left to itself, a network will eventually settle into one of its state cycle attractors and remain there. Yet if the network is perturbed in some way, its trajectory may change. Two types of perturbation are worth discussing here: minimal perturbations and structural perturbations.

A minimal perturbation is a transient flipping of a binary element to its opposite state of activity. If such a change does not move a network outside its original basin of attraction, the network will eventually return to its original state cycle. But if the change pushes the network into a different basin of attraction, the trajectory of the network will change: it will flow into a new state cycle and a new recurrent pattern of network behavior.

The stability of attractors subjected to minimal perturbations can differ. Some can recover from any single perturbation, others from only a few, whereas still others are destabilized by any perturbation. Flipping the activity of just one element may unleash an avalanche of changes in the patterns that would otherwise have occurred. The changes are "damage," and they may propagate to varying extents throughout a network [see "Self-Organized Criticality," by Per Bak and Kan Chen; SCIENTIFIC AMERICAN, January].

A structural perturbation is a permanent mutation in the connections or in the Boolean functions of a network. Such perturbations would include exchanging the inputs of two elements or switching an element's OR function to an AND function. Like minimal perturbations, structural perturbations can cause damage, and networks may vary in their stability against them.

As the parameters describing a complex Boolean system change, the system's behavior alters, too: a system can change from chaotic behavior to ordered behavior. A type of system that is perhaps surprisingly easy to understand is one in which the number of inputs to each element equals the total number of elements—in other words, everything is connected to everything else. (Such systems are called $K = N$ networks.) Because a random $K = N$ network is maximally disordered, the successor to each state is a completely random choice. The network behaves chaotically.

One sign of the disorder in $K = N$ systems is that as the number of elements increases, the length of the state cycles grows exponentially. For example, a $K = N$ network consisting of 200 elements can have $2^{200}$ (about $10^{60}$) different states. The average length of a state

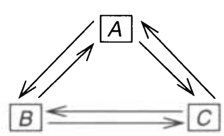
## Boolean Functions and State Cycles

Boolean functions are logical rules that describe how binary (on or off) elements in networks will respond to combinations of signals from other elements. By applying Boolean logic to a network, one can predict the system's behavior.

In this simple network (*a*), there are three elements, each of which receives signals from the others. Element *A* obeys the Boolean AND function: it becomes active only if both elements *B* and *C* were previously active. Elements *B* and *C* obey OR functions: each one becomes active if either of the other elements was active. By listing every possible initial combination of states in the network, one can deduce from the Boolean functions what all the successor states will be (*b*).

The long-term behavior of the system is remarkably simple. Although the network can initially have any of eight different states, it will eventually settle into one of only three state cycles—each one a recurrent pattern of change (*c*). If all the elements are off initially, the network never changes. If only element *B* or element *C* is active, the system will cycle back and forth between the two states. Any other network state inevitably leads to all the elements' becoming active and staying that way.

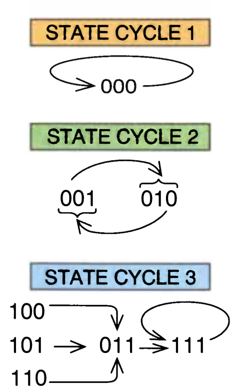
**a**




**b**

| INITIAL STATES OF ELEMENTS A | B | C | SUCCESSOR STATES OF ELEMENTS A | B | C |
|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 1 | 0 | 1 | 0 |
| 0 | 1 | 0 | 0 | 0 | 1 |
| 1 | 0 | 0 | 0 | 1 | 1 |
| 1 | 0 | 1 | 0 | 1 | 1 |
| 1 | 1 | 0 | 0 | 1 | 1 |
| 0 | 1 | 1 | 1 | 1 | 1 |
| 1 | 1 | 1 | 1 | 1 | 1 |

**c**



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cycle in the network is roughly the square root of that number, about $10^{30}$ states. Even if each state transition took only one microsecond, it would take billions of times longer than the age of the universe for the network to traverse its attractor completely.

$K = N$ networks also exhibit maximum sensitivity to initial conditions. Because the successor to any state is essentially random, almost any perturbation that flips one element would sharply change the network's subsequent trajectory. Thus, minimal changes typically cause extensive damage—alterations in the activity patterns—almost immediately. Because the systems show extreme sensitivity to their initial conditions and because their state cycles increase in length exponentially, I characterize them as chaotic.

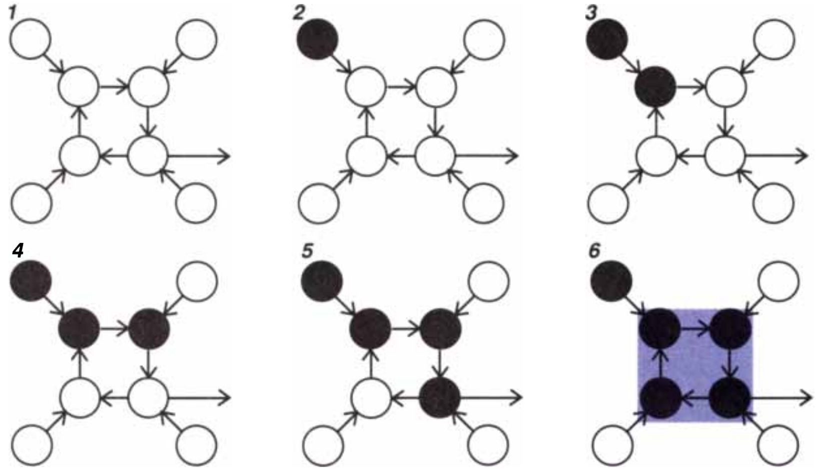
Despite these chaotic behaviors, however, $K = N$ systems do show one startling sign of order: the number of possible state cycles (and basins of attraction) is very small. The expected number of state cycles equals the number of elements divided by the logarithmic constant *e*. A system with 200 elements and $2^{200}$ states, for example, would have only about 74 different patterns of behavior.

Moreover, about two thirds of all the possible states fall within the basins of only a few attractors—sometimes of just one. Most attractors claim relatively few states. The stability of an attractor is proportional to its basin size, which is the number of states on trajectories that drain into the attractor. Big attractors are stable to many perturbations, and small ones are generally unstable.

Those chaotic behavioral and structural features are not unique to $K = N$ networks. They persist as $K$ (the number of inputs per element) decreases to about three. When $K$ drops to two, however, the properties of random Boolean networks change abruptly: the networks exhibit unexpected, spontaneous collective order.

In $K = 2$ networks, both the number and expected lengths of alternative state cycles fall to only about the square root of the number of elements. The state cycles of $K = 2$ systems remain stable in the face of almost all minimal perturbations, and structural perturbations alter their dynamic behavior only slightly. (Networks with only a single input per element constitute a special ordered class. Their structure degenerates into isolated feedback loops that do not interact.)

It has been more than 20 years since I discovered those features of random networks, and they still surprise me. If one were to examine a network of 100,000 elements, each receiving two inputs, its wiring diagram would be a wildly complex scramble. The system could assume as many as $2^{100,000}$ (about $10^{30,000}$) different states. Yet order would emerge spontaneously: the system would settle into one of but 370 or so different state cycles. At a microsecond per transition, that $K = 2$ network would traverse its tiny state-cycle attractor in only 370 microseconds—quite a bit less than the billions of times the age of the universe that the chaotic $K = N$ network requires.



**"FROZEN" ELEMENTS incapable of changing state can sometimes arise in a system. In this small sample network, all the elements are ruled by Boolean OR functions, and all are initially off. Changes cascade through the system after one element is turned on (*black*). Because of the configuration of the network and the Boolean functions involved, some elements (*blue*) freeze into the on state. Thereafter they will return to that state even if they or one of their inputs is altered.**

In the ordered regime of networks with two or fewer inputs per element, there is little sensitivity to initial conditions: the butterfly sleeps. In the chaotic regime, networks diverge after beginning in very similar states, but in the ordered regime, similar states tend to converge on the same successor states fairly soon.

Consequently, in random networks with only two inputs per element, each attractor is stable to most minimal perturbations. Similarly, most mutations in such networks alter the attractors only slightly. The ordered network regime is therefore characterized by a homeostatic quality: networks typically return to their original attractors after perturbations. And homeostasis, as I shall discuss presently, is a property of all living things.

Why do random networks with two inputs per element exhibit such profound order? The basic answer seems to be that they develop a frozen core, or a connected mesh of elements that are effectively locked into either an active or inactive state. The frozen core creates interlinked walls of constancy that "percolate" or grow across the entire system. As a result, the system is partitioned into an unchanging frozen core and islands of changing elements. These islands are functionally isolated: changes in the activities of one island cannot propagate through the frozen core to other islands. The system as a whole becomes orderly because changes in its behavior must remain small and local. Low connectivity is therefore a sufficient condition for orderly behavior to arise in disordered switching systems.

It is not a necessary condition, however. In networks of high connectivity, order will also arise if certain biases exist in the Boolean switching rules. Some Boolean functions turn elements on more often than off or vice versa. An OR function for two inputs, for example, will turn an element on in response to three out of the four possible combinations of binary signals.

A number of solid state physicists, including Deitrich Stauffer of the University of Köln and Bernard Derrida and Gerard Weisbuch of the Ecole Normale Supérieure in Paris, have studied the effects of biased functions. They have found that if the degree of bias exceeds a critical value, then "homogeneity clusters" of elements that have frozen values link with one another and percolate across the network. The dynamic behavior of the network becomes a web of frozen elements and functionally isolated islands of changeable elements.

That order, of course, is much the same as I have described for networks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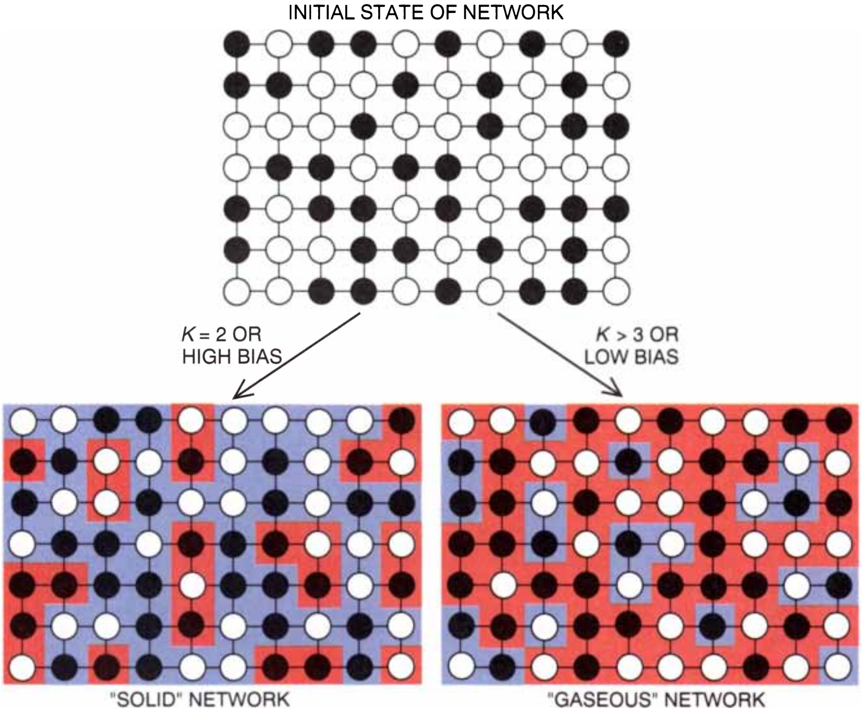


**PHASE CHANGES between "solid" and "gaseous" states can occur in self-regulating networks, depending on their local characteristics. If the elements' Boolean functions are biased or if each element has only two inputs ($K = 2$), then a network in which all the elements can initially vary will eventually become stable and hence solid. Such ordered systems consist of a large web of frozen elements (*blue*) and isolated islands of variable elements (*red*). If the functions are unbiased or the interconnectedness of elements is high ($K > 3$), the system becomes a gas and behaves chaotically. Only small islands of elements will be frozen.**

with low connectivity. Transient reversals in the activity of a single element typically cannot propagate beyond the confines of an isolated island and therefore cannot cause much damage. In contrast, if the level of bias is well below the critical value—as it is in chaotically active systems—then a web of oscillating elements spreads across the system, leaving only small islands of frozen elements. Minimal perturbations in those systems cause avalanches of damage that can alter the behavior of most of the unfrozen elements.

Christopher Langton, a computer scientist at Los Alamos National Laboratory, has introduced an analogy that helps one think about the change between order and disorder in different ensembles of networks. He has related network behavior to the phases of matter: ordered networks are solid, chaotic networks are gaseous and networks in an intermediate state are liquid. (The analogy should not be interpreted too literally, of course: true liquids are a distinct phase of matter and not just a transitional regime between gases and solids.)

If the biases in an ordered network are lowered to a point near the critical value, it is possible to "melt" slightly the frozen components. Interesting dynamic behaviors emerge at the edge of chaos. At that phase transition, both small and large unfrozen islands would exist. Minimal perturbations cause numerous small avalanches and a few large avalanches. Thus, sites within a network can communicate with one another—that is, affect one another's behavior—according to a power law distribution: nearby sites communicate frequently via many small avalanches of damage; distant sites communicate less often through rare large avalanches.

These characteristics inspired Langton to suggest that parallel-processing networks poised at the edge of chaos might be capable of extremely complex computations. On the face of it, the idea is plausible. Highly chaotic networks would be so disordered that control of complex behaviors would be hard to maintain. Highly ordered networks are too frozen to coordinate complex behavior. But as frozen components melt, more complicated dynamics involving the complex coordination of activities throughout a network become feasible. The complexity that a network can coordinate peaks at the liquid transition between solid and gaseous states.

Systems poised in the liquid transition state may also have special relevance to evolution because they seem to have the optimal capacity for evolving. As Darwin taught, mutations and natural selection can improve a biological system through the accumulation of successive minor variants, just as tinkering can improve technology. Yet not all systems have the capacity to adapt and improve in that way. A complex program on a standard computer, for example, cannot readily evolve by random mutations: almost any change in its code would catastrophically alter the computation. The more compressed the code, the less capacity it has to evolve.

Networks on the boundary between order and chaos may have the flexibility to adapt rapidly and successfully through the accumulation of useful variations. In such poised systems, most mutations have small consequences because of the systems' homeostatic nature. A few mutations, however, cause larger cascades of change. Poised systems will therefore typically adapt to a changing environment gradually, but if necessary, they can occasionally change rapidly. These properties are observed in organisms.

If parallel-processing Boolean networks poised between order and chaos can adapt most readily, then they may be the inevitable target of natural selection. The ability to take advantage of natural selection would be one of the first traits selected.

The hypothesis is bold, perhaps even beautiful, but is it true? Physicist Norman H. Packard of the University of Illinois at Champaign-Urbana may have been the first person to ask whether selection could drive parallel-processing Boolean networks to the edge of chaos. Sometimes at least the answer is yes. Packard found such evolution occurring in a population of simple Boolean networks called cellular automata, which had been selected for their ability to perform a specific simple computation.

Recently my colleague Sonke Johnsen of the University of Pennsylvania and I have found further evidence of evolution proceeding to the edge of chaos. We have begun studying the question by making Boolean networks play a variety of games with one another [*see box on opposite page*]. Our results, too, suggest that the transition between chaos and order may be an attractor for the evolutionary dynamics of networks performing a range of simple and complex tasks. All the network populations improved at playing the games faster than chance alone could


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accomplish. The organization of the successful networks also evolved: their behaviors converged toward the boundary between order and chaos.

If these results hold up under further scrutiny, then the liquid transition between ordered and chaotic organizations may be the characteristic target of selection for systems able to coordinate complex tasks and adapt. By that reasoning, such poised systems should occur in biology.

How much order and chaos do the genomic systems of viruses, bacteria, plants and animals exhibit? Usually each gene is directly regulated by few other genes or molecules—perhaps no more than 10. The Boolean wiring diagram for the genome is therefore sparse, and the individual gene elements have few inputs. Furthermore, almost all known regulated genes are governed by a particular class of Boolean switching rules called canalizing functions. In canalizing functions, at least one input has a value that can by itself determine the activity of the regulated element. (The OR function is a typical canalizing function.)

Like low connectivity or biases in the Boolean rules, an abundance of canalizing functions in a network can create an extensive frozen core. Increasing the proportion of canalizing functions used in a network can therefore drive the system toward a phase transition between chaos and order. Because genomic regulatory systems are sparsely connected and typically appear to be governed by canalizing functions, such networks are very likely to exhibit the traits of parallel-processing systems with frozen percolating elements: a modest number of small, stable attractors, the confinement of damage to small cascading avalanches and modest alterations in dynamics in response to mutations.

One interpretation of the meaning of antichaos in complex systems has particular relevance to biology: a cell type may correspond to an attractor in the genomic dynamics. A genome that contains 100,000 genes has the potential for at least $10^{30,000}$ patterns of gene expression. The genomic regulatory network orchestrates those possibilities into changing patterns of gene activity over time. But a stable cell type persists in expressing restricted sets of genes. The natural suggestion is that a cell type corresponds to a state-cycle attractor: it embodies a fairly stable cycle of expression in a specific set of genes.

Given that interpretation, the spontaneous order arising in networks with low connectivity and canalizing Boolean functions sets up several predictions about real biological systems. First, each cell type should correspond to a very small number of gene expression patterns through which it cycles. One can therefore calculate how long such cell cycles should be.

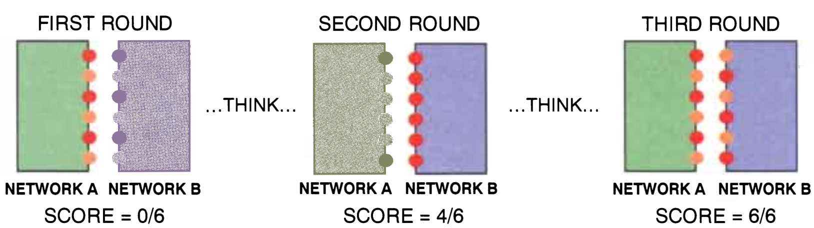
After receiving an appropriate stimulus, a gene in a eukaryotic cell needs about one to 10 minutes to become active. The length of an attractor in a genome with 100,000 genes would be about 370 states. Consequently, a cell should run through all the gene expression patterns of its type in roughly 370 to 3,700 minutes. This figure approximates the correct range for real biological systems. As predicted, the length of cell cycles does seem to be proportional to roughly the square root of the amount of DNA in the cells of bacteria and higher organisms.

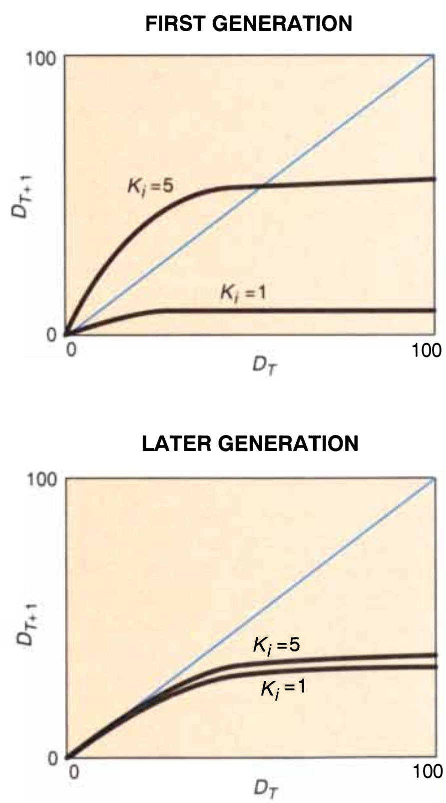
If a cell type is an attractor, it should be possible to predict how many cell types could appear in an organism. The number of attractors is about the square root of the number of elements in a network; therefore, the number of cell types should be approximately the square root of the number of genes. If we assume that the number of genes is proportional to the amount of DNA in a cell, then humans should

## The Mismatch Game

A computer game demonstrates how natural selection can push random networks to a point near the edge of chaos. Pairs of networks receive high scores for having patterns in six of their elements, designated as "matchsites," that differ maximally from one another. After a comparison, each network takes the pattern in the matchsites of the other as an input, works on its response and makes another comparison [*see below*]. After 10 comparisons, each network finds a new opponent. The networks with the highest scores reproduce preferentially to form the next generation. Occasional mutations randomly alter the local characteristics of the networks. Over several generations, the networks generally improve at playing the game. Regardless of their initial conditions, the networks approach the boundary between order and chaos.

These changes can be observed by measuring how a network's trajectories diverge or converge at various times. $D_T$ is the percentage of the elements that have different activities in two initial states of one network. $D_{T+1}$ is that percentage measured for the successor states. When $D_T$ is small in very chaotic ($K_i = 5$) networks, trajectories diverge ($D_{T+1} > D_T$). In very ordered ($K_i = 1$) networks, trajectories converge ($D_{T+1} < D_T$). After several generations of playing the Mismatch Game, chaotic and ordered networks moderate their behavior [*see graphs at right*].



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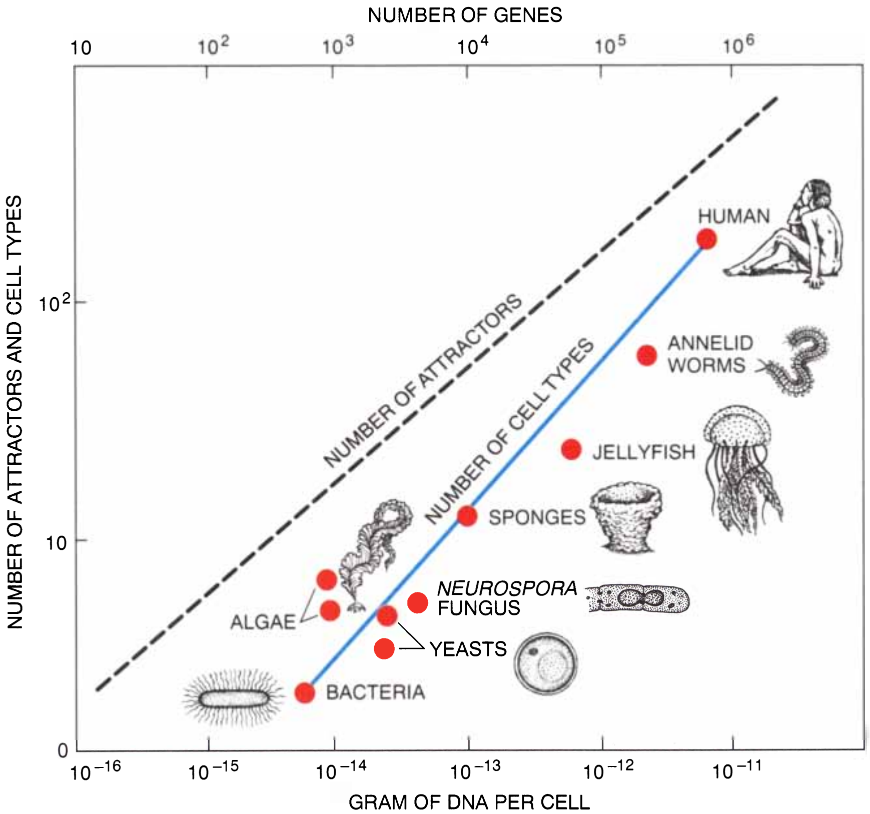


**NUMBER OF CELL TYPES in organisms seems to be related mathematically to the number of genes in the organism. In this diagram the number of genes is assumed to be proportional to the amount of DNA in a cell. If the gene regulatory systems are $K = 2$ networks, then the number of attractors in a system is the square root of the number of genes. The actual number of cell types in various organisms appears to rise accordingly as the amount of DNA increases.**

have about 100,000 genes and 370 cell types. By the most recent count, humans have about 254 distinct cell types, so that prediction is also in the right range.

Across many phyla, the number of cell types seems to increase with approximately the square root of the number of genes per cell (that is, with the number of genes raised to a fractional power that is roughly one half). Thus, bacteria have one or two cell types, sponges have perhaps from 12 to 15 and annelid worms have about 60.

Because not all DNA may have a function, the number of genes may not rise directly with the amount of DNA. The predicted number of cell types could therefore increase according to a fractional power greater than one half (the square root) but less than one. In fact, by conservative estimates, the number of cell types appears to increase at most as a linear function. Such a range of behavior is found in complex Boolean networks. In contrast, other simple mathematical models for genomic systems predict that the number of cell types would increase exponentially with the number of genes.

Another prediction refers to the stability of cell types. If a cell type is an attractor, then it cannot be altered by most perturbations: its stability is an emergent property of the gene regulatory system.

Differentiation, according to this model, would be a response to perturbations that carried a cell into the basin of attraction for another cell type. In a canalizing ensemble, however, each model cell can differentiate directly into only a few alternative cell types because each attractor is "near" only a few others. Consequently, ontological development from a fertilized egg should proceed by successive branching pathways of differentiation. In other words, once a cell has begun to differentiate along certain lines, it loses the choice of differentiating in other ways. As far as biologists know, cell differentiation in multicellular organisms has been fundamentally constrained and organized by successive branching pathways since the Cambrian period almost 600 million years ago.

In canalizing networks, order emerges because a large fraction of the binary elements falls into a stable, frozen state. That stable core of elements is identical in almost all the attractors. Hence, all the cell types in an organism should express most of the same genes. Typically only a few percent of the genes should show different activities. Both claims hold true for biological systems.

The attractor model for cell types also predicts that the mutation of a single gene should usually have fairly limited effects. Avalanches of damage (or changed activity) caused by the mutation should not propagate to the vast majority of genes in the regulatory network. Changes in activity should be restricted to small, isolated islands of genes. These expectations are met by real genetic systems.

Moreover, the expected sizes of the unfrozen islands in the gene systems come close to predicting the sizes of such avalanches. For example, a hormone called ecdysone in the fruit fly *Drosophila* can unleash a cascade that changes the activity of about 150 genes out of at least 5,000. The expected size of avalanches in canalizing genomes with 5,000 elements or in those with low connectivity and a frozen core containing roughly 80 percent of the genes is about 160.

Taken as models of genomic systems, systems poised between order and chaos come close to fitting many features of cellular differentiation during ontogeny—features common to organisms that have been diverging evolutionarily for more than 600 million years. The parallels support the hypothesis that evolution has tuned adaptive gene regulatory systems to the ordered region and perhaps to near the boundary between order and chaos. If the hypotheses continue to hold up, biologists may have the beginnings of a comprehensive theory of genomic organization, behavior and capacity to evolve.

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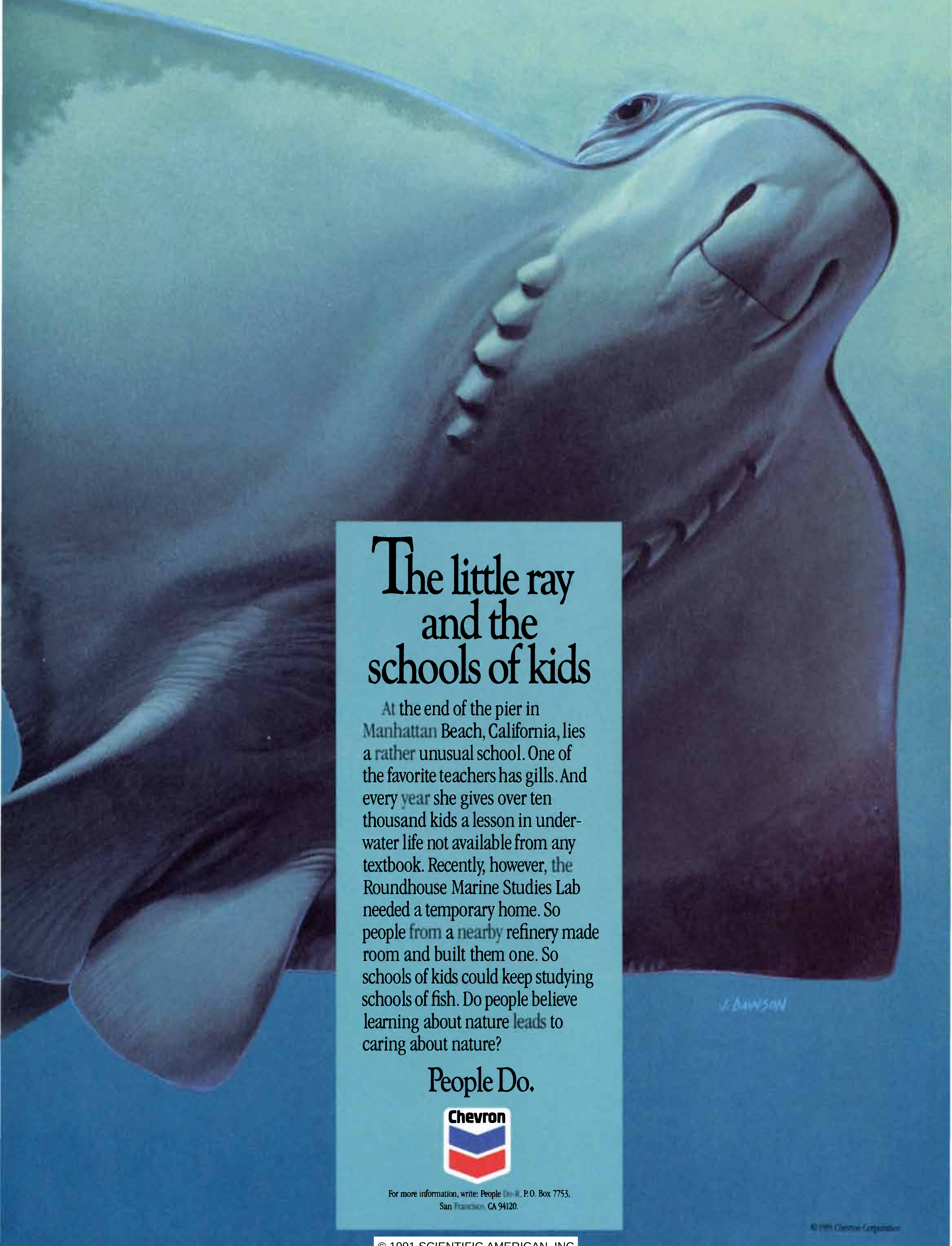



# The little ray and the schools of kids

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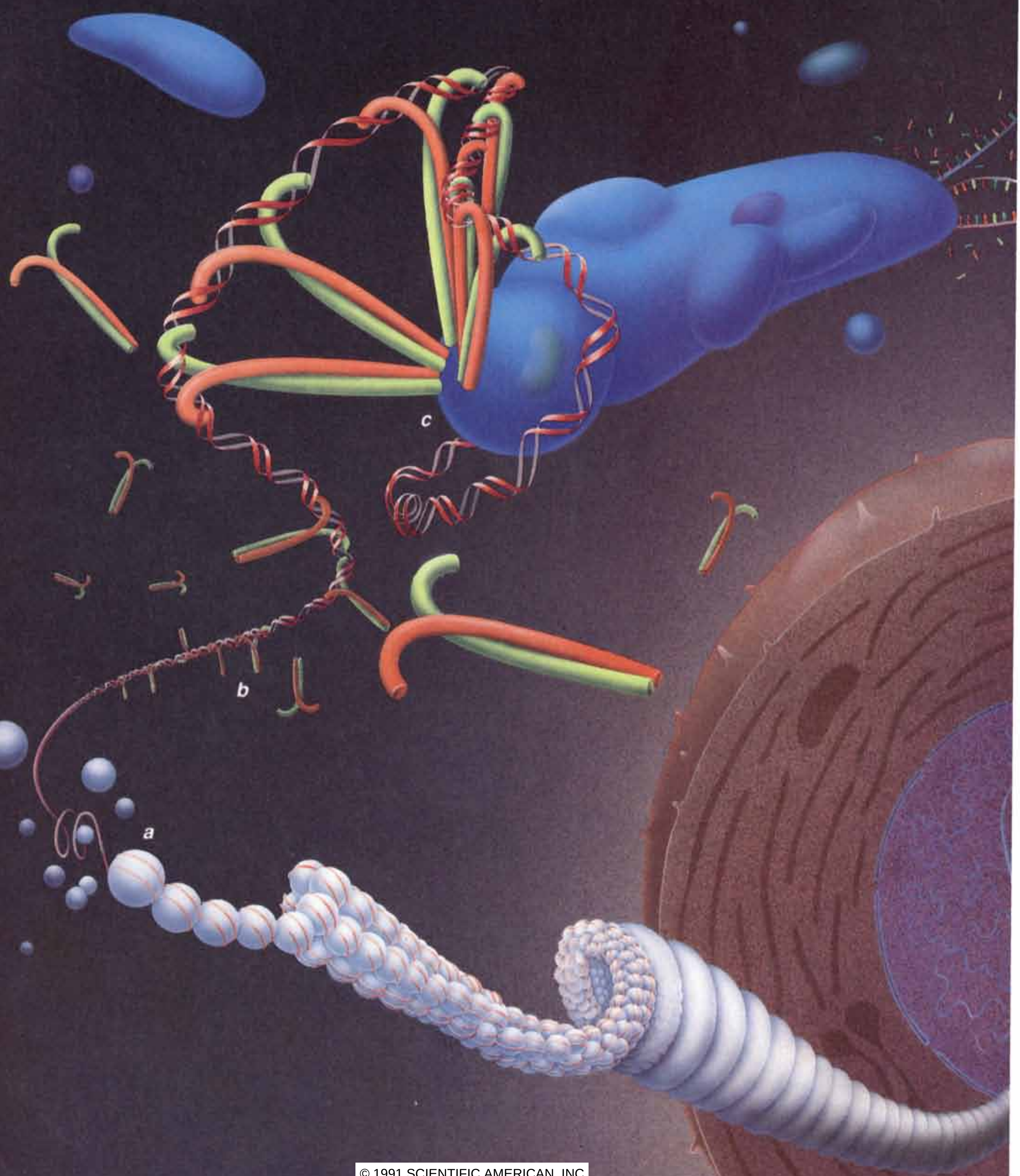
# SMART GENES

by Tim Beardsley, *staff writer*

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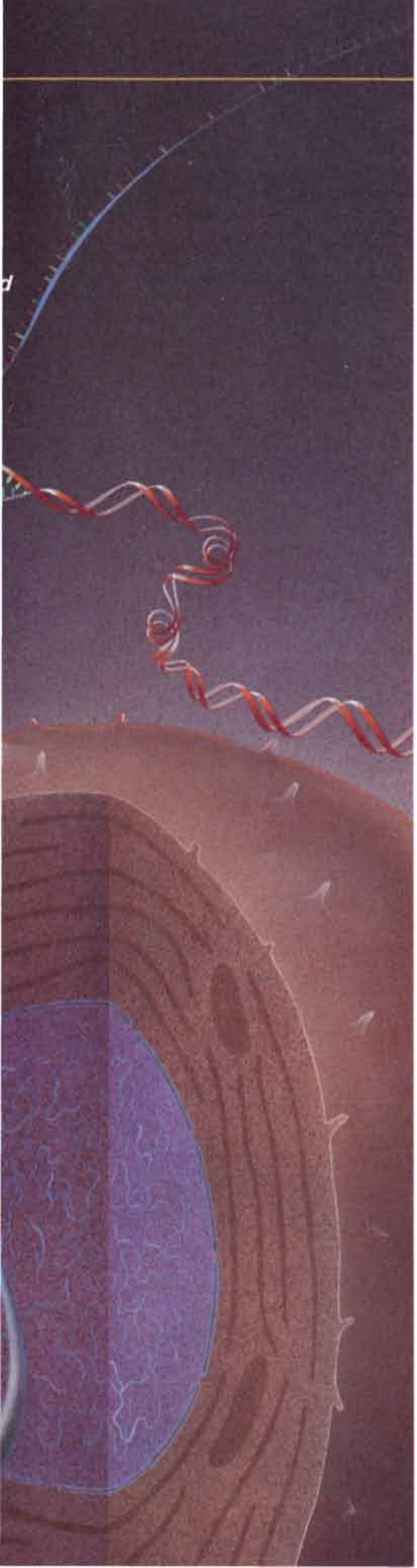

**How do very similar genes produce very different cells? It depends on which genes are activated and when. The elaborate chemical messages that control differentiation are now being deciphered.**

Biologists realized almost 50 years ago that as cells differentiate they switch some genes on and others off, making it possible for a simple fertilized egg to unfold into a flower, or a fruit fly or a human being. Cells migrate within a developing organism in complex patterns, changing their form and eventually coalescing into specialized tissues. A human being, for example, has more than 250 different types of cells, and each must occupy and function in its proper place. (Liver cells would be no use at all in the brain.) Yet virtually all cells have exactly the same genes encoded in their DNA.

The mystery of how developing organisms choreograph the activity of their genes so that cells form and function at the right place and at the right time is now being solved. Hundreds of experiments have shown that organisms control most of their genes, most of the time, by regulating transcription—the process by which genetic information is copied from DNA into RNA, which is used to make the myriad proteins that make one cell very different from another. "That gene control is achieved by regulating transcription is the main lesson of molecular biology in the past 20 years," says Eric H. Davidson, an embryologist at the California Institute of Technology.

More significant, Davidson and others are discovering how transcription is controlled in multicellular organisms. Davidson has coined the term "smart genes" to describe the many genes that respond to combinations of signals sent from one gene to another in control networks. "We're studying what I call the brain of the smart gene," Davidson says. The "brain" is a complicated assemblage of proteins known as a transcription complex. For the elaborate transcription process to get under way, the proteins—acting as chemical signals—must bind to the DNA near a target gene.

This complex is now being seen as a "sloppy computer," in which the signals are combined to make a decision about whether to switch on the gene. If these chemical messages—which may arrive from outside the cell—are present in the right combination, the enzyme that performs transcription is activated, producing RNA.

Much of the research is being conducted on tiny fruit flies, microscopic worms and even disembodied specks of protein. Yet there is good reason to think that such studies will illuminate all creatures, including ourselves. The reason is that—to a degree that has startled the scientists who have made the

*KEY GENES in cell differentiation are turned on by a complex of proteins that bind to specific sites on DNA. The process begins when DNA unwinds from histones* (a), *which keep it coiled when unused. Then transcription factors (paired structures) bind to the DNA* (b). *They form a transcription complex* (c) *that activates proteins coupled to the enzyme that transcribes the gene into a strand of RNA* (d).



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discoveries—the same basic processes seem to work in all multicellular organisms. "The smart gene may be one of the universal features on which embryonic and other developmental processes depend," Davidson contends.

Apart from its philosophical interest, understanding how genes control and are controlled by the developing organism could lead to new ways to combat diseases that result when the processes go awry. Those maladies include not only inherited pathologies but also cancer and autoimmune conditions. Already some pharmaceutical companies are working on drugs that will recognize and bind to specific DNA sequences. Once the control systems that regulate genes are better understood, it may be possible to design drugs that switch specific genes on or off—a quantum leap for medicine.

### Genetic Blueprints

The idea that chemical signals can affect gene activity dates to the early days of embryology. When researchers cut pieces of tissue from one part of an embryonic frog and placed them at another site, the transplanted tissue would sometimes grow into a form appropriate to its initial location—resulting, for example, in a frog with a misplaced limb. But if an embryo was manipulated early enough, it would recover and produce a normal animal. Such results suggested that undetected signals could affect subsequent gene expression.

Not until 1960 was a plausible explanation forthcoming. Then, French biologists François Jacob and Jacques Monod conducted a series of experiments on the ubiquitous gut-dwelling bacterium *Escherichia coli.* It was known that when *E. coli* is exposed to the milk sugar lactose, it quickly starts producing lactose-digesting enzymes. The French researchers suggested a separate protein was switching on previously quiescent genes in response to the presence of lactose.

"The genome contains not only a series of blueprints," Jacob and Monod wrote, "but a coordinated program of protein synthesis and means of controlling its execution." They also made the crucial suggestion that the protein switch operated by recognizing and attaching itself to a specific sequence of DNA bases near the genes it controlled. By doing so, they asserted, the protein could prevent transcription.

Jacob and Monod's idea turned out to be resoundingly correct. Many examples of gene control systems have since been worked out in *E. coli,* and most are variants of that initial scheme. Many involve genes that produce enzymes for metabolizing a nutrient or synthesizing one that is in short supply. In each case, DNA-binding proteins attach themselves to specific sites on the bacterial DNA, where they either repress—or promote—transcription of a usually nearby gene.

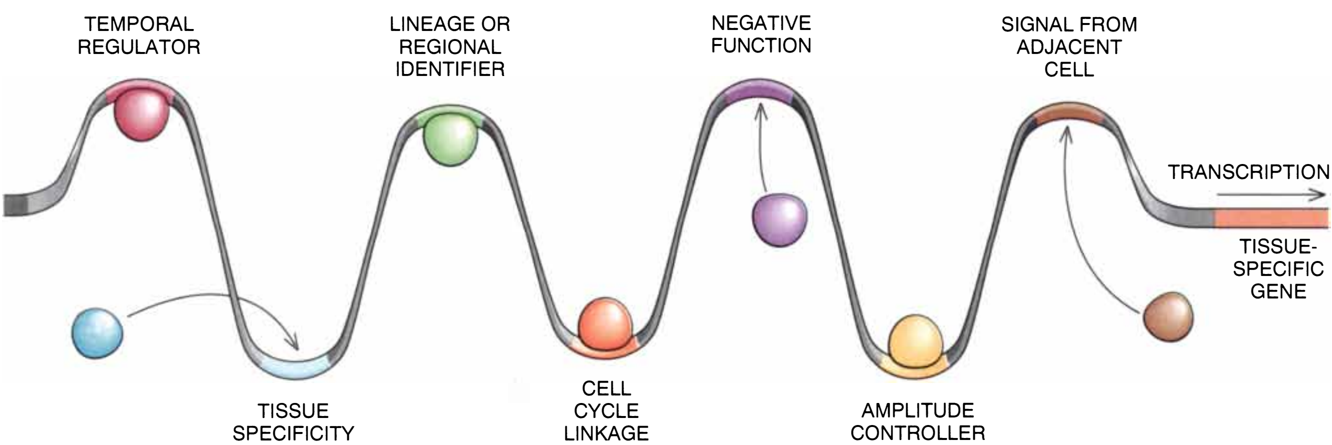
How well the DNA-binding proteins promote or repress transcription depends on how many such molecules there are, which can be influenced by a multitude of factors. Although some bacterial transcription control mechanisms are exquisitely sensitive, they resemble switches more than computers. Controlling the genes of a complicated multicellular organism is a very different challenge, and the mechanisms are correspondingly more complex.

A bacterium might use most of the genes it possesses during its short lifetime, switching them on or off rapidly in response to changing conditions. But a typical differentiated cell in a multicellular organism uses only a small proportion of its genes. Although there should be fewer changes in gene activity—because multicellular organisms strive to maintain a constant internal milieu—deciding which genes to switch on is not simple. Cells in a complex organism have to "know" where they are to decide which genes to express. And they still might have to respond to an emergency, such as an injury or a sudden surge of hormones.

Because the requirements of bacteria are very different from those of most other organisms, known collectively as eukaryotes, nobody thought it likely that they would use the same fundamental mechanism to control their genes. But it turns out that DNA-binding proteins are common in eukaryotes, too. "If you'd told a biologist 10 years ago how many genes encode DNA-binding proteins, he would have laughed you out of the room," says Robert T. N. Tjian, a biochemist at the University of California at Berkeley.

When researchers began to investigate transcriptional control in eukaryotes, however, they soon found some novel features. For instance, in 1982 Steven L. McKnight and Robert Kingsbury, then at the Fred Hutchinson Cancer Research Center in Seattle, created one of the first maps showing which regions of DNA near a gene affected its transcription in a eukaryotic cell. They used a gene from a herpesvirus that could be accurately expressed in egg cells of the African clawed frog *Xenopus laevis.*

By creating mutations in the vicinity of the gene, McKnight and Kingsbury found several distinct areas that had to be intact for normal transcription. One was close to the "promoter" site, very near where the transcription enzyme starts its work. That was expected from what was known about bacteria. The other two crucial sites were remote in molecular terms, one 50 and the other 100 base pairs away.




**TISSUE-SPECIFIC GENES are activated when proteins known as transcription factors bind to the proper combination of sites to form a unique complex. The binding sites are strung out along the chromosome, often distant from the gene. Each factor may convey specific information such as the time in the life cycle, the cell's lineage and so on.**



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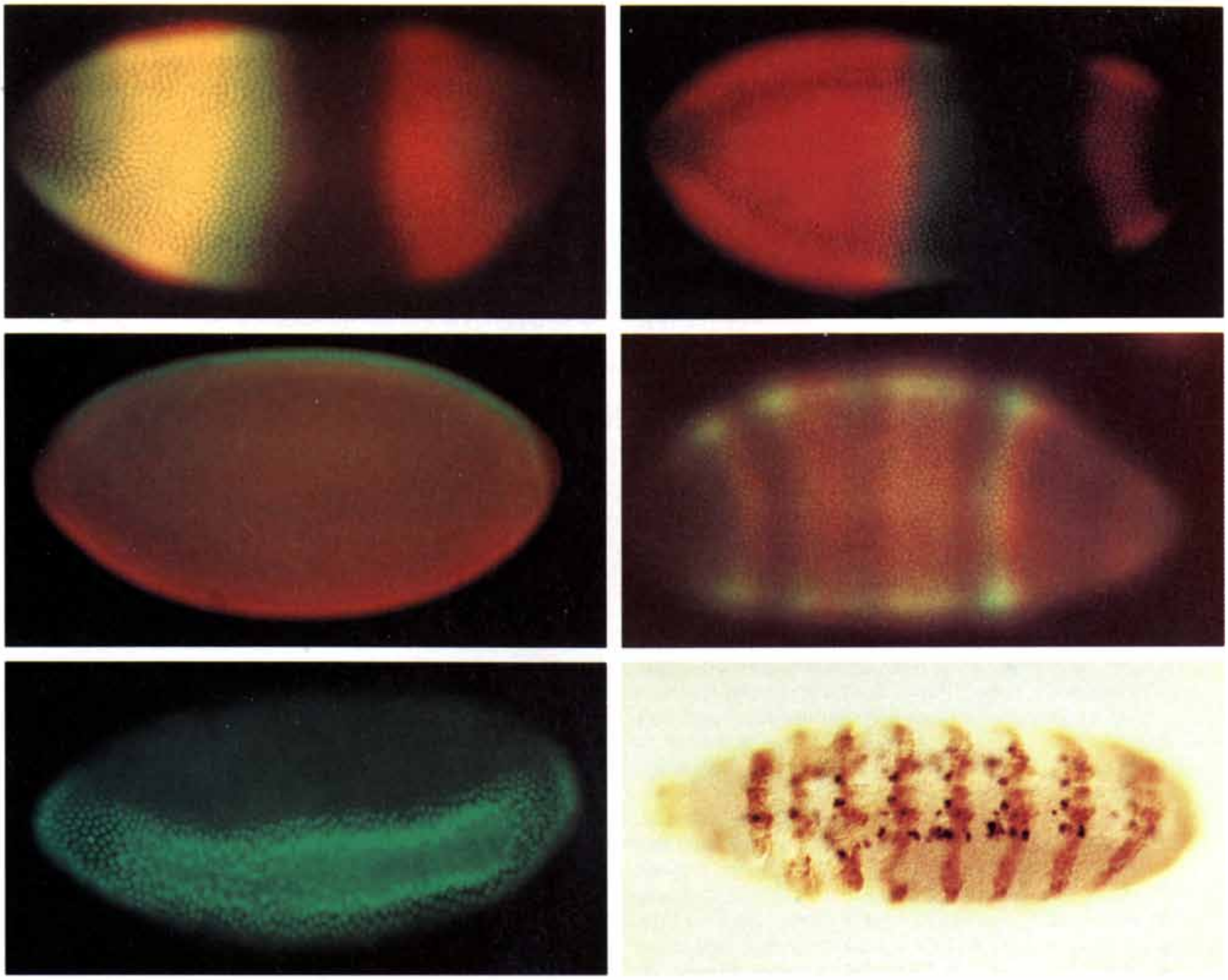

**STAINED EMBRYOS of *Drosophila* show how genes are selectively activated in certain regions during development. Proteins produced by *hunchback* are stained green and those by *giant*, red (*top at left*). *Zen* is green and *dorsal*, red (*middle at left*). Green shows activity of *twist* (*bottom at left*). *Hunchback* protein is red and *Krüppel*, green (*top at right*). *Even-skipped* protein is green and *hairy*, red (*middle at right*). (Yellow is overlap.) An older embryo was stained to show proteins from *engrailed* (*brown bands*) and from *S59* (*purple dots*), which precedes muscle development (*bottom at right*).**

It was a surprise to find that proteins so distant could affect transcription. Even so, "the best guess was that they were protein-binding sites," McKnight says. The conjecture was soon confirmed when Tjian isolated a protein that could demonstrably stimulate transcription of a gene in a eukaryotic cell, by binding to a distinct sequence of the chemical bases that make up DNA. Tjian found that his protein bound at five distinct places near one viral gene. "It has since turned out that that's what they all look like," McKnight says of eukaryotic genes.

Unlike DNA-binding proteins in bacteria, those in eukaryotes often controlled transcription from very distant binding sites. Before long, transcription factors were identified that bound as far as 40,000 base pairs from the target gene and were still able to stimulate—or repress—transcription. Also unlike bacterial DNA-binding proteins, the exact position of eukaryotic transcription factors seemed not to matter. They could be on either side of the promoter site or even attached backward.

Barbara R. Hough-Evans and others working with Davidson recently investigated a gene that produces the protein actin in certain cells in the sea urchin *Strongylocentrotus purpuratus*. There are no fewer than 20 DNA regions near the gene that are recognized by regulatory proteins. Davidson and his coworkers have showed that at least five of them must be bound by regulatory proteins for the actin gene to be transcribed. They also found two other regions to which regulatory proteins must bind in order to prevent the actin gene from being transcribed.

According to Davidson, the average number of regulatory sites for a gene in a multicellular organism is probably at least five. Most of the genes in complex creatures, it seems, must assemble on-board protein computers before they can be transcribed. "Our contention is that a eukaryotic promoter has to have multiple controlling sites," Tjian says. In contrast, the most complex known bacterial genetic switch—which was analyzed by Mark Ptashne and his colleagues at Harvard University and controls the multiplication of a bacterial virus—has only three adjacent protein-binding sites at its transcription starting points.

In addition to their other peculiarities, eukaryotic transcription factors are less finicky about where they bind to DNA than those of bacteria. To McKnight and others studying gene regulation, that presented a conundrum. In a eukaryotic nucleus, McKnight points out, "there are more genes, in a greater volume, yet the proteins have lower



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specificity. It was clear that they have to talk to one another."

In other words, McKnight was suggesting transcription factors in eukaryotes might by pooling their efforts compensate for what they lack in binding specificity. But the only way for a group of proteins to "talk to one another" when they are strung out along a filament of DNA would be for them to come together to form a single, large complex. The idea seemed plausible because the intervening DNA, being flexible, can loop out of the way.

The idea is now well established. Tjian, for one, has made electron micrographs that show such loops in isolated and reconstituted transcription complexes. He has found at least five proteins that must always be present to make them work.

Even so, these obligatory proteins alone are not sufficient to promote normally regulated transcription. They must also be activated by the complex formed by transcription factors around the gene. Only when all the components are present—the obligatory proteins, the enzyme and the right combination of specific transcription factors—will the smart gene be available for controlled transcription.

Several hundred different transcription factors have been found to date. About two thirds of the known factors fall into recognizable groups based on

## Still Learning from *Drosophila*

Tiny *Drosophila,* the common fruit fly, has been a favorite of geneticists for more than 60 years. Now it is making an equally important contribution to the understanding of development. During the past decade, researchers have pieced together a fairly complete picture of the interplay of genes during the early development of the *Drosophila* embryo.

The adult is divided into 17 segments, some bearing appendages such as wings or legs. Cells in the embryo look much alike, but even so, if they are transplanted to a new site, they produce structures appropriate to where they were taken from. That observation indicates that from an early stage, cells are programmed to form structures appropriate to a particular segment.

During early development, one set of genes makes its first appearance as a series of stripes of protein that can be made visible by chemical staining. The stripes divide the embryo into segments. The process gets under way when maternal nurse cells secrete into the egg RNA from a gene called *bicoid.* The RNA is trapped at one side of the egg, where it is translated into protein that slowly diffuses across the egg. At the same time, RNA from another maternal gene, called *nanos,* diffuses in the opposite direction.

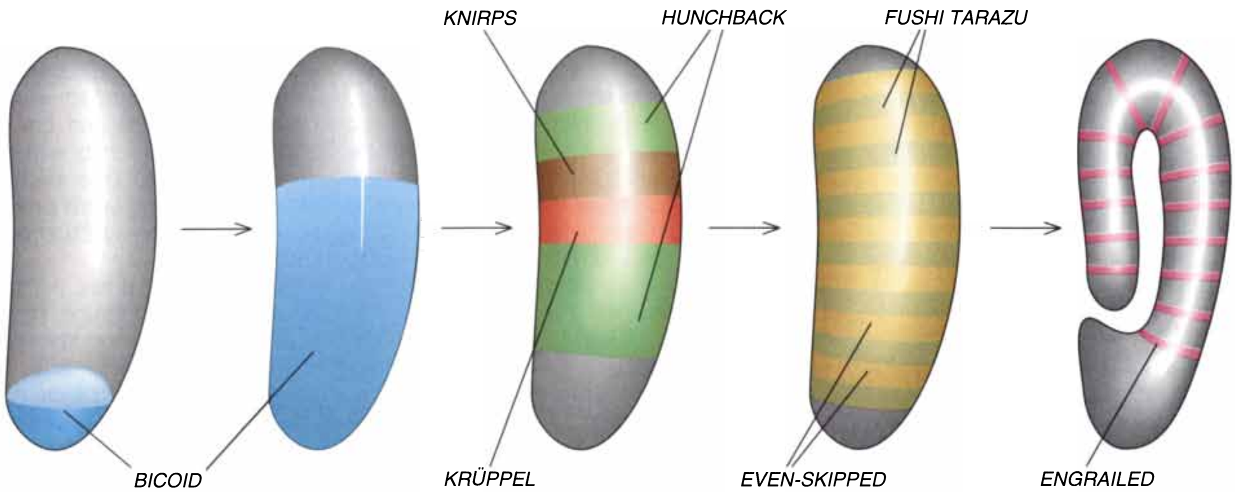
*Bicoid* protein then stimulates—through a combination of activation and repression—transcription of so-called gap genes, the first genes belonging to the embryo to play a part in patterning. Four broad stripes are established—two of *hunchback* protein separated with stripes of other proteins from *Krüppel* and *knirps* genes. Christiane Nüsslein-Volhard and Wolfgang Driever of the Max Planck Institute for Developmental Biology in Tübingen have proved the role of *bicoid* protein. If it is altered, the expression of the gap genes changes.

Gap genes give place to seven overlapping stripes of *even-skipped, hairy* and *runt* expression. Later, seven stripes of *fushi tarazu* protein alternate with seven of *even-skipped.* Later still, 14 narrow bands of *engrailed* protein emerge. Each stripe appears to use a unique combination of active genes. Other genes, mostly still unknown, are believed to respond to these combinations by producing the specialized structures needed by the segment.

While all this is taking place, a separate hierarchy is dividing up the embryo in a dorsal-ventral direction, a process crucial for generating different tissue types. The process involves a gradient of *dorsal* gene product, which may act like *bicoid.* Later, genes called *twist* and *snail* are expressed in specific regions along the dorsal-ventral axis.

Some developmental genes seem to counteract the effects of others; still others seem to act in concert. Many genes autoregulate: once turned on, they keep themselves switched on until something interferes. And some, such as *even-skipped,* do different jobs at different times, just as an actor might appear in different scenes in a play in different roles.

Some biologists who work with other organisms point out that *Drosophila* is unusual because cell walls form late, allowing proteins to form concentration gradients. But Nüsslein-Volhard replies that cells may create the equivalents of gradients, if they vary in how much signal they take up. "I am absolutely confident gradients work in more complex animals," she says.



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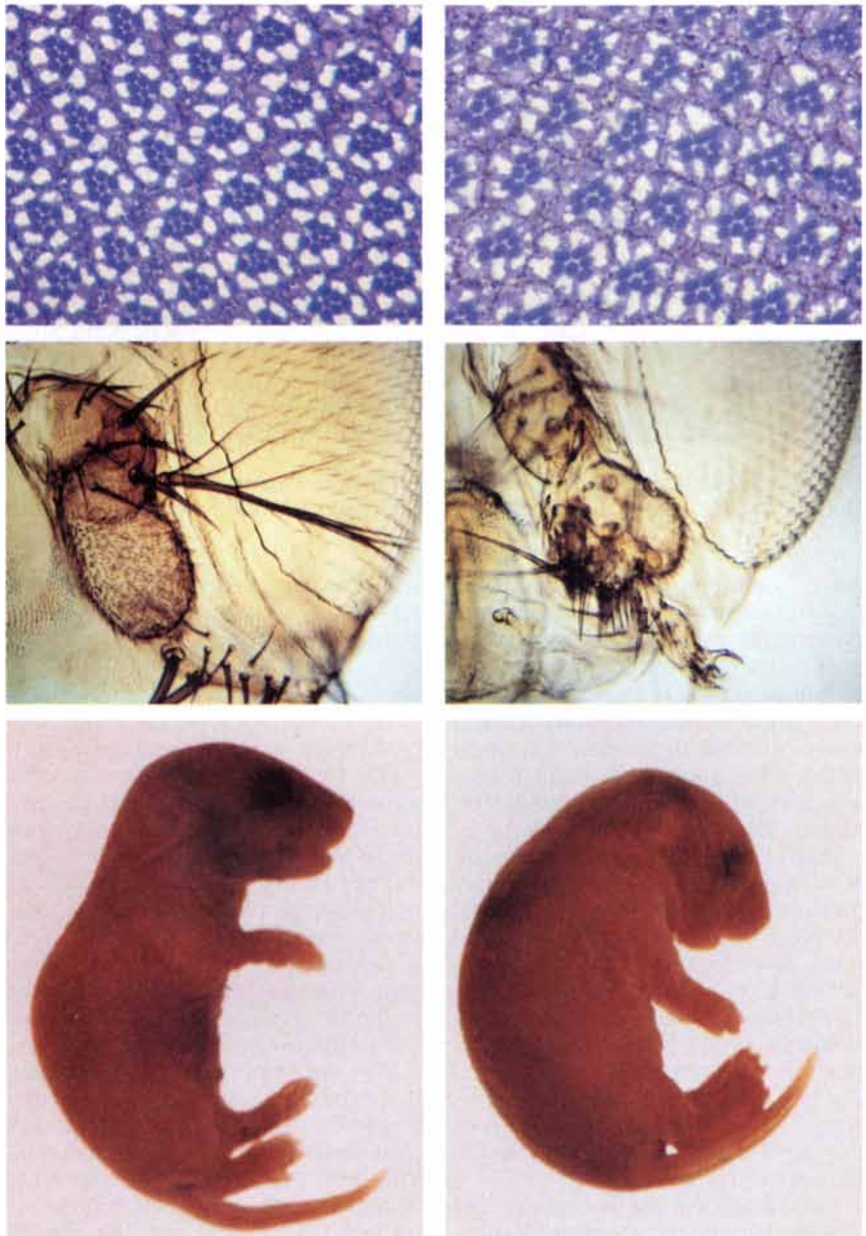

**ABNORMAL STRUCTURES result from mutations in developmental genes. A normal *Drosophila* eye appears at the top left. On the right is one with mutations in the *sevenless* gene in which groups of photoreceptors lack a seventh cell. Transplanting a mouse homeobox gene into *Drosophila* has produced legs (*middle right*) where a normal fly (*left*) has antennae. At the bottom left is a normal mouse pup; at the bottom right, a malformed pup created by mutations in a homeobox gene.**

their molecular structure: helix-turn-helix, zinc finger, leucine zipper, helix-loop-helix. The remainder seem to be one-of-a-kind proteins, some of them restricted to a particular type of tissue.

Generalizations are dangerous, but Ptashne and Kevin Struhl, also at Harvard, have performed crafty experiments in which they produced hybrid transcription factors in cells. The experiments showed that transcription factors have at least two distinct regions. One recognizes and binds to specific DNA sequences. A separate region seems to be responsible for the activating effect.

Many questions remain about how the transcription complex works as the "brain" of a smart gene. Although it appears that some sort of quorum of transcription factors may have to be present, molecular modelers are having a hard time trying to visualize how as many as 20 proteins can interact.

Nevertheless, it seems to be agreed that transcription factors can help one another to bind to DNA. One idea has been proposed by Tjian. He says he has isolated a type of protein (he calls it a co-activator) that might link the sequence-specific transcription factors with the transcription enzyme and its associated proteins. Others are skeptical: Ptashne, for example, thinks Tjian's claim is based on a misconception about how transcription factors work.

### Mixed Signals

However the details may fall out, little doubt remains that the transcription complex determines when a gene will be transcribed. And that suggests an explanation for embryologists' observations that signals from both outside and inside the cell can influence whether a gene is switched on or off.

If a cell has the right combination of transcription factors for a particular gene, the complex will form properly and transcription of the smart gene will start. Davidson points out that many different types of signals might be processed in this way: information about the cell's lineage, its interactions with other cells, the stage of the cell division cycle and so on.

Smart genes also offer a way out of an awkward problem that had been troubling theoreticians. If each gene in an organism had to have a unique controlling protein, then the question would arise of how production of the controlling proteins was regulated. But if a variety of regulatory proteins can interact, then a few control proteins could control many genes.

Many transcription factors are dimers, meaning that they consist of two subunits bound together [see "Molecular Zippers in Gene Regulation," by Steven Lanier McKnight; SCIENTIFIC AMERICAN, April]. That feature increases still further the number of genes they can control. Because the two subunits do not have to be identical, a much larger number of different dimers can be created from a small group of subunits. For example, four subunits *A, B, C* and *D,* can form 10 different dimers: *AA, AB, AC, AD, BB, BC, BD, CC, CD* and *DD.*

It is not possible to say how many different genes the 10 dimers could control without knowing exactly how transcription complexes work, but it could be hundreds, especially if the system tolerates some errors. And there are some indications it can. Many cells seem to produce some proteins at a low level that have no recognizable function. Perhaps, suggests James E. Darnell of the Rockefeller University, they are the result of harmless inaccuracies in the transcription control system.

Although early studies of eukaryotic transcription factors used single genes, the transcription complex plays a piv-



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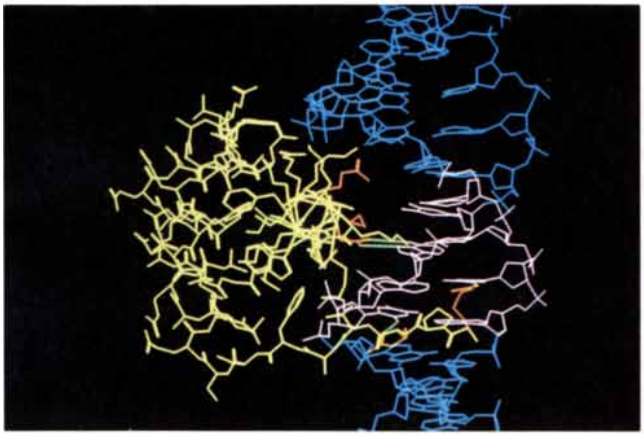

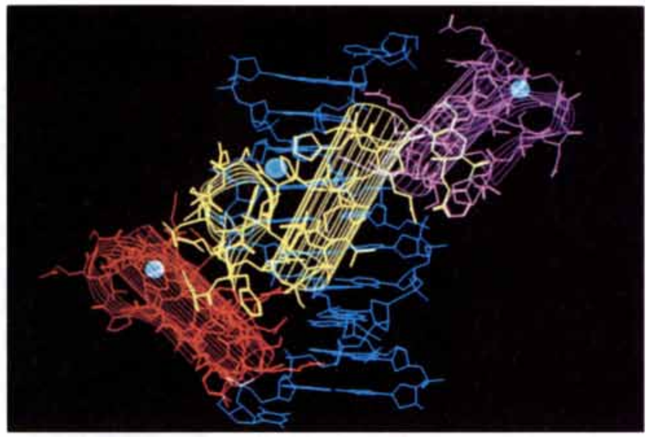

**COMPUTER MODELS show how transcription factors bind to sites on DNA. At the left, a homeobox protein (*yellow*) binds to DNA (*blue and lilac*). At the right, a DNA-binding protein of zinc-finger class (*orange, yellow and lilac*) binds to DNA (*blue*).**

otal role in more complicated systems. One example that shows what transcription complexes can do has been uncovered by Ira Herskowitz and Alexander D. Johnson of the University of California at San Francisco, who study budding yeast. Although the organism is single celled, it has a eukaryotic chromosome structure, and like a multicellular organism, it has distinct cell types.

One of the cell types is nonsexual. It reproduces by budding, simply dividing in two to produce identical offspring. Two other types are sexual forms produced under unfavorable conditions and must mate with each other. Herskowitz and Johnson have painstakingly traced the genetic controls that make the three cell types distinct. The principal locus of control is a transcription factor for controlling genes that are differentially expressed in the different cell types.

The control scheme is complex and elegant. The key transcription factor is a dimer whose subunits can be identical or different. A dimer composed of two dissimilar units causes a cell to become a nonsexual type, because its binding properties make it repress all the genes needed to form the sexual cell types. If the dimer is composed of identical units, the genes used in the sexual cell types are activated.

The yeast cells use pheromones to coordinate their reproductive activities, and even these hormonelike chemical messengers work by influencing gene transcription. A small protein released from a cell of one "mating type" readily attaches to special receptors on a nearby cell of the opposite type. The union triggers a cascade of chemical reactions that leads to the priming of another specialized transcription factor. It then turns to "full on" the genes used for mating. Overall, at least 13 genes are somehow involved in controlling cell type in the yeast, and most of them are transcription factors.

### The Homeobox

Although it was clear in the early 1980s that transcription factors were important in eukaryotes, finding examples that were important in development was difficult because biologists did not know what genetic sequences to look for. In 1983, however, researchers working in the laboratory of Walter J. Gehring of the University of Basel and, separately, Matthew P. Scott, then at the University of Colorado, made a crucial discovery.

They were studying a group of genes in the fruit fly *Drosophila* that, when disrupted by a mutation, caused adult segments to develop the wrong structures. The most famous gene of that type, *Antennapedia,* can cause flies to develop legs where their antennae should be. Scott in Colorado and Ernst Hafen, Michael Levine and William J. McGinnis in Basel discovered that several such genes, known as homeotic genes, all contained a distinctive sequence of DNA bases that has since been named the homeobox.

The homeobox provided a vital toehold by giving molecular biologists a sequence to search for. Once a sequence contained in a gene has been identified, it is often relatively easy to find similar sequences elsewhere among the chromosomes. One reason is that mutations occasionally duplicate genes. If a duplicate copy does no harm, it could over generations evolve a new function. And if the new gene is important, new species might continue to carry it.

The homeobox sequence, or close variants of it, was soon turning up everywhere. *Drosophila* had several copies, all in genes that can disrupt development. But that was not all. The physical order of homeobox-containing genes along a chromosome corresponded like a map to the order of their domains of activity along the body.

Soon McGinnis and others had found homeoboxlike sequences in other organisms: beetles and worms, frogs and chickens, mice and men. In all of them the order of the genes along the chromosome was conserved, as well as the homeobox sequence itself—but not only in invertebrates and vertebrates. Even homeobox connoisseurs were flabbergasted when a (somewhat altered) version was recently found smoothly controlling development in plants.

The extreme conservation of the homeobox sequence over at least a billion years of evolution suggested that it plays a vital role. It did not take long to discover it. In 1984 Allen Laughon noticed that the region of protein encoded by the homeobox DNA sequence had subtle similarities both with sequences for bacterial DNA-binding proteins and for yeast mating-type proteins. The similarities prompted Laughon and Scott to propose that the homeobox encoded a protein region—called a homeodomain—that bound to DNA.

Not long afterward, Patrick H. O'Farrell of the University of California at San Francisco and Claude Desplan of Rockefeller provided evidence that homeobox proteins do indeed bind to DNA. In 1988 O'Farrell took the final step by demonstrating that the proteins produced by a *Drosophila* homeobox gene called *fushi tarazu* (Japanese for "not enough segments") and by one other homeobox gene not only bound to DNA but also activated and repressed transcription of nearby genes. By then, other results also pointed in the same direction. Homeobox genes, which were iden-



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tified because they produce bizarre abnormalities in *Drosophila,* turned out to produce transcription factors that control genes in multicellular organisms.

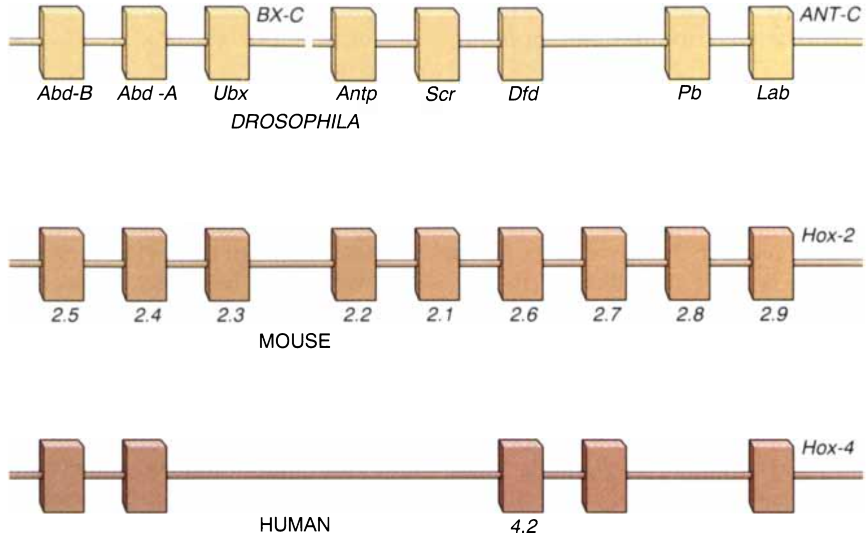
Showing an effect in the test tube is one thing, but showing that it actually operates in nature is another. McGinnis, who is now at Yale University, and his colleague Michael A. Kuziora recently demonstrated the importance of a homeodomain in a live animal. They replaced the homeobox of one *Drosophila* gene with a slightly different homeobox from another gene and expressed the resulting chimeric gene in the insect. The result was larvae with head segments that resembled thoracic segments. A possible explanation was that the introduced homeodomain was recognizing and binding to a specific region of DNA.

As techniques to identify gene products have improved, researchers have uncovered a wondrously complex tangled hierarchy of developmental genes that lay out the body plan in *Drosophila* [*see box on page 90*]. Many are homeobox genes. In the first few hours after fertilization, the hierarchy progressively subdivides the ellipsoidal embryo in different directions. Proteins produced by these genes form gradients of concentration that in turn switch other genes on or off, according to Martin Hülskamp and Diethard Tautz of the University of Munich.

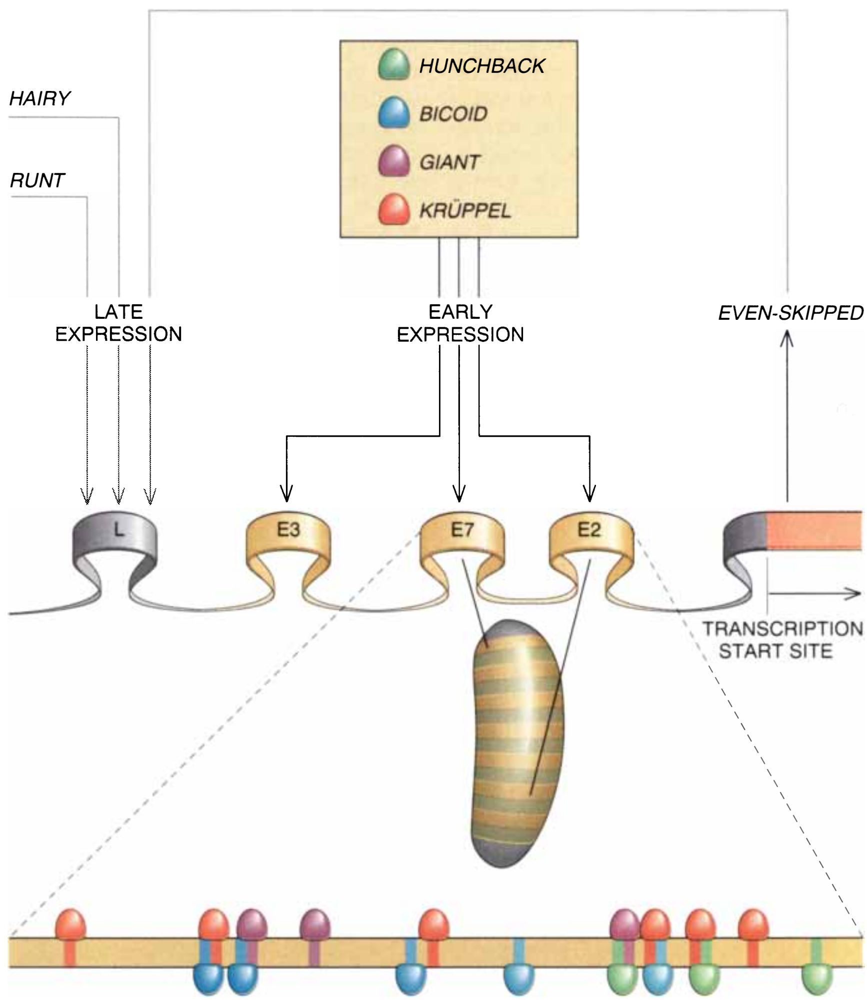
Smart genes, it seems, talk to one another a good deal during development. The process repeats, fractallike, at successively smaller scales, eventually elaborating stripes of protein expression. Each stripe has a unique combination of active genes, and it seems likely that they determine the genes to be turned on in each segment of the adult fly.

One well-studied homeobox gene in the hierarchy is called *even-skipped,* so named because some mutants are missing even-numbered segments. The example shows just how complicated the logic of the smart gene can be. The *even-skipped* protein first appears in seven poorly defined stripes that subdivide the embryo. Later the stripes become more precise. Mutations in the *even-skipped* gene disrupt the activity of a gene below it in the hierarchy, known as *engrailed.* And *even-skipped* is affected by mutations in genes above it in the hierarchy: *hunchback, Krüppel, giant* and *bicoid.*

Tom Maniatis and his colleagues at Harvard and Levine, now at the University of California at San Diego, have found that the *even-skipped* gene has several distinct regions where regulatory proteins bind, thus controlling the gene's expression. One region, which controls




**HOMEOBOX GENES with similar base sequences appear in the same order on the chromosomes of various species. Their order along the chromosomes also matches the order of the regions of activity in the body. For example, *Drosophila Abd-B* and mouse *Hox 2.5* are active at the posterior tip of the embryo.**




**ACTIVATION of the *even-skipped* gene in *Drosophila* requires transcription factors produced by numerous other genes. Regions E7 and E2 (*enlarged at bottom*), which control *even-skipped* stripes 7 and 2 in early development, contain many sites for *hunchback, bicoid, giant* and *Krüppel* proteins. Later activity (*L*) is controlled by *hairy, runt* and *even-skipped* itself.**



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the early appearance of a particular *even-skipped* stripe, has sites for *bicoid, hunchback, Krüppel* and *giant* proteins. A different set of proteins binding elsewhere controls *even-skipped*'s late expression. The surface has only just been scratched: in all probability, each of the seven stripes has its own set of regulatory proteins.

The number of vertebrate genes known to have an equivalent in *Drosophila* seems to go up every week. The *Drosophila dorsal* gene product, for example, is similar to a mammalian "emergency response" transcription factor known as NF-κB. Darnell and his colleagues have found a liver-specific transcription factor that resembles the product of a known *Drosophila* homeotic gene, *fork-head,* which is expressed in the fly's gut precursor cells. Those cells give rise to *Drosophila*'s equivalent of a liver, the fat body.

Over the past year audacious experiments have tested whether the sequence similarities reflect similar functions. Researchers have transplanted developmental genes (or parts of them) between species. McGinnis and his colleagues introduced into *Drosophila* a mouse gene equivalent to *Antennapedia* and deliberately overexpressed it. The resulting flies had "nearly identical" defects to those created by overexpressing *Antennapedia* itself: they had legs where their antennae should be [*see illustration on page 91*].

McGinnis has also introduced into *Drosophila* a human homeobox gene similar to one found in the insect. When the human gene was deliberately overexpressed in *Drosophila,* it caused head deformities like those produced by overexpression of the equivalent *Drosophila* gene.

Earlier this year Osamu Chisaka and Mario R. Capecchi of the University of Utah produced direct proof of the role of homeobox genes in mammals. They disrupted a mouse homeobox gene and then produced mouse embryos that carried only the disrupted version of the gene. The resulting pups, which survived only a few hours, had catastrophic malformations of the heart and throat and were missing some glands. The malformations closely parallel a rare human affliction, DiGeorge's syndrome.

Teasing out the implications for human developmental diseases will require more work. Maniatis notes that "we are completely in the dark" about mammalian genes that act in very early development. Ignorance reigns, too, over most of the genes at the opposite end of the control hierarchy, the ones that control specific tissue identity.

One exception is a mammalian gene called *MyoD,* investigated by Harold Weintraub and his colleagues at the Fred Hutchinson Cancer Research Center. *MyoD* is a potent transcription factor that can single-handedly turn cells into muscle. It should be no surprise that Maniatis and his colleagues recently found a *Drosophila* gene, *nautilus,* with a sequence similar to *MyoD,* and it is also expressed in cells destined to become muscle.

The discovery that so many of the genes key to development are transcription factors is a clear sign of the overwhelming importance of transcriptional control. But other developmentally important genes also affect gene transcription indirectly.

Last year, for example, Andrew P. McMahon of the Roche Institute for Molecular Biology and Allan Bradley of Baylor College of Medicine wondered whether a mouse gene called *Wnt-1,* which is similar to a *Drosophila* gene, *wingless,* might be important in mammalian nervous system development. When they made mouse embryos with two defective *Wnt-1* genes, they found the embryos lacked a large part of their brains. Yet *Wnt-1* does not code for a transcription factor. Rather it apparently specifies a diffusible substance that influences gene transcription in neighboring cells.

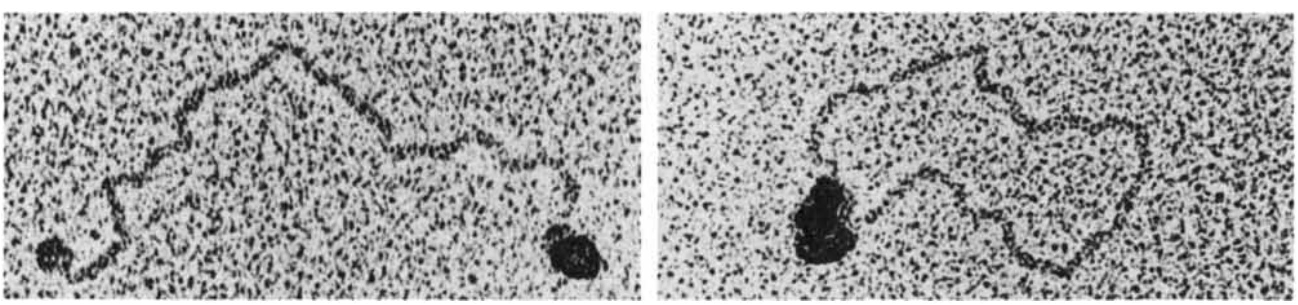
Some extracellular signals that smart genes respond to are well understood. Steroid hormones and vitamin D, for example, both diffuse from outside a cell right into its nucleus, where they bind to receptors to form active transcription factors. But many other vital signaling molecules are hardly known at all. They include substances usually lumped under the heading "peptide growth factors," as well as so-called cell adhesion molecules. These signaling molecules bind instead to cell-surface receptors that somehow relay a message to the nucleus. "The whole area of how extracellular communication affects transcription is what I see as the wave of the future," Darnell says.

Gerald M. Rubin of the University of California at Berkeley investigates how an intricate interplay of lineage-specific determination and diffusible signals specifies the fate of photoreceptor cells in *Drosophila* eyes. Normally the cells form eight-member groups, but mutants of a gene called *sevenless* lack the seventh member of the group. The *sevenless* gene, Rubin believes, encodes a receptor in the seventh cell that should receive a signal from its neighbors telling it what to become; if the gene is damaged, the signal is not received.

"The molecules involved in cell signaling in simple animals work also in higher organisms," maintains H. Robert Horvitz, a developmental biologist at the Massachusetts Institute of Technology. He recently backed up his claim. Horvitz showed that a gene called *let-60* is one of several key switches in development of the six cells that are precursors of the vulva in the microscopic worm *Caenorhabditis elegans.*

### Cancer Clues

*Let-60,* which like the *sevenless* gene in *Drosophila* encodes a component of a signal pathway, resembles a human oncogene—one that can cause cancer. Indeed, it is not surprising that many oncogenes turn out to be mutated forms of genes that play a role in development. Many oncogenes encode either transcription factors or other molecules involved in developmental signals that affect gene expression. Mc-



**TRANSCRIPTION FACTORS (*gray blobs*) bind to each end of a strand of DNA in the photomicrograph (*left*). Under suitable conditions, the transcription factors assemble into complexes, making loops of DNA (*right*).**



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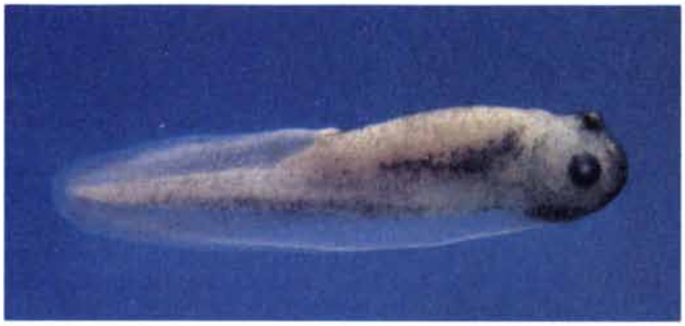

**NORMAL TADPOLE of African clawed frog appears on the left. Tadpole injected as an embryo with RNA for human activin (*right*) has an extra body axis. The RNA causes overproduction of activin, which affects developmental genes.**

Mahon and Bradley's mouse *Wnt-1* gene, for example, has an oncogenic form. So, too, do two critical "early response" transcripton factors known as *fos* and *jun*, which seem to be activated whenever mammalian cells respond to peptide growth factors.

Correspondences between genes that control transcription and substances linked to cancer are now cropping up with almost monotonous regularity. Douglas A. Melton of Harvard has shown that the growth factor activin turns on homeobox genes in the developing *Xenopus* frog. Gradients of activin probably tell cells in the developing animal where they are, because when Melton manipulated the levels of activin in embryos he produced a startling disruption of the body axes [*see illustration above*]. And activin, it appears, is very similar to a growth factor that can turn some cells cancerous.

In mammals and birds, a chemical called retinoic acid may play a role resembling that of activin in *Xenopus*. And within the past year researchers have found evidence that a mutated protein receptor for retinoic acid causes one form of leukemia.

The emergence into the limelight of transcription factors stole the show from researchers who in the early 1980s were betting that histones, proteins present in large amounts in the eukaryotic nucleus, would hold the key to gene regulation. When DNA is not being transcribed, it is wrapped around histones, which form particles called nucleosomes. DNA packaged in nucleosomes is called chromatin.

"The chromatin people have not progressed a hell of a lot," says Donald D. Brown, an embryologist at the Carnegie Institution of Washington in Baltimore. Brown, who studied histones in the early 1980s, complains that "the transcription-factor people act as if chromatin doesn't exist." Ptashne, to take a prominent example, acknowledges that nucleosomes impose a "nonspecific barrier" to transcription, but he believes they are "unlikely to cause us to greatly modify" models of gene control based on transcription complexes.

Several recent experiments, however, point to a more vital role for histones. James T. Kadonaga of the University of California at San Diego is investigating how transcription factors compete with histones for access to DNA. He predicts "the customary view of how a gene is turned on will be changing drastically." Other workers are starting to follow similar lines of inquiry. Robert E. Kingston and his colleagues at Massachusetts General Hospital have shown that some transcription factors compete better than others.

If so, histones might be an essential component of smart genes. "Scientists are just like anyone else—they go overboard for a fashion," says Gary Felsenfeld, a researcher at the National Institutes of Health. "Everyone rushes to one end of the ship, and someone has to yell that you're taking on water."

Felsenfeld is not alone in believing that histones will receive more attention in the 1990s. Tjian raises a problem that models based exclusively on transcription complexes are hard put to explain. "What's to prevent a transcription factor from activating all the genes near it?" he asks.

Some possible clues are now emerging. Rebecca Kellum of the University of California at San Francisco and Paul Schedl of Princeton University have demonstrated that in *Drosophila* certain DNA sequences insulate a chromosomal region from outside influences. They suggest that the insulating sequences might affect how DNA is packaged in nucleosomes. Dorothy Tuan of Harvard was the first to notice what might be the flip side of insulated regions: regions that somehow prime enormously long stretches of DNA, making it ready for transcription.

Michael Grunstein of the University of California at Los Angeles now believes that DNA-binding transcription factors are only part of the story. "I think histones are part of the transcription apparatus," he insists. Grunstein has shown that certain parts of histone molecules must be intact for transcription to be controlled. And he says he is starting to think of transcription as a two-step process. In the first step, DNA in a set region is unpackaged from the nucleosomes. Only in the second step do specific transcription factors come into play.

With the resurgence of interest in histones, "we're starting to put the whole system together," Felsenfeld says. But even if transcriptional control is understood within the next few years and the brain of the smart gene completely fathomed, transcription is not the only way genes are regulated. Processes that take place later—such as RNA editing—are almost certain to add another layer of complexity that will keep researchers busy for the foreseeable future. "The longer you spend studying regulatory regions, the more intelligent you realize they are," McGinnis says. "You just hope you're intelligent enough to figure them out."

FURTHER READING


HOW EMBRYOS WORK: A COMPARATIVE VIEW OF DIVERSE MODES OF CELL FATE SPECIFICATION. Eric H. Davidson in *Development*, Vol. 108, No. 3, pages 365–389; March 1990.

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ACTIVATORS AND TARGETS. Mark Ptashne and Alexander A. F. Gann in *Nature*, Vol. 346, No. 6282, pages 329–331; July 26, 1990.

NUCLEOSOMES: REGULATORS OF TRANSCRIPTION. Michael Grunstein in *Trends in Genetics*, Vol. 6, No. 12, pages 395–400; December 1990.

PATTERN FORMATION DURING ANIMAL DEVELOPMENT. Douglas A. Melton in *Science*, Vol. 252, pages 234–241; April 12, 1991.




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## Ordering Chaos

*Researchers are beginning to harness nonlinear systems*

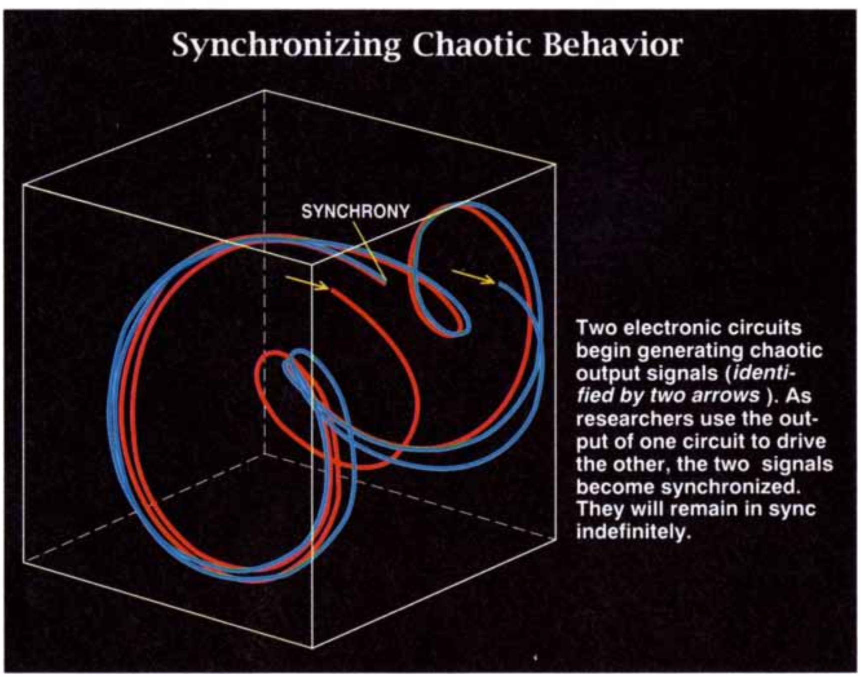
Chaos implies disorder and confusion. But over the past decade, research into the physics of chaos has revealed a surprise: the existence of subtle structure in such systems. And within the past few months, a handful of investigators have shown that they may be able to exploit these patterns in commercially important ways.

Although the experimental work is still new, the investigators say they are unlocking a previously unexplored realm of engineering. Instead of avoiding chaos, declares William L. Ditto, a researcher at the Naval Surface Warfare Center, "there's an explosion of new work showing you can really use the richness in chaotic systems."

The experiments build on a rapidly expanding theoretical understanding of chaos. For instance, last year Edward Ott, Celso Grebogi and James A. Yorke of the University of Maryland observed that chaotic motion actually consists of an infinite number of unstable, periodic motions, or orbits. They consequently reasoned that any chaotic behavior could be nudged into regular, periodic motion by continually applying small forces that would push it into one of these orbits.

Last December, Ditto and two colleagues proved that hypothesis true. Along with Steven N. Rauseo and Mark L. Spano, Ditto had been working with "smart" materials, ones that often have nonlinear reactions to applied forces. One such material was a magnetoelastic ribbon that changes its stiffness in the presence of a varying magnetic field. Near a small magnetic field, the ribbon stands upright, but as the field grows stronger, the ribbon becomes more elastic and starts to droop. Increasing the field strength eventually throws the ribbon into an undulating, chaotic dance.

By tracking the ribbon's changing posture, the investigators created a map of its chaotic attractor, or pattern, of motion. According to theory, some points of that pattern should correspond to specific periodic orbits. Ditto and his colleagues picked an orbit, waited until the ribbon was moving near that orbit, then applied small adjustments to the magnetic field. As long as they modulated the force, the ribbon moved with a regular periodicity. As soon as they stopped, it once again acted chaotically. "It's like balancing a marble on a saddle," Ditto says.




*SOURCE: Louis M. Pecora and Thomas L. Carroll, Naval Research Laboratory*

Ditto also recently began collaborating with Louis M. Pecora, a researcher at the Naval Research Laboratory who has developed experimental techniques for synchronizing chaotic signals. "I got the idea in January 1989," Pecora says. Within a year, Pecora and his colleague Thomas L. Carroll had built their first synchronized chaotic circuits, which are so simple "you can build them with equipment from your local electronics shop," Pecora points out.

Yet the mathematical principles behind the circuits and the coordination of the signal are less commonplace. Pecora developed a stability criterion, which describes the specific chaotic signals that cause the nonlinear systems to synchronize. In the laboratory, Pecora and Carroll built a simple circuit that generated a chaotic signal and a subcircuit, which reproduced part of the first circuit. This, too, operated chaotically. But when the researchers imposed the signal from the full circuit on the signal from the subcircuit, the outputs became synchronized.

More recently, Pecora and Carroll have demonstrated another kind of synchronization. In a paper submitted to *Physical Review Letters,* the researchers describe how they built two separate circuits that are driven by the same periodic signal. At first, the systems behave in a nicely periodic fashion. But a small difference in initial conditions eventually throws the circuits out of phase with each other. "The surprise is that adding chaos cures this," Pecora says.

Currently nearly all engineering designs aim to eliminate any nonlinear behavior in systems. But "I see the time coming when people will want to use more nonlinearities," Pecora says. For instance, many biological patterns, such as a beating heart, are naturally chaotic. Pecora is investigating whether his techniques may provide a gentler technique for pushing a fibrillating heart back into its proper rhythm. Similarly, neural network computers may eventually benefit from chaotic synchronization.

Among others exploring the signal-processing applications of chaos is Stephen M. Hammel, also at the Naval Surface Warfare Center. He has developed a technique for finding a chaotic signal amid random noise. Hammel, along with Yorke and Grebogi, began by tack-



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# SCIENCE/SCOPE®

A new navigational aid will help pilots flying the night attack version of the U.S. Navy's and Marine Corps' F/A-18 Hornet aircraft see through smoke, haze, darkness and adverse weather. The main element of the Hornet's night attack system is a forward-looking infrared (FLIR) sensor, called a Thermal Imaging Navigation Set (TINS). The TINS, made by Hughes Aircraft Company and designated AN/AAR-50, generates a daytime, TV-like image of the dark world ahead of the aircraft and presents this image on an improved "raster" head-up display (HUD). The improved HUD and TINS systems will allow passive low-level navigational and - along with a targeting FLIR - help pilots locate, identify and attack ground targets at night.

A self-leveling thermode greatly reduces adjustments in a new reflow soldering system. The Hughes-built system, designated the Model HTT-SLT, is especially designed for soldering edge connectors and flex circuitry to printed circuit boards. The self-leveling feature makes it easier to align the work piece and heater bar in the same plane for even heating, while thermocouple control provides highly uniform temperature distribution with rapid heating and cooling for higher throughput. The system also incorporates the Hughes HTT-650 power supply that provides an accurate and repeatable timed pulse for consistently high quality reflow solder connections.

A night vision system has demonstrated it can increase the operational effectiveness and survivability of M1 Abrams tanks and Bradley Fighting Vehicles. The Driver's Thermal Viewer (DTV), under development at Hughes for the U.S. Army, is a low-cost thermal imaging system that enables drivers to see through darkness, dust, battlefield smoke, haze, and rain. During simulated combat exercises, the DTV demonstrated that it improved both vehicle maneuverability and crew safety and target acquisition. The DTV, designated AN/VAS-3, can replace the existing AN/VVS-2 image intensifier driver's viewer without modification to the vehicle's armor or driver station.

A state-of-the-art workstation will help improve air traffic control in Germany. Thirty-two of the workstations, developed and built by Hughes and designated the AMD 44 airspace management display, will be installed in the Karlsruhe Upper Air Control Center. In addition to the full color, common controller workstations, Hughes has developed and installed five software test stations. The AMD 44 workstations use high resolution, 20 by 20-inch monitors along with built-in processors that can be upgraded easily to increase the workstations' performance if more computer power is required. The displays will be fitted into console structures already in the center.

Hughes's Space & Communications Group needs Senior Scientists to design and develop advanced digital communication systems for DoD satellites, using digital processing techniques. The job involves technical supervision, subsystem requirement definition, simulation/analysis, implementation trade studies, and detailed architectural design. Applicants should have an MSEE and 12 years experience, with a strong knowledge of hardware and software design plus proven ability to interact with customers, system engineers, analysts and designers. For immediate consideration, please send your resume to: Hughes Aircraft Company, Space & Communications Group, S40-T370, P.O. Box 92919, Los Angeles, CA 90009. Proof of U.S. citizenship may be required. Equal Opportunity Employer.

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ling a classic computational dilemma: Is the result of a complicated series of computer calculations correct, or have the calculations chaotically diverged from the proper answer? By examining partial solutions to the problem in a computer-assisted proof, they mathematically showed that a "true" solution does indeed exist near the answer produced by the calculations.

Hammel then used the proof to develop a practical technique for reducing the noise cluttering a chaotic signal. Unlike linear systems, which reduce the overall noise of a system by some average percent, Hammel finds that he can dramatically improve certain sections of a signal—even if other sections are unimproved—depending on the mathematical characteristics of the underlying signal.

Working only with sections of a signal may provide enough information to characterize the essence of the signal, Hammel points out. Recently colleagues at Oak Ridge National Laboratory have suggested he test his techniques on a collection of data—a time series of the noises made by the heat-transfer system inside a nuclear reactor. "It's a complicated signal of all sorts of noise, from pumps to bearings to flowing coolant," Hammel says. He believes he can re-create enough of the underlying signal to enable him to compare how the components functionally change over time. "This is outside the domain of traditional signal processing," he says. If he can unravel the data, chaotic signal-processing may become a handy technique for noninvasive testing, he adds.

A nearer-term application for signal processing may be chaotically based codes for cellular communications and for encryption. For instance, Harold M. Fredricksen of the Naval Postgraduate School has been using chaotic patterns to develop a data-coding scheme that may ease crowding on the airwaves. The breakthrough, he says, was simply the idea of marrying two fields—dynamic systems and signal communications-coding algorithms.

The current broadcast transmission schemes use algorithms that apportion data into time slots in a predictable order or in a seemingly random sequence. Receivers later reassemble the data into a coherent message. By using chaotic signals instead, Fredricksen calculates that he will be able to increase dramatically the amount of traffic that can be sent without losing the signal to debilitating interference. "The power comes from the known but nonpredictable nature of the chaotic process," Fredricksen says.

Just how rapidly researchers will push their theories into practice will probably become evident this October at the first official conference on experimental chaos, which Ditto and Pecora are helping organize. "We're trying to make the conference a lens to focus where applied chaos is going from here," Ditto says.

And there is another sign: one long-time player in the field is already circulating a business plan, hoping to attract investors keen on commercializing signal-processing techniques based on chaos. Helena S. Wisniewski, who directs advanced computer and software applications at Lockheed Corporation, spent three years at the Defense Advanced Research Projects Agency funding research on chaos theory and applications. She reckons that much work, such as Friedricksen's codes, is ripe for development. "Within two to three years, we'll have a prototype of these codes," she predicts. "Not a final product but enough to get it into the hands of the people who will use them and test them out." *—Elizabeth Corcoran*

## Can Japan Put the Brakes on Global Warming?

A Japanese plan to reduce the impact of global warming—known as "New Earth 21"—did not receive much attention when introduced at the economic summit in Houston last October. So the Ministry of International Trade and Industry (MITI) decided to make a formal announcement of its proposal for what industrialized and developing nations should do over the next 50 years to protect and restore the earth's atmosphere.

MITI representatives asked the Georgia Institute of Technology to invite the highest-ranking U.S. global warming experts to an early June conference in Atlanta. Japan's message is something like noblesse oblige. "Global warming is to a great extent the result of the burden humankind imposes on the global environment through energy use," said Sozaburo Okamatsu, MITI's director-general of the industrial location and environmental protection bureau. Since industrialized nations use more energy, it is their responsibility to take the lead in developing new technologies to reduce the impact of global warming, he reasoned.

The Japanese emphasize a menu of energy conservation, renewable energy sources and the safe use of nuclear power, but they also believe that a lasting solution will depend on new technology. To that end, Japan's focus includes capturing carbon dioxide and converting it into energy via photosynthesis as well as harnessing microorganisms to convert biomass into fuel. The country has high hopes for such technologies as biodegradable plastics and substitutes for the ozone-destroying chlorofluorocarbons (CFCs).

Once the new technologies—whatever they may be—are developed, Japan says it intends to transfer that knowledge to other countries. But it will not be a giveaway. "There is a limit to the amount of aid a government can provide," Okamatsu stated. The idea is to tailor the technology, and its price, to the recipients' level of development. Japan wants countries to earn access to the technology by disclosing information concerning their environment and by implementing means of self-control, such as legislation.

Although John E. Endicott, director of Georgia Tech's Center for International Strategy, Technology and Policy, hailed the Japanese willingness "to play a greater role in the new order," others were more cautious. The plan, observed Henry R. Nau, a professor of political science and international affairs at George Washington University, is "missing much regard for institutional and diplomatic processes." This, he added, "contributes to the suspicion that this is an effort by the Japanese to exploit their technological leadership."

As they have in the past, U.S. government officials shied away from a policy of picking technological winners and losers. "Whenever the government favors a particular technology, it creates problems for the market to do its work," said Richard J. Smith, a deputy assistant secretary of state. Predictably, Smith called for an international study before very strict measures are imposed. "That may strike some as too cautious," he said, "but it is not good to say ready, fire, aim."

There is precedent for initiatives like New Earth 21 to be successful in the Montreal protocol to limit CFCs. "It's a classic situation, where the risks of acting and not acting are taken under unknown conditions," observed Richard Elliot Benedick, senior fellow at the World Wildlife Fund. "I'd rather err on the side of caution, which is taking action." *—Deborah Erickson*



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# Firewater Fish

*A distiller looks for diversity in aquaculture*

*AQUACULTURE at Brown-Forman uses waste by-products from whiskey production to help feed and warm tilapia* (shown here) *and hybrid striped-bass fingerlings.*

Declining sales of liquor during the past decade have worried wine and spirits producers. This anxiety has touched even the conservative folks who run the stills for Jack Daniel's Tennessee Whiskey, whose label invokes antebellum tradition with its proud assertion, "Whiskey made as our fathers made it for seven generations."

So Brown-Forman Corporation, which also makes Early Times Old Style Kentucky Whisky, Canadian Mist and Southern Comfort to name a few, sees diversification as a vital part of its business strategy. Among other nonliquor-related businesses, it owns Lenox China and Hartmann Luggage. And now it is taking a plunge into another market: fish farming.

What attracted Brown-Forman to aquaculture was whiskey. The company was trying to find a way to capitalize on by-products from the distillery in Louisville, where it makes Early Times Kentucky Whisky. Every year the facility must dispose of 10,000 tons of spent grain mash, a mixture of corn, rye and malted barley. In addition, vast amounts of heat are recovered in condensing the whiskey from the distillation process.

In 1987 the job of figuring out how to turn a profit from the spent mash fell to Joseph Main, now the company's director of aquaculture operations. At the time, Main's job was to buy and sell grain futures and options at the Chicago Board of Trade in order to minimize price fluctuations in the company's grain supplies.

Dried mash is sold as cattle feed or for flavoring in bread. But Brown-Forman thought it might be able to fetch a better price by selling the mash to catfish farms in the Mississippi Delta. Mixed with soy and fish meal, Brown-Forman's mash could probably serve as a major supply source for the U.S. aquaculture industry, which shipped 860 million pounds of fish last year, more than four times the volume in 1980.

At an aquaculture conference in 1987, Main met an executive from an industrial ethanol producer, who said his company was considering going into the fish-farming business. The idea of a distiller raising fish intrigued Main enough to make a proposal to Brown-Forman's top management. The company slowly began to explore the fickle technology of aquaculture, starting first with a small tank and building up to its present warehouse-size facility, which is complemented by outdoor ponds in Mississippi.

An oft-cited adage asserts that a company has not mastered aquaculture until it has lost a million fish through disease, poor filtration or a host of other ills. And Brown-Forman has chosen the most technically difficult path to enter the business. Rather than raising fish in outdoor ponds, the facility in Louisville relies on indoor tanks in which water is recirculated as many as 30 times a day. Waste heat from the distillation process raises the water to a balmy 83 degrees Fahrenheit, and grain mash has begun to be used as fish food.

Because conditions can be carefully controlled, the system has the potential to be very productive. But if something goes wrong, the losses can be catastrophic. "There's not one sizable recirculating facility that is financially viable, and it has yet to be seen whether their facility is going to be viable," says James H. Tidwell, the principal investigator for aquaculture at the Aquaculture Research Center at Kentucky State University, which has advised Brown-Forman on the project.

Tidwell emphasizes that Brown-Forman has done its homework on a process that requires around-the-clock vigilance of a fragile environment in which thousands of fish can die within minutes. As with any fish tank big or small, water temperature must be regulated and oxygen replenished. The technical challenge is to remove fish waste from the series of narrow, five-foot-deep tanks, called raceways. A two-stage process uses filters lined with bacteria that first convert the ammonia secreted by fish through their gills into nitrite and then into less toxic nitrates, which are flushed out. Another filtration system rids the tanks of solid wastes.

If Brown-Forman succeeds with its indoor facility, it will be remembered as a pioneer of a process that transformed aquaculture. Success with this technique would permit fish to be raised near their markets year-round. Fish also grow much faster. "You can get a year's growth in three or four months," Main says.

The technology also allows for more intensive production: a million gallons of water can yield a million pounds of fish, an amount 200 times greater than that for fish raised in ponds. "It's like growing a pound of fish inside a milk jug," Tidwell says.

So far Brown-Forman has spent more than $7 million on aquaculture, including purchasing the latest European filtration technology and backup systems for power and oxygenation. It is making the investment even at a time when a company such as J. R. Simplot, the Idaho potato processor that supplies McDonald's, has dropped an advanced aquaculture project after losing millions of dollars.

Besides buying the best available technology, Brown-Forman's strategy is to eschew the lowly but hardy catfish. It is also considering whether to continue with the easy-to-grow but exotic tilapia, which is largely unknown by the U.S. fish-consuming public. Instead it is concentrating on raising hybrid striped bass—a fast-growing genetic cross between striped and white bass, which is



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more frail than some of the other species bred at fish farms. At $3 a pound wholesale, it commands four times the price of the down-home catfish.

The company has purchased two million fingerlings so far and by year's end expects to sell two million pounds of bass, making the company a medium-size aquaculture supplier.

Brown-Forman is not placing all its fish in one tank, however. It is also using the more conventional method of raising fish in ponds in Mississippi. Only a quarter of the fingerlings were routed to its indoor facility. But the distiller is betting that its indoor mix of fish and firewater will make it a profitable player in aquaculture. *—Gary Stix*

## Off the MAP

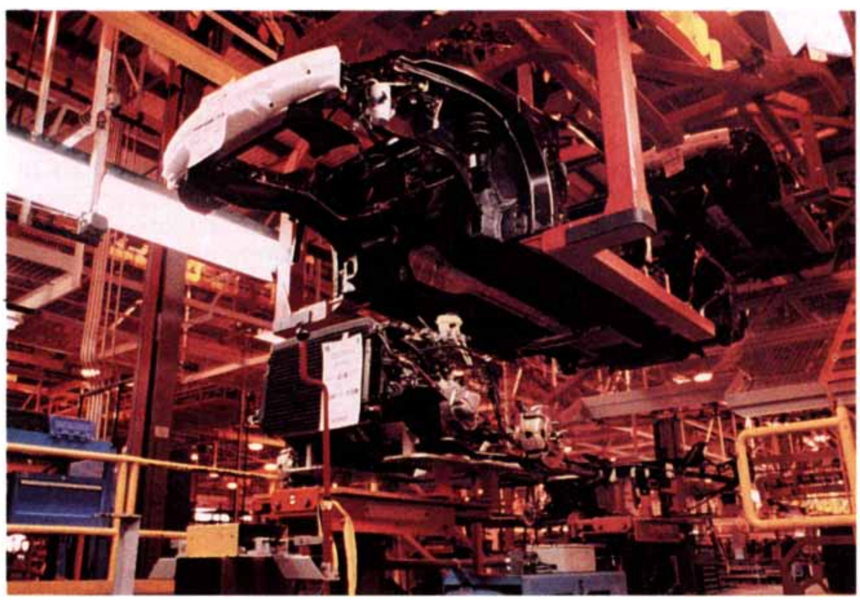
*Has GM's factory automation network lost its way?*

Seven years ago General Motors helped to sign up an impressive roster of corporate luminaries for a traveling road show called MAP, or, more formally, Manufacturing Automation Protocol. This grand plan for networking industry's computers, robots and other automated devices was trumpeted as the way to turn the factory into one seamless production organism, turning out Saturns faster than you can say Soichiro Honda.

But what General Motors thought would be good for it and the rest of industrial America has turned out to be slow going. Finished products that incorporate the full set of protocols that make up the standard network began to trickle in to the market only last year. And GM is one of the few U.S. customers, if not the only one, placing big orders. "Most of the plants outside GM are really pilot programs done on a small scale," says Paul Eastman, head of a group for one of the computer networking standards for MAP.

The heart of MAP is a protocol for a type of local-area network (LAN) that passes a pattern of computer bits, called a token, down a stretch of coaxial or fiber-optic cabling, a bus, at 10 million bits per second. This token-bus LAN, which has been endorsed by international standards groups, tells devices on the network when to transmit a message so that they do not all do so at once and retard response time.

MAP involves smaller networks feeding like streams into rivers of larger networks, not unlike the layout of some automobile assembly plants. But, in practice, the technical sophistication of MAP and other components of so-called computer-integrated manufacturing (CIM) has taken a back seat to hard-headed cost considerations—and some companies have opted against a complex multi-tiered production scheme. In fact, the fastest-growing segment of the factory network market is for simpler LANs designed to hook together personal computers. "People were led to believe that MAP had solved all problems, whereas GM had solved a small section of its own problems," says J. Roy Cadwallader, vice chairman of the European MAP Users Group.



***MANUFACTURING AUTOMATION PROTOCOL is used to monitor machines that "marry" a frame and a chassis at General Motors's Saturn plant.***

GM took on the role of MAP missionary in the mid-1980s, when its engineers predicted that plans to quintuple the number of computerized devices would only inch along if the company failed to eliminate the "islands of automation" that populated the factory floor. Only 15 percent of GM's 40,000 computerized controls, tools, instruments and other systems could exchange information. And as much as half of the amount the company spent on automation systems was allocated for jury-rigged networks of custom software, hardware and wiring.

As one of the largest buyers of computers after the U.S. government, GM promised to exercise its purchasing muscle to persuade automation suppliers to adopt a common network standard that would eliminate the babble that pervaded the factory floor. By simply tying into a MAP network, a robot from one supplier could relay production-status information to a minicomputer from another manufacturer. To sway further its suppliers, the automaker helped to start a campaign to enlist hundreds of other industrial manufacturers to specify MAP when purchasing equipment.

For a while, MAP seemed irresistible. Along with just-in-time production, flexible manufacturing and computer-aided design and manufacturing, MAP joined the lexicon used by corporate executives to convince customers and shareholders of their sincerity in stemming foreign inroads into U.S. markets. GM argued that the ease with which factory machines could be linked would lower capital costs and make U.S. industry more competitive. Some MAP evangelists even translated the acronym as Motherhood and Apple Pie.

But despite the system's early promise, equipment suppliers were not quick to embrace the idea of MAP. Because they often had a large base of existing products in the marketplace, suppliers had little incentive to allow customers access to a network that would readily connect to the equipment of other manufacturers. Instead they tried to sell computers and software that worked with their own networks, which did not conform to MAP.

Digital Equipment Corporation, the dominant factory-floor computer vendor, has been decidedly tepid about MAP. By peddling its own network scheme, DECnet, the company garnered about 45 percent of the $337-million market for factory networks last year, according to Advanced Manufacturing



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Research, a market research firm in Cambridge, Mass. In contrast, sale of MAP products took up 5 percent of the pie, with GM doing much of the buying.

Meanwhile the laborious standard-setting process for MAP consumed the better part of a decade. And potential customers avoided purchases of early incomplete MAP versions, a decision that drove the largest supplier, Industrial Networking, Inc., out of the market in 1988. "We couldn't make any money; it was that simple," says Roger Biery, a marketing manager with Ungermann-Bass, which formed the company as a joint venture with General Electric.

For its part, GM still acts as MAP cheerleader, although even its fervor has cooled. The company has stepped back from its leadership role in a group promoting MAP. It is several years behind schedule in making MAP a corporate-wide purchasing specification, and there are still new networks being installed that do not use MAP, because products are hard to find. But GM is also starting to see benefits from the technology. At a GM truck and bus plant in Pontiac, Mich., a network that sends messages telling a robot what color to paint a truck was set up in about a month, a third the time it would normally take to complete such a project.

The need to tie together equipment from different suppliers—the reason GM originally pushed MAP—is as cogent as ever. Both suppliers and their customers acknowledge that, if not MAP, other standard networks may eventually fulfill the same role. But the time it has taken to get MAP moving may have cost the U.S. any opportunity the technology might have offered to gain a competitive edge over foreign rivals.

In fact, MAP may already have as many or more adherents in Europe and Japan. European companies have embraced MAP with support from the European Community, and in Japan the Ministry of International Trade and Industry has backed the concept. "We Americans aren't good implementers of technology," laments David A. Bilger, communications manager at GM's Saturn plant in Tennessee. "We often lead the world in developing technology, but then we don't implement it."

The promise of MAP was that of a quick fix for the ills of U.S. industry. "This country loves to keep pushing a technology as a panacea," says Anthony J. Friscia, president of Advanced Manufacturing Research. "If we do CIM, we'll be number one; if we do MAP, we'll be number one. There's only one way to be number one again, and that's to make better cheese." —*Gary Stix*

## Painkiller

*There's still room for luck in industrial chemistry*

Chemists at the Hoechst Celanese Advanced Technology Group in Corpus Christi, Tex., were not thinking about painkillers when they set to work in 1983 to create an inexpensive starting material for liquid-crystal polymers. Yet what they ended up with was a low-cost synthetic precursor for acetaminophen and ibuprofen as well as a host of other fine chemicals, from resins for computer chips to ingredients for fragrances, insecticides and pharmaceuticals.

Thanks to that serendipitous discovery, the Somerville, N.J., company is becoming one of the world's leading producers of bulk analgesics. Hoechst Celanese used the new technology to enter the acetaminophen market in 1990; in 1992 it will begin rolling out 3,500 metric tons of ibuprofen a year—enough for 15 billion tablets. The key to both drugs is a process that uses hydrofluoric acid as a catalyst to produce an industrial chemical called 4-hydroxyacetophenone, or simply 4-HAP.

The ability of hydrofluoric acid to catalyze the conversion of phenyl acetate to 4-HAP was studied in the early 1950s, but the commercial potential of the reaction was not recognized at that time. "They had higher yield than they thought," says Charles B. Hilton, who headed the development team for the process conceived by Kenneth G. Davenport. Hilton is now R&D director at the company's Coventry Technical Center in Rhode Island.

The hydrofluoric acid pathway to 4-HAP proved to be far superior to the conventional route, which uses aluminum chloride as a catalyst. The hydrofluoric acid is easily recovered, whereas spent aluminum chloride must be separated from the product and then disposed of as waste. Moreover, the new process yielded a 96 percent conversion, compared with 20 to 50 percent for the commonly used technology.

At first, Hilton and Davenport did not quite realize the potential of the discovery. Their boss, Rudy J. H. Voorhoeve, did. He assigned Hilton to a business development group in Dallas for three months and directed him to come back with three or four products based on 4-HAP or hydrofluoric acid catalysis. After two months of pondering "how to look two steps away at all the products on the market," Hilton had come up with nothing.

After two months and a day, "the whole picture unfolded," Hilton recalls. "I thought, well, acetaminophen, that's got structural similarity to 4-HAP." People were consuming 25 billion tablets, or some 18 million pounds, of the drug a year in the U.S. at that time, so he decided it was a market big enough to interest the company. "What is the chemistry that can get you from 4-HAP to acetaminophen?" he asked himself on the way to a laboratory meeting in Corpus Christi.

The researchers stood for hours in front of a blackboard, Hilton remembers. "It finally dawned on us that the solution was the 80-year-old Beckmann reaction." The process, a key step in the synthesis of nylon, rearranges oximes to amides. The chemists reasoned that if they could convert 4-HAP into an oxime by reacting it with hydroxylamine, then the Beckmann rearrangement would convert it directly into acetaminophen. "If you had asked somebody how to make acetaminophen, that's the last thing they would have thought to do," Hilton declares.

It took two years and some proprietary chemistry before the process produced pristine white crystals of acetaminophen. Yet Hoechst was able to hustle the drug into commercial production just seven years after finding the synthetic pathway for its manufacture. Now that chemists are aware of the company's technology, they are suggesting other products the firm might wish to manufacture. —*Deborah Erickson*

## Binding Bone

*Will new bioceramic coatings improve orthopedic implants?*

Artificial joints can satisfy the mechanical requirements of bearing weight and repetitive motion. But getting bone to bind tightly to the metal surfaces of those orthopedic implants is another matter. Porous surfaces with dimples, grooves or beaded coatings have helped, but a poorly fitted joint can still wobble painfully and become encapsulated in fibrous tissue.

Now bioengineers think they have found a way to induce bone cells to grow right up to the surface of an implant, making the replacement nearly as strong as healthy bone. Ceramic coatings whose chemical structure resembles natural bone may do the trick. Major orthopedic companies, including Zimmer, Howmedica, DePuy and Biomet, as well as Osteonics, Intermedics and Richards, are all developing bioceramic coatings.


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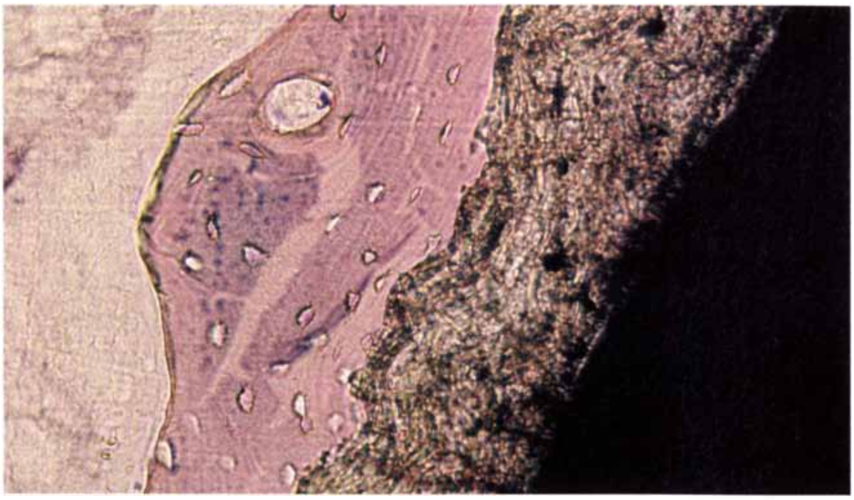

***BIOCERAMIC COATING of hydroxyapatite* (brown) *encourages bone cells* (purple) *to grow close to the surface of an artificial hip* (black). *Photo: John P. Collier.***

The material getting the most attention is hydroxyapatite (HA), a crystalline form of calcium phosphate that mimics the major mineral component of bones. Fine crystals of HA sit exactly 640 angstroms apart on the strands of collagen that give long bones their tensile strength. Different proportions of the same atoms also form tricalcium phosphate (TCP), a similar ceramic that invites bone growth before dissolving. "Everyone is looking at calcium phosphate coatings," observes John A. Szivek, director of the orthopedic biomechanics laboratory at the University of Arizona Health Sciences Center in Tucson.

So far the Food and Drug Administration has given two manufacturers permission to market HA-coated hip prostheses. Osteonics, an Allendale, N.J., firm using technology from the Netherlands, was first to get the go-ahead in December 1990. Intermedics, in Austin, Tex., followed in March 1991. At least two other firms are testing their HA-coated joints in patients.

A product perceived as superior could indeed win a handsome market share. Nearly 400,000 artificial hips were implanted throughout the world last year, as were some 150,000 knees. Replacement hips cost between $800 and $4,000. The more expensive ones are sold mostly in the U.S., where a custom coating accounts for 10 to 15 percent of the price.

Some experts question whether the coatings are worth the extra cost. To win FDA approval, manufacturers were not required to prove that the products were better than what was currently on the market—merely that they were "substantially equivalent," points out John P. Collier, director of the Dartmouth Biomedical Engineering Center. "You have to ask, if you can't show it's better, how can you justify charging a premium?"

Furthermore, the long-term stability and efficacy of the coatings are uncertain. Although Collier concedes that bioceramic coatings have certainly been shown to act as a scaffold for new bone growth in animals, he points out that "we don't know if it works the same way in humans." Animals are so much faster at repairing bone than humans are, Collier contends, that data from them may not mean much. In addition, "none of these coatings is completely stable," declares J. Russell Parsons, director of orthopedic research at New Jersey Medical School in Newark. "Sometimes you go back and find they are not there. The consequences of that are completely unclear."

The theory is that bioceramics are so similar to natural bone that dissolution is not a problem and may even be desirable in some cases, Parsons explains. But the first HA-coated devices were implanted in European clinical trials just four years ago. "Most of them are less than two years out. You have an impression of what's going on, but you don't really know yet," Parsons says.

Proponents of bioceramic coatings point out that a particulate form of HA has been used in dentistry for 10 years, with no reported ill effects, to fill tooth sockets and build up jaw bones. The granules also are sometimes mixed with blood and freshly ground bone fragments and pasted around bone grafts or bad fractures.

For the orthopedic surgeon, coatings are a much more convenient form of HA. Orthopedic device makers apply the bioceramic coatings themselves or send their implants off for treatment at companies such as Bio-Interfaces in San Diego or Syntex in Palo Alto, Calif. "There are a lot of trade secrets in this industry," says John F. Kay, president of Bio-Interfaces.

The powdered ceramic is usually applied by plasma spraying, which blasts the implant with ionized HA at 10,000 to 15,000 degrees Celsius. The implant's shape and even the angle of spraying influence the final coating's properties, which in turn determine how likely it is that the material will crack or fret. The wide variety of manufacturing processes leads to differences in solubility, adhesion to substrate and crystallinity, says Norman C. Blumenthal, associate director of the department of bioengineering at the Hospital for Joint Diseases, an affiliate of New York University's Medical School. "There is no industry standard. What you've got is just generic plasma-sprayed material; what you've got is anybody's guess."

"There are some interesting physical chemical reactions going on with these coatings," adds John L. Ricci, a research scientist at the hospital. A number of researchers have found that bioceramics release at least some calcium and phosphate, he explains, which the body then precipitates into a mineralized organic matrix at the bone surface. Mechanical testing shows this interface between bone and the HA coating to be very strong. But Ricci worries that the process could be weakening the coating. "When the implants fail, it's in the coating itself or between the HA and the metal," he points out.

Disintegration of the coatings could spell trouble in the long term. Loose particles could abrade both the surrounding bone and the implant, sloughing off particles that provoke inflammation. In the wake of recent negative publicity about cracked heart valves and chemicals leaching from breast implants, orthopedic researchers are redoubling their efforts to stabilize their coatings.

"There are a lot of biomaterials in people—and we don't know how they work," declares Jonathan Black, a professor of bioengineering at Clemson University in South Carolina. "What are the real corrosion and wear rates in humans? Just because the site of the infection appears trouble free, how do we know what is happening at a systemic level elsewhere in the body?" The uncertainty is not likely to deter commercialization of the new coatings, Black concedes. "People want to be fixed." —*Deborah Erickson*



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## The Rise and Fall of Cities

In the 1950s Pittsburgh was an industrial hotspot. It was the seat of the U.S. steel industry, and prevailing wisdom held that a city with such a concentration of an important technology was likely to keep growing. Phoenix, on the other hand, appeared to be on the economic fringe. Its largest industrial sector, "wholesale trade," was a hodgepodge—ranging from farm equipment to plumbing fixtures.

Thirty years later, however, Phoenix is thriving, and Pittsburgh has sunk into decline. Why? "A cynic might say that temperature played a more important role in city growth or that we are only observing the decline of U.S. manufacturing," says José A. Scheinkman, an economist at the University of Chicago, who is collaborating with Andrei Shleifer of Harvard University and their graduate students, Edward L. Glaeser and Hedi D. Kallal. The economists think they have found a better explanation, one proposed several years ago by urban specialist Jane Jacobs: cities flourish when their industries are highly diverse and highly competitive.

Precisely what fuels growth has fascinated economists for centuries. Economists formally attribute growth to increases in the capital-to-labor ratio, increases in the size of the labor force and improvements in technology. More specifically, Nobel laureate Robert M. Solow further showed that among these three factors, technology plays the dominant role.

Yet why some places seem to incubate technology better than others remains the pivotal question. Economists agree that technological change spreads more quickly in places where people can easily and frequently interact. For this reason, cities grow more rapidly than do rural areas. Economists part company, however, over how concentrated industries should be to promote growth.

The two dominant theories assume that companies will thrive in regions that specialize in—and so support—that industry, such as the steel industry in Pittsburgh or semiconductors in Silicon Valley. One line of reasoning then maintains that monopolies will best foster growth; the other argues for fierce competition among many firms.

Those who have looked to monopolies for new technologies include Alfred Marshall, Kenneth J. Arrow and Paul M. Romer. They suggest that innovators realize that competitors are likely to copy—and capitalize—on their ideas. Eventually the innovators tire of supporting their competitors and decide to slow down their research efforts. But if the innovators had few competitors, the economists argue, they would worry less about copycats and spend more time and money on research. In this way, a dominant company can generate more technologies, which in turn fuel the growth of the city.

Not so, counters Michael E. Porter, a professor at Harvard Business School. Instead Porter proposes that when a large number of firms make similar products in the same geographic area, they spur one another to produce more innovations. Industrial spies promote technology transfer; those firms that do not exploit and enhance the technologies developed by others will be squashed by their competitors.

When Jacobs first began analyzing urban growth in the 1960s, her views seemed out of the mainstream. She agreed that competition promoted the spread of technology but argued that the most robust cities are those that are most diverse.

According to Jacobs, important technologies develop most rapidly when an idea from one industry is transplanted into another. For instance, New York City grain and cotton merchants saw the need for making national and international trade deals and so gave rise to the financial services industry.

Perhaps because Jacobs offered no formal models or quantitative evidence for her observations, her theory was largely overlooked by economists for nearly two decades. Scheinkman and his collaborators discovered her work only serendipitously, when a colleague suggested they read Jacobs's 1969 book, *The Economy of Cities.*

To sort out which cities have grown and which have slipped, Scheinkman and Shleifer compared the 1956 and 1987 rates of industrial employment in some 170 large metropolitan areas. The economists found that declining cities tended to be highly concentrated, generally noncompetitive midwestern industrial centers, such as Pittsburgh and Kenosha, Wis., in which 60 percent of the jobs were provided by four industries. In Phoenix, one of the fastest-growing cities in their sample, just more than 20 percent of the jobs were in the top four industries.

Scheinkman and Shleifer identified other characteristics of growing and declining cities as well. For instance, those industries represented more heavily in a particular city than they were on average across the nation grew slowly. On the other hand, if the average size of companies (based on numbers of workers) was smaller than the national average, the industry grew rapidly. Finally, those industries that thrived were in cities where the other dominant industries were relatively small—apparently having a greater variety of neighbors helped. "The overall results are not favorable on the Marshall-Arrow-Romer theory, mixed on Porter and quite favorable to Jacobs," the economists report.

Other economists are intrigued but not yet convinced. Many wonder whether the data offer adequate support for Jacobs's ideas. Many past econometric studies indicate it *is* important for an industry to be concentrated—that "the people from whom you learn and who help you innovate are the people in your own industry," points out J. Vernon Henderson of Brown University.

It may be, Henderson adds, that the traditional view supports static growth, a situation in which an industry is improving on existing products. In contrast, Jacobs's hypothesis may describe more dynamic growth, where industries are developing radical innovations that become the basis for altogether new technologies and products.

Scheinkman and Shleifer plan to continue their investigations. In the meantime, millions of other Americans will have front row seats for watching the saga of the country's largest metropolis, New York. The city remains an enigma. Although New York's five boroughs are highly diversified, newspaper headlines proclaim the city's slow decline; growth slowed to a virtual standstill over the past decade. Still, the economists point out that New York's tremendous size and idiosyncratic nature may put it in a category by itself.

—*Elizabeth Corcoran and Paul Wallich*



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# What in Heaven Is a Digital Sundial?

Brother Benjamin enjoyed his work for the order of Euclidean monks and believed devoutly in their solemn maxim: *Salus per geometriam,* salvation through geometry. He was particularly adept at creating fractals, a talent he was currently using to illuminate a manuscript. He was painting the tree of life, intertwining its branches through a golden capital O. To each branch of the tree, he added exactly two smaller ones. Like fractals, like life, the tree was limited in dimension but infinite in detail.

Leather sandals slapped across the stone floor, and Benjamin turned to see who it was. Oh dear, he thought, Brother Daniel. Benjamin normally avoided Brother Daniel because he was always sticking his rather large nose into everyone else's business. But on this occasion Daniel bore an important message: "The Abbot requests your attendance," he said.

Benjamin's hand began to tremble, and he had to put the brush down before the tree of life turned into the burning bush. A summons from the Abbot was always bad news. As he set off along the echoing corridors, he tried desperately to think of the sins he might have committed or the calculations he might have botched.

He stopped for a moment outside the Abbot's door. Then, stiffening his back and his resolution, he knocked on the worn oak panels. His heart sank as a thin, reedy voice bade him enter.

"Brother Benjamin, I must say that I am greatly displeased."

"My Lord Abbot, if I have made some error, then I—"

"Why no, Brother Benjamin. I merely seek your excellent advice on a matter that displeases me. I hear you have considerable knowledge of mechanisms." Benjamin hoped that the Abbot wouldn't ask him to fix his lap-top hymnal again. The Abbot had a knack for buying and breaking high-tech gadgets. The monk's prayers were answered.

"You may recall," the Abbot said, "that the monastery recently replaced the venetian blinds. I am perplexed. With the old blinds, I could angle the slats in midmorning to admit partial light into this room, suitable for reading, after which they required no further adjustment until the late afternoon. But now I find I must fuss with the blinds almost hourly to maintain a constant level of lighting. Why is that?"

Benjamin walked across to the window. The slats of the new blinds, he noticed, were vertical, whereas the old ones were horizontal. The Abbot had bought them from a salesperson who made great virtue of the fact that very little dust would adhere to a vertical slat. Benjamin fiddled with the cords that adjusted the angle of the slats, turning them this way and that. The room sank into almost total darkness, then a beam of sunlight illuminated the far wall, then it fell dark again.

Metaphorical light dawned. But how could Benjamin put this in a way that would not offend the Abbot? "I believe, my Lord Abbot, that it is a consequence of the vertical slats."

"Nonsense. Slats are slats. Turned one way, they keep the light out; turned another, they let it through."

"Indeed, my Lord Abbot. The sun is a moving source of light, however, and that has a profound effect on the—er—geometry." It was a good word to use: like any good Euclidean, the Abbot always approved of it. "The slats are closely spaced parallel planes. When the light source is aligned with those planes—that is, when the rays of light that it emits are also parallel to them—then the greatest proportion of the light that impinges on the blind is admitted. If the slats are infinitely thin, then almost all the light is let through—the proportion blocked is vanishingly small." The Abbot nodded, permitting a degree of impatience to cloud his brow, and Brother Benjamin made haste to explain. "If the incident light meets the slats at an angle, then much of it is blocked. The greater the angle between light rays and slats, the less light the blinds admit."

"Brother Benjamin, this is admirably and concisely put, but I do not yet find that it clarifies the distinction between horizontal and vertical blinds."

"Lord Abbot, if you wish to maintain the illumination at a constant level, then the angle between the light rays and the slat must change as little as possible. Here the source of light is the sun, which moves through the sky as the day progresses. Yet, because our

***DIGITAL SUNDIAL stands in the courtyard of the Cartesian Monastery, home of Brother Benjamin and the Euclidean monks.***



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monastery is placed in northern latitudes, the sun's angular variation in altitude is considerably less than its motion from east to west. A horizontal blind can therefore be set in a position of compromise, a little dark in the early morning and late evening, a little bright at midday, but acceptable for the entire period. A vertical blind, on the other hand, must be adjusted every few hours to follow the sun's movement" [*see illustration at right*].

The Abbot nodded but also frowned. *He* had ordered the blinds.

"If I may be permitted a personal observation," Benjamin added quickly, "it is a small price to pay for the noticeable absence of dust on the blinds. And the more frequent adjustments actually help to dislodge any dust that might be attracted by static electricity."

"Well spoken, Brother Benjamin. You may take the reading at matins tomorrow. And since you seem to be so clever these days, perhaps you would offer your advice on a matter of greater importance. It concerns the monastery's sundial." This rusty device, some five centuries old, had crashed to the ground a week ago, when a flock of pigeons had alighted on it.

"I could build a replacement, my Lord," Benjamin offered eagerly. "The design is based on the same geometric principles of the motion of the sun, in combination with that of the earth."

"Hmm. I think not," the Abbot said. He pulled back the sleeve of his robe to reveal an expensive gold watch. "I have something more akin to this in mind."

"We could decorate the sundial with gold leaf, my Lord."

"No, I was not referring to the decorations. Observe the face."

"Ah. It's a digital watch."

"Precisely. I feel it would be more in keeping with the modern age if our monastery were equipped with a digital sundial."

"Lord Abbot, it would be no trouble to incise on the rim of the sundial the angular numerals favored by designers of digital watches."

"No, Brother Benjamin, you do not catch my drift. Let me demonstrate with this ring. See, when I hold it to the light, it casts a shadow on the desk."

"Yes, my Lord."

"And in what form is that shadow?"

"A circle, my Lord. Like the ring."

"Indeed. But when I twist the ring on edge to the sunbeam, so?"

"A single line, my Lord."

"Exactly! And do those two shapes remind you of anything?"

"The numbers 0 and 1, my Lord."

"Excellent! Yes, the ring casts a shadow that, when illuminated from one angle, resembles the digit 0; but from another, the digit 1. What I have in mind is an object whose shadow changes with the motion of the sun and at each minute resembles the appropriate time written out in digits."

"You mean at 23 minutes past seven the shadow should look like 7:23?"

"Yes. And the shadow should correspond to the time at every minute of the day, as long as the sunlight lasts."

"It is a great challenge, my Lord."

"I am sure, Brother Benjamin, that the task will not prove to be beyond your ability—at least I certainly hope not. Now I must attend to more pressing business. You may go."

That evening Benjamin had a vision of a system of etched-glass plates that would pop up out of a box, cast a shadow and thereby display the time of day. On hearing the idea, the Abbot rejected it, grumbling that digital devices did not have moving parts.

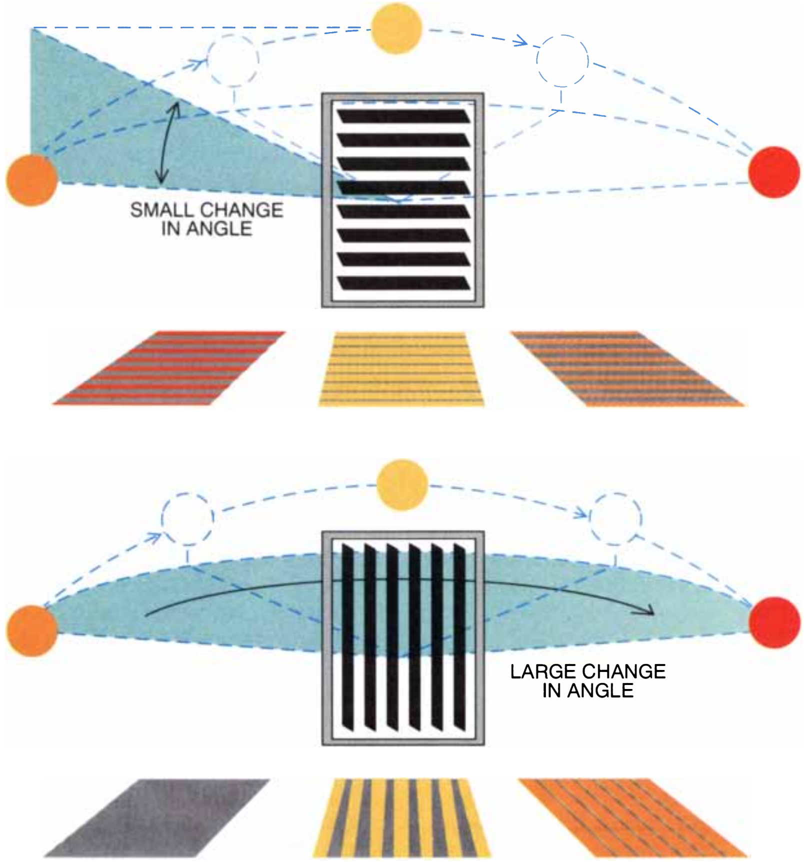
Brother Benjamin was sitting downcast in a cloister, at his wit's end, when Brother Daniel sat down beside him. Benjamin, who needed all the help he could get, poured out his troubles.

"Casts different shadows, eh? From different directions? Wait, reminds me of something—back in a minute." Daniel reappeared with a book. Benjamin caught a glimpse of the title.

"But, Daniel, this book is on the Index! It's proscribed. I can't read it. Where did you—"

"The Abbot's private library, Brother. The old duffer keeps the titillating stuff for himself."

"You could get me in really serious trouble with this," Benjamin muttered. Daniel handed him the copy of *Gödel, Escher, Bach: An Eternal Golden Braid.*




***HORIZONTAL BLINDS require less adjustment than vertical blinds because the altitudinal angle of the sun changes less than the azimuthal angle.***

***THREE DIFFERENT SHADOWS can be cast by the same object.***



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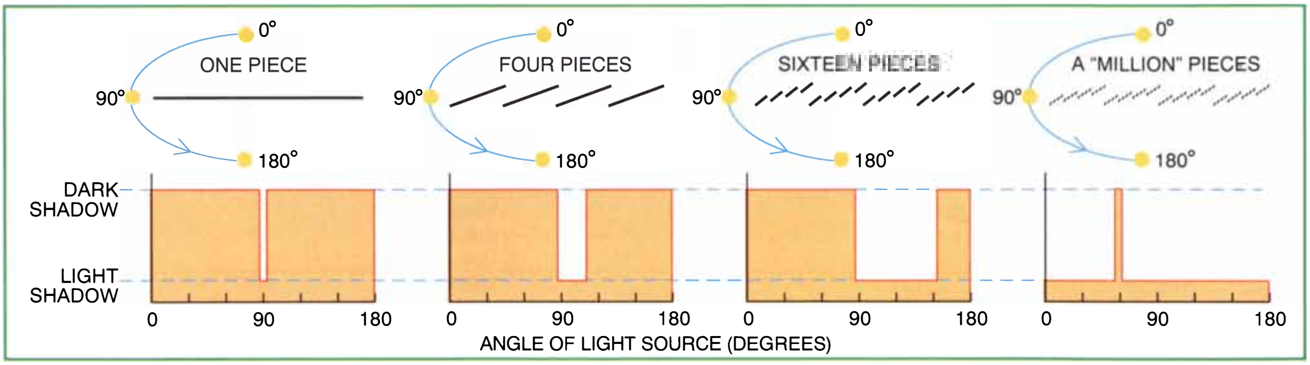


***VENETIAN BLIND PRINCIPLE: a slat can be broken down into smaller and smaller pieces so that it casts a shadow in only one direction. The graphs above show the shadows that slats cast as a light source moves around them.***

Benjamin skimmed through a few pages and found nothing salacious. "Why is it prohibited?"

"They say that the relationship between Achilles and the Tortoise is a bit unsavory."

"Oh. And is it?"

"Don't know. Haven't read that far. But let me show you the bit that I was thinking of. Look at the cover."

The cover depicted an oddly shaped wooden object. It cast three shadows. To the left, the shadow was shaped like the letter G. Below, B. To the right, E [*see bottom illustration on preceding page*]. "I thought it might give you a clue," Brother Daniel said. "At least it shows how you can get three totally different shadows from the same object. Maybe there's a general principle."

"You know, Brother, you may just have a point. I've been concentrating too much on details, like getting the shape of the digits right. What I should have done was to study a more general problem: What is the relation between the shadows that an object can cast in different directions?"

"And do you know the answer?"

"I think so," said Benjamin, turning the book in his hands. "This picture makes that much clear."

"So what *is* the relation between the shadows that an object can cast in different directions?" Daniel asked.

"There isn't one," Benjamin replied. And without explaining, he set off to work out his idea.

After weeks of nonstop effort in the workshop, the monk was satisfied. He carried the finished artifact to the Abbot's quarters for a demonstration.

"My Lord, the scale model is finished," Brother Benjamin said proudly. "If it meets with your approval, I will order the construction of a full-size version for the courtyard." The Abbot looked down at the table, where the faint but clear shadow of 1:52 was visible. He looked at his watch, which read 4:17.

"My apologies, Lord Abbot," Benjamin replied when the discrepancy was pointed out. "A small maladjustment." He fiddled with the sundial until it, too, read 4:17. The Abbot placed his watch on the table next to the sundial. As the watch flickered over to 4:18, the shadow looked a bit fuzzy; an instant later it, too, read 4:18. For several minutes, the digital sundial was synchronized with the digits on the watch face.

"Ingenious," the Abbot said. "Perhaps you will explain how it works."

"My Lord, I began to understand the nature of such a device when I asked myself a very general question. What is the relation between the shadows that an object casts in different directions? For the common objects of daily life, which are relatively simple in structure—that is, composed of flat planes or smooth surfaces—the answer is that the shadow must vary continuously. Consequently, small changes in the illumination angle produce small changes in the shadow.

"My training as a monk of the Euclidean order has, however, left me well versed in all aspects of geometry. As you are aware, my specialty is fractals. Now, fractals have fine structure on all scales of magnification. It occurred to me that if I could somehow 'amplify' that fine structure, I might create a fractal whose shadow varied discontinuously. I conceived the notion that, given any list of shadows whatsoever, there should exist a shape that, when illuminated from a fixed series of directions, exhibits those shadows. In a very strong sense, the shadows cast by a suitable fractal can change in shape and size in a totally arbitrary way.

"It remained to establish whether that notion was true. I found that in essence it was: a mathematical theorem to that effect was proved in 1986 by Kenneth Falconer of the University of Bristol in England. To make the proof work, however, the shadows may have to be changed by the addition or subtraction of a very small set of points. Because such sets are virtually invisible to the eye, this change does not affect the operation of the sundial. The underlying idea, remarkably, is the venetian blind principle, which is used in an iterative manner to obtain a set whose shadow in some directions is large, but in others vanishingly small [*see illustration above*]. By piecing together many such sets and applying a limiting argument, one can demonstrate that the theorem is correct. In our workshops I was able to carry out this procedure in sufficient detail to produce the digital sundial that now sits on your desk."

The Abbot, despite himself, was impressed. "Brother Benjamin, your sundial is a marvel! Your reward will, of course, be in heaven, this being spiritually more uplifting than any earthly recompense." A thought struck him. "Perhaps you would care to assist in another small task?"

The monk had no choice but to agree.

"I hear that in Tibet they use machines in which a written prayer is wrapped around a wheel. When the wheel is spun, the prayer revolves and is deemed to have been 'read.' That is a highly efficient innovation, which I believe has much to commend it. As a devout Euclidean, however, you will be aware that only spoken prayers are meaningful. I wonder whether principles similar to those that underlie your digital sundial could be used to create a machine that, as it revolves in the wind, creates the appropriate sounds."

Good heavens, Benjamin thought. How will I ever construct an alternative-energy prayer synthesizer.

FURTHER READING


FRACTAL GEOMETRY—MATHEMATICAL FOUNDATIONS AND APPLICATIONS. Kenneth Falconer. John Wiley and Sons, 1990.





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# BOOK REVIEWS by Philip Morrison

## The Great Pox

**HISTORY OF SYPHILIS,** by Claude Quétel. Translated from the French by Judith Braddock and Brian Pike. Johns Hopkins University Press, 1990 ($39.95).

Charles VIII, king of France (the big-head, they called him), entered newly conquered Naples in May of 1495 costumed as a Byzantine emperor, riding in a chariot drawn by four white horses. He left unceremoniously a week later, for his polyglot mercenary infantry at once gave themselves over to "nothing but disorder, pillaging and debauchery."

The French carried away with them from Italy "the germ of the Renaissance," but with it the germ of a nameless and terrifying disease that was first described in July 1495. The Italian military physicians were keen observers. Within two years they recognized the disease as a new affliction of both men and women, sexually transmitted and protean, marked by gnawing genital ulcers, hideous pustules all over the body and face ("except the eyes"), then horrifying pains and frightening monstrosities of eruptions and swellings. In time—it took nearly three centuries to nail down all the facts—the physicians would establish a long-delayed neurosyphilis as well. Three decades and more after infection, many patients would suffer either a meningoencephalitis that ended in general paralysis with insanity or a creeping spinal disorder, called tabes, in which coordination of the body wasted slowly away.

The Great Pox had come. Before 1520, it had spread like a conflagration both by land and by sea, to flame in turn in North Africa, Asia Minor, India, coastal China and Japan. More quietly, it diffused through the times of religious wars and into the Enlightenment. After the revolutionary end of the *ancien régime,* syphilis remained to mock the good intentions of that 19th-century world bound for progress. There was still no cure; mercury, a favored specific from the first, can be seen as the cause of as many horrific symptoms as the disease whose cure it purports to be. The illness persists after five centuries, with some 70 million patients declared worldwide, even though we now hold a secure 20th-century therapy and a very good prognosis. (The name we use was given the disorder after impious Syphilus, a poor shepherd who became its first sufferer in a famous allegorical poem written in Latin in 1530 by a physician of Verona, fellow student of Copernicus at Padua. The term did not become current until the 18th century.)

What feats of pen and brush this grim condition has inspired! Erasmus and Rabelais, Rowlandson and Boswell, de Maupassant, Flaubert and the brothers Goncourt, even Karen Blixen, are all cited tellingly, as moralists of the disease or reflective victims, or both. Inextricably woven into the very fabric of human behavior, syphilis could not remain a topic for physicians alone. This humane and gently ironic historian places before us, period by period, the changing responses of morality and medicine, of writers and dramatists and of the state power itself. One recurrent aberration is the abuse of women, who are seen more often as hazards than as victims. A long struggle arose in many lands over prostitution and its social role. Abolition and regulation each found embattled adherents and theorists; their arguments seem now as uncompelling as on the whole they were lacking in compassion.

***FIRST MEDICAL ILLUSTRATION of syphilis, this 15th-century Viennese woodcut shows a couple covered with pustules. One doctor examines the woman's urine, while another uses a spatula to apply ointment to the legs of her husband.***

Only one real defense was known, a fragile one, the preventative condom. It is probably an early 18th-century English invention; no wise French physician Condom is known to this French scholar, who suggests that the word derives from the Latin verb *condere,* to hide or protect. But a turning point came at last with the flowering of classical microbiology. In 1905 the causative organism was identified. That delicate protozoan, a spirochete, cannot even yet be successfully cultured, so the long-sought vaccine for "syphilization" has not yet emerged. Instead the 20th century was armed by the tireless chemists with specific arsenicals that surely improve on but hardly transcend the toxic mercurials of Albrecht Dürer's day.

Society came to find the terrors of syphilis everywhere, especially among lower-class women. The scourge was fought mainly by inexplicit and shamefaced public propaganda, plus a doubtful arsenal for bureaucratic prophylaxis, full of paperwork at state expense. Some even saw the need for widespread serological monitoring, available as a somewhat shaky diagnostic since the work of August Paul von Wassermann in 1906. (Enthusiasts thought it would be wise to test all applicants for driving licenses.)

Then, in wartime 1943, Our Lady of Penicillin appeared in radiance, an antibiotic cure, cheap, effective and quick. In a decade the syphilis rate dropped tenfold; the book shows the falling curves for four countries. A strange literary furor over hereditary syphilis disappeared at once in the face of the new facts. Hereditary syphilis had been seen between the wars as the archetype of secret decadence, the mythic source of the genius of modernity in art as well as of madness itself. But syphilitic women treated with penicillin during the first five months of pregnancy did not bear syphilitic infants: the disease can be congenital, but certainly not genetic.

Would syphilis itself disappear? The unhappy answer was a clear no. The curves turned up again, and the disease, with a few other venereal infections, some rather new, is now seen as endemic. It is certainly urban, even touristic; it peaks in summer, the infected mostly men, chiefly single or



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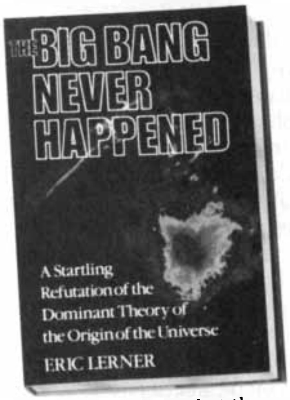


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alone. One or 2 percent of the cases found in Paris are nonvenereal; the outside chance of that contaminating lavatory seat has "saved a good many marriages." The one-night stand, the casual relationships, both homosexual and heterosexual, manifestly continue apace, as does prostitution itself in most lands.

Whence came this cruel, unwitting thread? Voltaire had no doubt. His poor Pangloss in old age, a pustuled beggar, his nose eaten away, still philosophized on the hapless round of lovers who had brought it to him: "from an old countess... from a cavalry captain... from a marquess... from a page... from a Jesuit... in a direct line from one of the companions of Christopher Columbus." That indictment is old, but the evidence is entirely circumstantial. The year 1493 saw Columbus return, of course. The few West Indians he first carried back across the ocean seem an inadequate vector. But other Spanish captains brought back more men and women in 1494 and 1495. The documents seem to confirm that syphilis was known in Spain a few months before the raging Italian outbreak.

The study of historic bones is inconclusive for this soft-tissue disease: plenty of bone lesions are found, but they may all represent the effects of kindred treponemas. Such nonvenereal diseases, including the major ailment, yaws, are still endemic in the rural tropics, in Central America as in Africa and Eurasia. What was new in 1495 besides overseas voyaging was probably a change in the spirochetes; we simply do not know in which tropical region that happened.

Syphilis has learned to perpetuate itself by moderation. We no longer fear it; we allow it to remain tacitly in the shadows, where "it spares us in order to spare itself." But a new, unbridled killer has come. Fast-spreading through the transfer of semen and blood, HIV, the human immunodeficiency virus, is a virulent retrovirus that parasitizes the *T4* lymphocytes to endanger and, in the stage of AIDS itself, even to depopulate the cellular immune system. The condom remains an available preventative. The AIDS rate in the U.S. is now about the same as that for syphilis before penicillin, but AIDS victims stand in peril of death within a few years. Here the five centuries of syphilis are viewed in fast forward, grimmer by an order of magnitude. Our early social response has been on balance better than the long tale told above, informed perhaps by that experience itself. Whether we will be wise enough in reason and generous enough in solidarity is still open to decision.

## Logic and Strategy

**ETHNOMATHEMATICS: A MULTICULTURAL VIEW OF MATHEMATICAL IDEAS,** by Marcia Ascher. Pacific Grove, Calif., Brooks/Cole Publishing Company, 1991 ($38.95).

The theory of graphs, plane figures in which lines join a set of points, is prominent these days; such networks attract increasing attention, all the way from the iterative task of linking computers to the step-by-step analysis of the behavior of interacting particles. The formal subject began with Leonhard Euler, by tradition (although it seems not in fact) with the seven bridges of staid Königsberg and the agreeable puzzle of how to enjoy a walk around the town that would cross each bridge once and once only, yet end at home where it began. Such a path, dubbed Eulerian, can be found for a large known set of graphs. Out of such problems the cultures of children and of amateurs have been enriched, the mathematicians have won whole disciplines, and the philosopher Wittgenstein could exemplify his discussion of "the essence" of mathematics itself.

In this engaging, highly original book—there is not another to set beside it—the author, at once a deft mathematical reasoner and calculator and a learned ethnographer, opens for us the content of an arcane global literature of ethnographic sources that record such ideas among traditional or small-scale cultures. They extend far past mere practical reckoning in their logical depth and analytical demands.

The Eulerian path itself is the nub of children's games among the Bushoong, a group who live around the capital of the old Kuba chiefdom, well east of modern Kinshasa in Zaire. They trace sand figures, not with seven edges or even a dozen but with meshes of several tens of lines that cross to form hundreds of connected squares. Their tracing procedures are known for a few figures; they can be seen to be systematic and indeed to have recovered the fact that success demands a start and an end at vertices from which an odd number of links emanate. Among the Tshokwe, another, larger Central African culture not very far south of the Kuba lands, men accompany their storytelling by sand figures. Their figures, complex meshes occupied by arrays of dots, often tell of camps, children and their guardians or other tales of enclosure and escape. The most basic form of the stories turns on the fact that a simple closed curve always divides the



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plane into a disconnected inside and outside, the same result the European mathematicians found as graph theory grew to topology.

A third culture, in the islands called New Hebrides far away in the Coral Sea, now the Republic of Vanuatu, has gone further still. We have as many as 100 of their intricate figures, some ritually drawn in all care and gravity to instruct of proper access to the Land of the Dead. Marcia Ascher has analyzed most of them, using an algebraic procedure of her own, to tease out the fact that all those forms for which an Eulerian path exists were in fact traced that way. Visual symmetries were common in their tracing schemes that explicitly involved such transformations as reflections and rotations. "Whether in the context of...traveling to the Land of the Dead, abstract line systems, or Sunday strolls...different peoples have pondered the same problem." Each "found the idea sufficiently intriguing to elaborate it well beyond practical necessity."

Such mathematical ideas are set out here in six chapters. They open with number words and symbols, including the still puzzling quipus, the knotted cord records of the Inca empire, whose decimal place notation for numbers Ascher and husband Robert have been pioneers in analyzing. Next come the graphs, followed by the logically elaborate patterns of kinship relations, then by games of chance and strategy found around the world. Here is a theory of the Maori game of strategy, a kind of hyperbackgammon played with counters on an eight-pointed star, proved by the author to have well-optimized rules and board design. Neither fewer nor more than eight points would make anything like so good a game. The modeling of space provides a chapter topic too subtle, perhaps, to support much mathematical closure. The last topic is the geometric and color symmetry of strip decorations, using Maori and Inca materials.

The decimal base of many numeral systems surely begins with our 10 fingers and encourages mental excursions to twenties and fives and their multiples and differences. But even your own hands as a model are more complex than that. The Yuki of California felt that their own number system arose from the nature of the human hand, although it is on an *octal* base! Hold both hands before your eyes and count the conspicuous spaces between pairs of digits. The base 10 is no logical requirement of 10 fingers, although it is a probable choice.

Like the discrete infinity implicit in language itself, like the universal natu-

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ral numbers, many more deep mathematical ideas belong to the commons of humankind. This book, as attractively designed as it is well written and supported, puts that beyond all cavil. It is exciting reading for those who would know human nature and for all who enjoy mathematical ideas; in particular, teachers and students will find it a lasting resource. But it should not go down all that easily, either; the author is caught in a natural tension between the thrust of her book toward human unity and the celebration of human diversity. The claims of modern mathematics to transcend context are certainly imperfect and merit examination, but its unmatched power as an abstract covering system, manifest in these pages themselves, ought not to be hidden under an easy relativism, however sympathetic. This reader believes that Leonhard Euler and the Bushoong children would have much admired each other, each with very good reason.

## Seeing Stars

A CELEBRATION OF COLOUR IN ASTRONOMY, by David Malin. *Current Science,* special issue, Vol. 60, No. 1, 1991. P. B. 8001, C. V. Raman Ave., Bangalore 560 080, India (US$15; paperbound only, price includes airmail delivery).
SPACE PLACES, by Roger Ressmeyer. Collins Publishers, 1990 ($45).

Practical, fast gelatin dry plates reached the eye end of the telescope during the 1870s and have since become the medium of professional astronomy. Silicon video photon-counting devices are now rivals to photography. But silver is still far from obsolete in the dome; its fine grains still outnumber the memory bins of the computers, and its color palette remains subtler.

The first of these books of colorful photographs is a bargain gift to readers from an inventive Australian astronomer, by way of a special issue of the fortnightly journal that links the scientific community of India. The second is a hefty volume by a celebrated magazine and portrait photographer, as devoted an amateur astronomer as he is a globetrotter, whose unexpected and fascinating images center on the world's great instruments caught against the stars. (We meet a few astronauts, cosmonauts and astronomers as well, including David Malin himself in the prime focus cage of the Anglo-Australian four-meter telescope.)

Malin's masterful way with film—he was trained as a chemist—has brought vivid color into astrophysics to stay. We all know that stars do not easily show color to the human eye. (Malin cites what C. V. Raman said of star colors, to suggest that the redoubtable physicist may well have had "remarkably acute color vision...under very low light levels.") Most of us see the stars as white, with only a hint of color. Color film does much better with starlight, provided the film is not overexposed. But the visible stars display a brightness range that outstretches the capabilities of any color film, extending as it does over about 10 photographic f-stops.

The first two of the 60 well-annotated color prints in this "celebration" compellingly disclose what commercial color film can do. Malin aims a stationary 35mm camera first at the constellation Orion. Every few minutes he gently defocuses the lens, allowing say half an hour of total exposure. The track of each bright star appears on the film as the sky drifts past. All the tracks start narrow, in focus, overexposed and therefore white. Step by step, the defocused image is made wider and fainter, until at last it fades from underexposure. One or more of that set of out-of-focus images will come close to optimum exposure and true color. Indeed, Betelguese shows up yellow-orange (red giant stars are red only in the spectroscopist's jargon), and Rigel is dazzling blue. In the second picture, we see instead the sun's famous neighbor and counterpart, Alpha Centauri. Its image is white over many focus steps, checking the color balance of the film by its response to sunlight from four light-years away. Few bright stars so closely match our sun.

The showy nebulas that dazzle us in most of these pictures set another problem. Color film is not meant for light like theirs, no rainbow spectrum but one dominated by narrow atomic emission lines. The right way to make color photographs is then the oldest way, first used by James Clerk Maxwell himself in 1861: three color filters matched to emulsions to give three separated black-and-white negative plates. These can be enlarged, manipulated, registered and recombined through the same filters to add the dimension of verifiable color.

The rich results charm and instruct. Two yellow rings record the delayed light of the 1987 supernova, still reverberating from dust layers that lie between us and the explosion. They echo the long-faded color of the outburst. The great Orion nebula, mainly a dust reflection of starlight, is itself seen in reflection off an adjoining dusty cloud. The famous Trifid nebula, a gassy red



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emission nebula, is encircled by a faint blue nebular ring. Out there, the ultraviolet light from the central blue stars that can excite the red atomic emissions has been absorbed in its long passage through the gas. But gas and dust still extend beyond the sphere of the UV, so that at its boundary they appear as a faint bluish reflection in dust. These pictures are prime, and their interpretation is a lesson in astrophysics made visible.

The astronomers must make do with the light they are given, but the artful photographer of this world brings his own. Roger Ressmeyer blends the lights he carries with the reddened low beams of the sun and with the bright stars to generate wondrous images, without any manipulation once the film has left his camera. Ian Shelton, the discoverer of Supernova 1987A, works within a small dome at Las Campanas, its interior washed with red light. Behind him in the opening, the Milky Way and the Large Magellanic Cloud shine bright in the blue night sky, "just off the front end of the telescope." A curious red arabesque winds out to the silvery submillimeter-wave dish at La Silla in Chile; it is the flashlight carried by the photographer, who likes to walk his way across the inviting images he takes.

In the same fresh style, he shows us most of the celebrated earthbound sites where humans confront space, from old Samarkand to modern domes and dishes on summits from the Crimea past Hawaii to La Palma in the Canaries, even to the low green fernland that lies in eternal dapple below the suspended radio dish at Arecibo. His camera went to the places of spacefarers, too. The ranked consoles of the flight controllers in Kaliningrad evoke our familiar Houston, apart from the Cyrillic legends on the big front screens. We see other launch pads, in French Guiana, in rural Xichang and in beautiful Tanegashima. Malin's Horsehead nebula spreads over two crimson pages, among many another select sky shot from ground or from space.

Two unexpected images stay in the mind. One is a Trident submarine berthing area on board the USS *Alabama* undersea, nine padded cubicles packed into a crystalline array for the 70-day tour of duty under red light. An early realization of spaceship architecture? The other is the dome at Palomar Mountain seen at night below star trails. It might be a cliché—save that here that ponderous dome is made magically transparent by strict control over light and motion, to reveal within its hollow the gleaming structure of the Hale Telescope.


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# ESSAY: THE SECOND BOTTOM LINE by Charles E. Ziegler

Our planet, like a rubber band, possesses considerable elasticity. If we were to halt all of modern society's activity tomorrow, the world's polluted waters and atmosphere would eventually cleanse themselves of their toxins. Although the notion is comforting, cessation of industrial activity is clearly not a viable option. Instead we must ask ourselves: To what extent can the planet's ecosystems be stretched before they will lose their resiliency and break apart? This question looms as the most pressing problem of the coming century.

Concern for the environment is growing at a feverish rate. Such anxiety is hardly surprising. The local problems that triggered environmental alarms in the 1970s and 1980s are still with us. In the 1990s they have been joined by more global ones, most notably the loss of our stratospheric ozone layer and the perceived threat of climatic change.

At the same time, it is becoming all too apparent that industry, environmentalists and the government are at an unfortunate impasse—one we can ill afford. As a member of the chemical industry for the past 30 years, I have witnessed, as well as participated in, numerous environmental disputes. Sadly, I have not seen many victories for any side. Instead I have watched all sides expend considerable resources to arrive at outcomes that seem to satisfy no one: policies that are costly to implement but do little to improve the environment. The legislation mandating funds for the cleanup of toxic dumps across the U.S. is a case in point. Despite billions of dollars spent on the program to date, only a fraction of the superfund sites have been treated successfully.

Most distressing to those of us in industry is that the past failures of the free market to protect the environment are being projected by the public to the future. Long touted by most Americans as the method of choice for all problems, the marketplace proved to be ineffective when it came to environmental protection. The impositions made on the earth's ecosystems over the years have been at a low out-of-pocket cost to the waste generator but at a high price to the environment. Companies under the gun of the quarterly dividend tended to focus on short-term results, particularly when "cheap" short-term waste-disposal options were readily available.

Corporate attitudes are changing because the environmentalists have made their case that the short-term waste-disposal solutions are, in fact, the highest-priced ones. That lesson has been learned in many boardrooms. Corporations such as Ciba-Geigy and others are committing major resources to correct ongoing environmental problems and to avoid further harm to the ecology. Unfortunately, the public remains unconvinced.

For that reason, a proactive strategy, which I hope will encourage greater commitment by all of business to the environment, is essential. The plan I suggest is simple: industry must look beyond the financial bottom line and focus more on the public at large. We must respond to the growing demands of citizens everywhere for a healthy environment. In doing so, we need to acknowledge the emergence of what I call the second bottom line: public trust. Although less tangible and not as easily measured over the short term as the first—the financial—bottom line, it heralds a company's prospects for long-term survival. As the marketplace becomes more competitive, consumers tend to choose products based on the manufacturer's overall reputation and so are having a subtle, but measurable, effect on a company's profit margins. If the trend persists, the long-term consequences could be profound.

The significance of the second bottom line is revealed by drawing an analogy between it and R&D activities. Like other chemical and pharmaceutical manufacturers, Ciba-Geigy spends vast amounts on research—in excess of $1 billion a year. Despite the expenditure of such large sums, there is seldom a guarantee that new and commercially successful products will result. Yet experience suggests that sooner or later product ideas spring forth from basic research.

We invest money in research as if it were an act of faith. But there is no choice: research is critical to our future. Without it, we will lose our ability to produce new products, and the company will fail—not tomorrow but perhaps 10 or 20 years from now. Similarly, we must recognize that failure to understand and accommodate changing attitudes may ultimately deprive us of the acceptance needed to market our products and stay in business. Thus, establishing public acceptability mandates a second act of faith on the part of management.

But how does one contact the public at large? How does one engage their trust? And how might such interaction lead to a more secure planet? Recent experience suggests that environmental issues are best addressed through a candid exchange of ideas. Such exchange occurs not only within a company but between it and its "stakeholders," those citizens who feel they have a stake in the company's activities because, in many ways, they are affected by these decisions. It is time for industry to realize that open discussions and collective action can benefit all parties involved. Unless corporations and their executives—including myself—adhere to the moral standards demanded by society, their future, like that of the planet, will be questionable indeed.

As we look to an uncertain future, I call on my colleagues to consider the following steps. Establish advisory groups made up of individuals from diverse segments of society. Periodically hold open meetings at which stakeholders, who often are customers, can share their views with corporate executives before a major problem erupts. As individuals, let us talk to our friends and neighbors. Stakeholders can be found in local groups, environmental organizations, consumer coalitions, women's groups and religious associations. Many of these organizations maintain a lively contact with several branches of the United Nations, such as the U.N. Environmental Program and the U.N. Center on Transnational Corporations. Companies must do the same. Create an office of external affairs to foster contact with the public, track environmental and related health issues and influence company policy accordingly.

Above all, remember that a corporation can learn from its stakeholders. Carried out correctly, such an exchange will create higher levels of knowledge and trust, resulting in better policies and in improved relations between the company and its stakeholders. In the long run, this can only lead to a healthier corporation—and a better score on both bottom lines.

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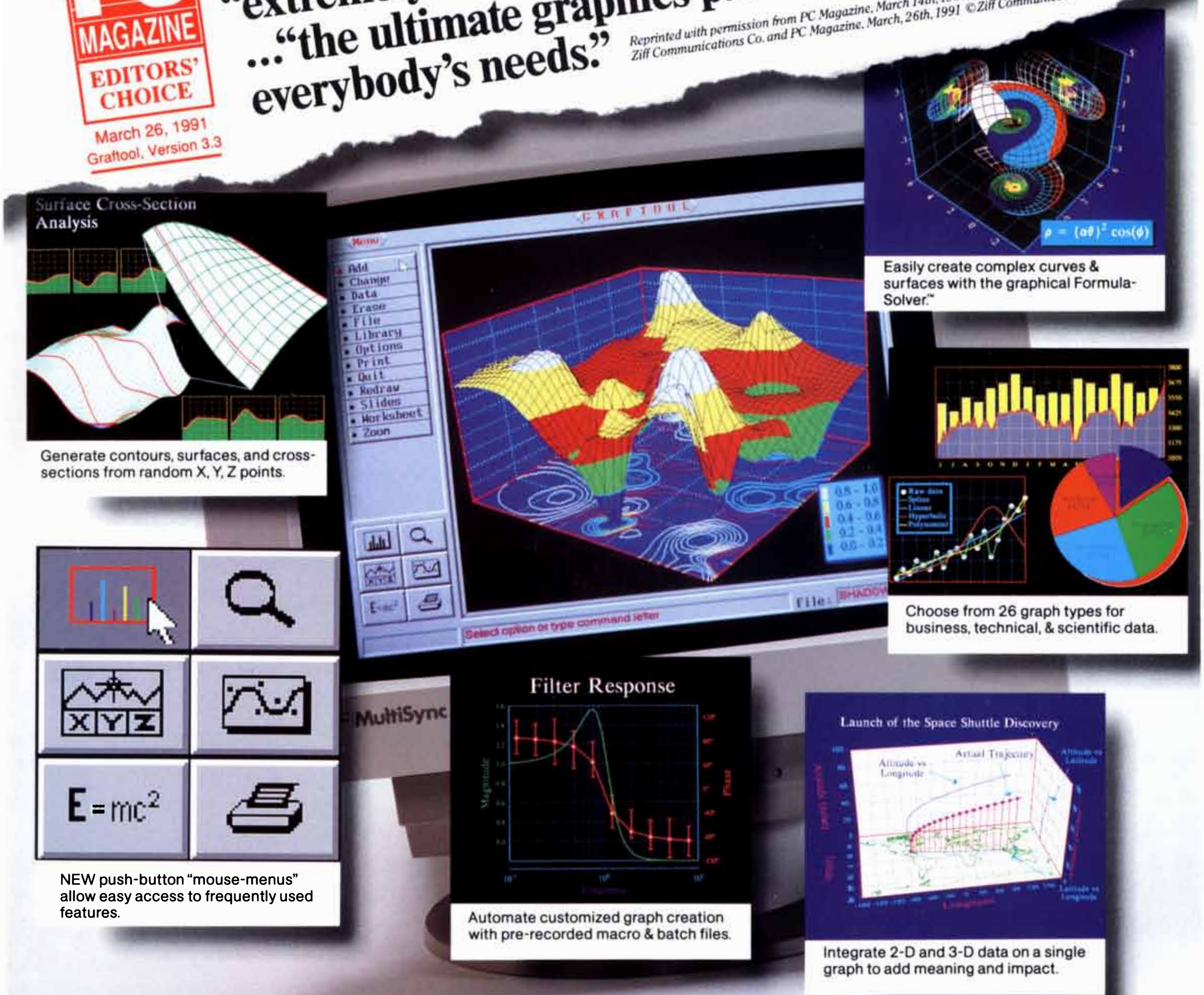


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