BEATING PROSTATE CANCER • THE FUTURE OF CLONING • ULTRABRIGHT X-RAYS

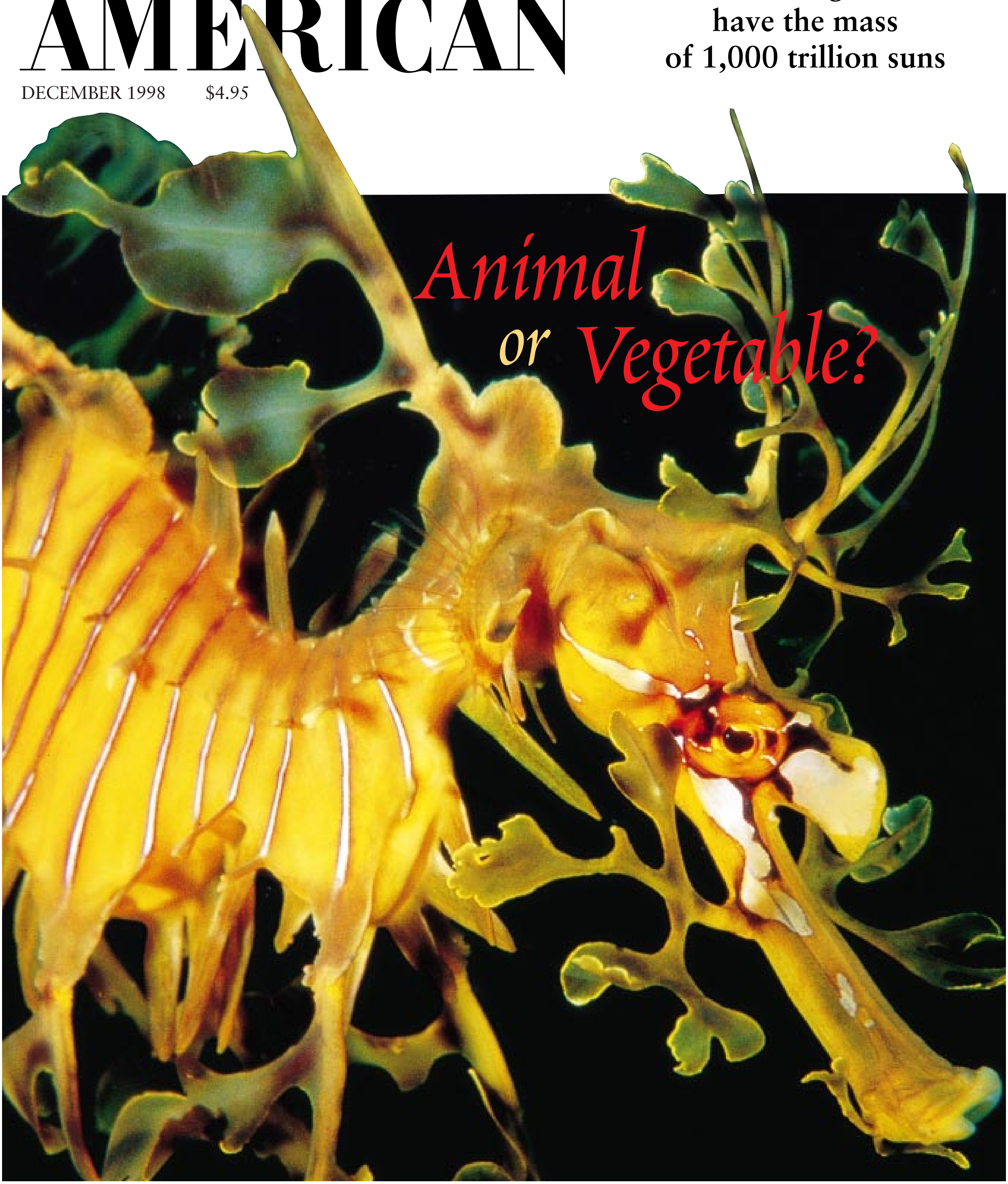
SCIENTIFIC AMERICAN

DECEMBER 1998 $4.95

THE HEAVIEST OBJECTS IN THE UNIVERSE:

Clusters of galaxies have the mass of 1,000 trillion suns

Animal or Vegetable?



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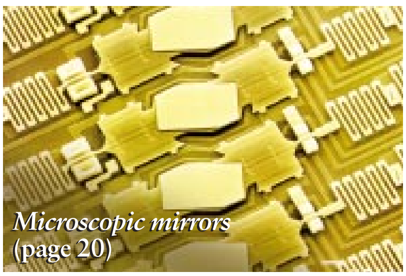
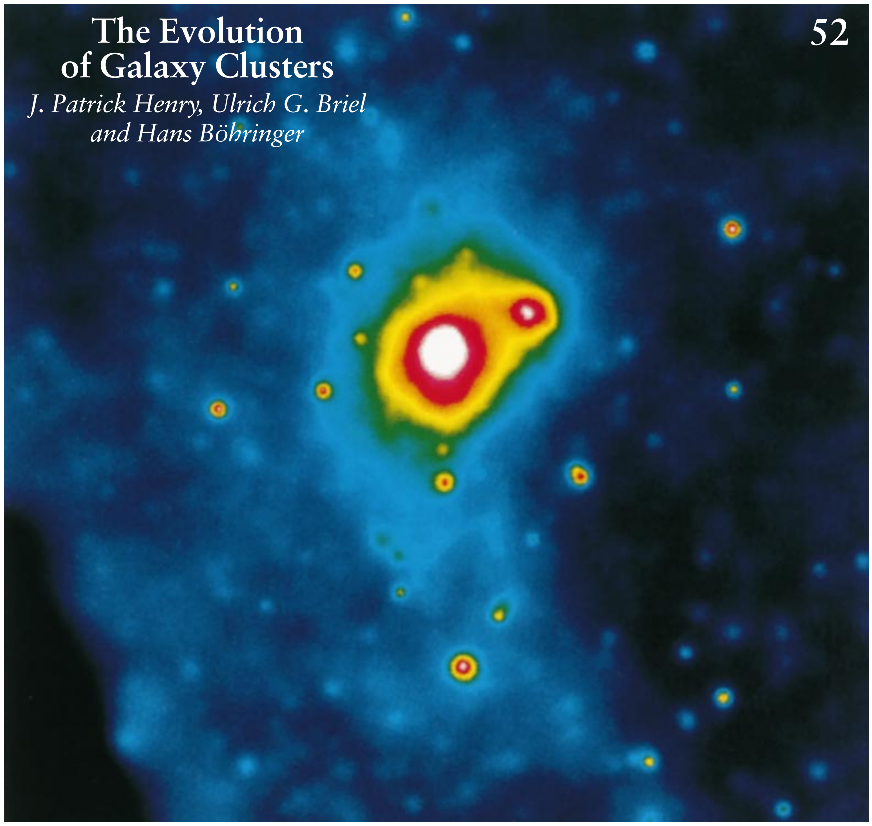
December 1998 Volume 279 Number 6

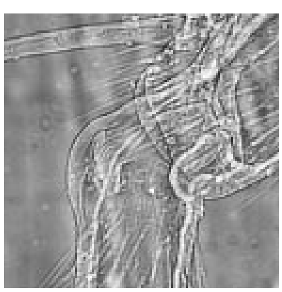


Microscopic mirrors (page 20)

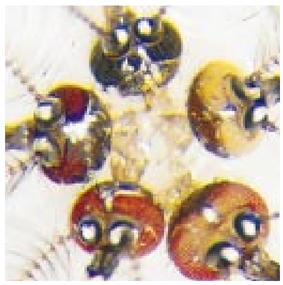


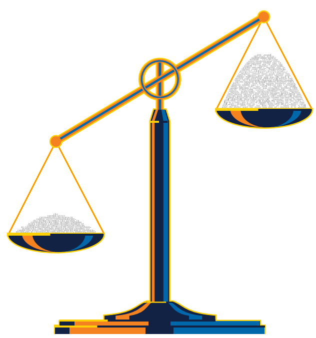
Gravity binds galaxies into discrete clusters, just as it binds stars into individual galaxies. These galaxy clusters are miniuniverses in their own right, and by studying them, astronomers are trying to grasp the properties of the cosmos as a whole. Surprisingly, the galaxies themselves hold only a tiny fraction of the mass in the clusters. Much more resides in a mysterious hot gas threading through space, and most of the mass is embodied as invisible, unidentified dark matter.

Cloning can be a boon to medical science—even without ethically dubious attempts to duplicate humans. As the creator of Dolly the cloned sheep explains, the real benefits will come from the speedy production of genetically engineered animals useful for drug manufacture, transplants and basic research.



Accelerators several hundred meters in diameter controllably emit brilliant bursts of x-rays that outshine the sun a billion times over. This radiation can be used to peek intimately at the atomic structure of crystals, to map the inside of a mosquito's knee or to analyze blood cells.





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About the Cover
Animal, vegetable or mineral? The frondlike appendages that give the leafy sea dragon its name help this peculiar fish camouflage itself among floating weeds off the Australian coast. Photograph by Paul Sutherland.

THE SCIENTIFIC AMERICAN WEB SITE

Readers debate the future of the International Space Station: www.sciam.com/explorations/1998/100598station/index.html

And see this month's articles and departments linked to science resources on the World Wide Web.

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FROM THE EDITORS

Counting Our Blessings

Is it really better to give than to receive? Not if your friends know where to shop. But, Scroogish observations aside, the holiday season naturally prompts thoughts of gifts. *Scientific American* received some presents early this year, for which I would like to give my thanks.

First, *Scientific American* was selected as the winner of a 1998 *Folio:* Editorial Excellence Award in the category of consumer science/technology magazine. *Folio:*, the magazine of the magazine industry, confers these awards on publications that are judged to meet best the standards set by their own editorial mission statements. The mission statement for *Scientific American* reads, in part, "To share the intellectual adventure, fun and beauty of science in a manner that is clear, accurate and accessible to nonscientists." Credit for fulfilling that promise belongs to all the people behind the scenes (their names are found on the masthead at the right). They do the heavy lifting and 11th-hour miracle-working that makes this magazine what it is, and I'm grateful to them.

Congratulations also go to *Scientific American Frontiers,* the television series now in its ninth year on PBS. The Council of Scientific Society Presidents has selected *Frontiers,* host Alan Alda, and producers Graham Chedd and John Angier collectively to win the Sagan Award for the Public Understanding of Science. As its millions of steady viewers know, *Frontiers* offers a great blend of information and entertainment. Past winners of the Sagan award include astronomer Carl Sagan himself, biologist E. O. Wilson, the National Geographic Society and the TV program *Nova*—a distinguished company to be in and well deserved.

Frontiers has also received the Parents' Choice Gold Award for excellence in children's media. Groups of adults and children selected *Frontiers* for its high quality, entertainment value and contribution toward helping children to develop ethical attitudes. This endorsement is particularly heartwarming because many schools have incorporated *Frontiers* programs into their curricula.

Speaking of children, we have some honors to present, too. The tireless Philip and Phylis Morrison—lovers of science, books and children (in no particular order)—have once again selected the winners of the *Scientific American* Young Readers Book Awards. Out of the many hundreds of books on science for children published recently, the Morrisons have chosen 18 of the best. As they remark happily in their introduction, beginning on page 116, this job grows no easier from year to year, thanks to the high quality of so much of what is being published. Is it better to give or receive one of these books? We'll leave that experiment to you.

JOHN RENNIE, *Editor in Chief*
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LETTERS TO THE EDITORS

Talking about religion is often dangerous unless you're ready for an argument. Some readers were awfully mad about the discussion of religion in an article by senior writer W. Wayt Gibbs, "Beyond Physics" [News and Analysis, August]. John C. Hatt wrote by e-mail that "science is not a philosophy but an intellectual tool. Much of science is uncertain; that is the nature of human knowledge. To suggest that this uncertainty is resolved by faith is not an area of scientific exploration. I would prefer that *Scientific American* not include articles on matters of faith in my monthly reading." Karl Eklund commented in an e-mail that "to those of us who have been through a scientific education, science is 'truth' the way the Nicene Creed is 'truth' to a Christian. Science is a lot better than other religions in begetting technology that makes life more comfortable." A slightly less heated dispute also came up concerning "The Caiman Trade" article from the March issue (*below*).

PROTECTING CAIMANS

"The Caiman Trade," by Peter Brazaitis, Myrna E. Watanabe and George Amato [March], presents outdated and inaccurate information and does a great disservice to the successful conservation of caimans under way in most countries of Latin America. There are numerous factual errors, ranging from improper attribution of sources of data (for example, the World Conservation Union, or IUCN, does not estimate caiman trade) to erroneous biological data, such as the distribution of species, number of eggs laid and accepted scientific nomenclature of this group.

Scientific surveys conducted since 1989 in Nicaragua, Honduras, Colombia, Venezuela, Guyana, Brazil, Ecuador, Bolivia, Paraguay and Argentina have found, without exception, that every species mentioned in the article remains abundant in many locations. In fact, none of the species discussed are in danger of becoming extinct, and trade—legal or illegal—is not a current threat to their survival. The total volume of skins traded has been reduced, and the supply of legal skins entering international trade has demonstrably displaced much of the previous illegal trade.

Despite these advances, there are still serious threats to caimans' existence. The destruction of wetlands, pollution and rapidly expanding human populations all continue to threaten the caiman in Latin America. Creating incentives and funding to address these real problems is an urgent need. The authors ignore the good work being done by many people and agencies in the region.

JAMES PERRAN ROSS
Executive Officer
Crocodile Specialist Group
Gainesville, Fla.

Brazaitis, Watanabe and Amato reply:

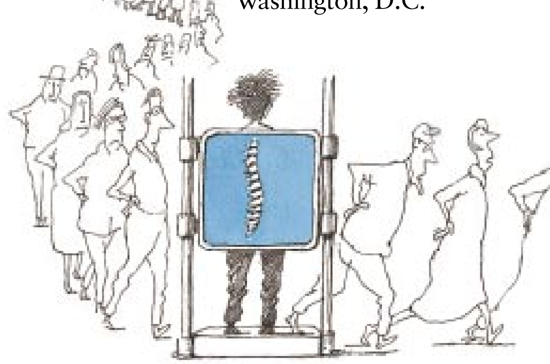
Other than a production error on a map, corrected by *Scientific American* ["Errata," Letters to the Editors, May], we fail to identify the pervasive problems with our article that Ross describes. Indeed, the focus of his letter on minutiae diverts attention from the main issues. The trade data cited were largely based on IUCN Crocodile Specialist Group reports—from Ross's own office. His comment that "every species mentioned in the article remains abundant in many locations" parrots the leather trade philosophy of citing numbers of caimans that might still be killed. The abundance of caimans today is, in fact, immaterial, as habitats remain unprotected, 40 percent of the skin trade is unregulated, monitoring and law enforcement are inadequate, and many regions have declining or absent populations. Ross's enumeration of current, serious threats to wild caiman populations, however, is consistent with our concerns.

Although Ross may disagree, there is no scientific disagreement about the molecular taxonomy within the *Caiman crocodilus* complex, which contains different taxonomic units, or phylogenetic species. Our work has been published in at least seven peer-reviewed scientific journals and books in four countries. Publications from the Crocodile Specialist Group—an organization largely funded by the crocodile leather and tanning industry—are unreviewed and unedited. Our concern is the preservation of wild caimans, not the preservation of the crocodilian leather trade.

BACK TO BASICS

Richard A. Deyo's article on back pain [August] offered an excellent insight into the complexity of back pain and the diversity of treatments used to control it. If people heeded Deyo's advice, however, they would pop some pain pills, increase their amount of exercise and wait until the pain goes away. Pain is not a sign that your body is low on painkillers. Pain is your body's way of telling you something is wrong. The underlying cause of back pain must be treated, not just its symptoms. In 1994 the U.S. Agency for Healthcare Policy and Research (AHCPR), in a landmark study on back pain, found that the treatment of choice was chiropractic care. The worst thing readers can do is say that "maybe the pain will just go away."

MARK L. WALZ
Washington, D.C.



DUSAN PETRICIC

BACK PAIN
can be treated in a variety of ways.

Deyo replies:

Back pain has many causes, patients have varying treatment needs and preferences, and optimal therapy must be individualized. I was a member of the AHCPR panel that produced the report Walz mentions. It did not indicate that chiropractic therapy was the "treatment of choice." The guideline did, however, discuss spinal manipulation, which may be provided not only by chiropractors but by osteopathic physicians and physical therapists, among others. The report concluded that "the evidence for effectiveness of manipulation varies depending on the duration and nature of the patient's symptoms. For . . . acute low back symptoms without radiculopathy . . . spinal manipulation is effective . . . within the first month of symptoms. . . . [B]eyond one month, the scientific evidence . . . was inconclusive."

MATH IS FUN

Martin Gardner's suggestions in "A Quarter-Century of Recreational Mathematics" [August] bring to life what most math instructors beat to death. When I was teaching sixth-grade math some years ago, I asked fellow math teachers about available geometry instruction materials because I wanted to teach tessellation, geometric solids, line segments and spirals through a series of art activities. I was told that they didn't teach much geometry, and certainly not art, because there wasn't enough time. Students needed to practice for math proficiency tests. I went ahead and obtained my own materials—and am I glad I did! My students enjoyed themselves while learning important math concepts. As pressures increase to raise standardized test scores, movement toward Gardner's suggested teaching style will become even more glacial. We must put some of the fun back into education.

MINDY PINES
Corralitos, Calif.

SYSTEM SHUTDOWN

I loved Leonard Adelman's "Computing with DNA" [August], which showed that we could make a Turing machine and software using DNA. I wonder about the converse. Is the implication that DNA is a computer and that life is based on software? If so, I must ask the obvious: Is life vulnerable to the millennium bug?

DICK MILLS
Amsterdam, N.Y.

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50, 100 AND 150 YEARS AGO

SCIENTIFIC AMERICAN

DECEMBER 1948

OPINION POLLS—“However wrong George Gallup, Elmo Roper and other pollsters may have been in their forecasts of the recent election [Harry S Truman against Thomas E. Dewey], no social scientist believes that public opinion polling itself was thereby discredited as a useful tool. Science often learns more from mistakes than from successes. In this case, the polling fiasco of 1948 had at least two healthy results: 1) it demonstrated dramatically that polling is far from being an exact science (which apparently needed public demonstration) and 2) it will force more rigorous standards upon the polling business.”

Polling machinery for the 1948 election featured the latest punch tapes (foreground) *and tabulators* (center)

FISHY FOOD—“In response to the twin pressures of world food needs and severe overfishing, fishery experts are advocating the wide use of fertilizer to speed up the growth of fish. About two years ago a Scotch biologist fertilized a closed-off arm of the North Sea with superphosphate and sodium nitrate, greatly increasing the plant food supply and the number of fish. Similar experiments with fresh-water fish at the Alabama Polytechnic Institute used a nitrogen-phosphorus-potassium mixture. For $20 of fertilizer, the yield of fish was increased fivefold.” [*Editors’ note: For the unintended consequences of this idea, see “Enriching the Seas to Death,” by Scott W. Nixon;* SCIENTIFIC AMERICAN PRESENTS: The Oceans, *Fall 1998.*]

A TASTE FOR ALCOHOL—“Human beings show enormous variation in their responses to alcohol. A study made of young children from four to ten years of age gave evidence of inherent differences in the taste for alcohol. Most of them did not find the taste pleasant, but eight per cent of the children actually liked solutions submitted to them which contained as much as 50 per cent alcohol.”

DECEMBER 1898

CANCER ON THE RISE—“‘In England four and a half times as many people die now from cancer as half a century ago,’ W. Roger Williams says in *The Lancet.* ‘Probably no single factor is more important in determining the outbreak of cancer in the predisposed than high feeding. Many indications point to the gluttonous consumption of meat as likely to be especially harmful. Statistics show that the consumption of meat has reached the amazing total of 131 pounds per head per year, which is more than double what it was half a century ago. No doubt other factors co-operate, among these I should be inclined to name deficient exercise and deficiency in fresh vegetable food.’”

CRIMINAL ASYMMETRY—“Criminal anthropologists have naturally marked the murderer of the Empress of Austria for scientific study. The corpus vile of the criminal will doubtless be reserved for some expert, but in the meantime eager investigators have been studying photographs of Luigi Luccheni. To the ordinary observer he looks a commonplace ruffian, but the criminal anthropologists, we are assured, at once see complete asymmetry of the body. Amyotrophy on the left side is very marked. These stigmata are the consequences of grave cerebrospinal lesions occurring in infancy. It would have been more satisfactory if these evidences of criminality were recognized before Luccheni had perpetrated his infamous crime.”

ULTRAVIOLET EXPERIMENTS—“Prof. Zickler, of Brünn, has shown that a telegraphic instrument can be actuated at considerable distances by ultra-violet light. He employs a powerful arc lamp as his transmitter, using a screen of glass, to produce flashes of the ultra-violet beam. The receiver is regulated to just below the sparking point. He was able to produce an effect at 200 meters. It is extremely interesting to physicists to learn that the easily absorbed ultraviolet light can influence a spark discharge at so great a distance.”

DECEMBER 1848

IRRESISTIBLE FORCE—“The huge dam over the Connecticut River at Hadley Falls, Mass., was completed on the 16th of last month, and the day of its completion was the day of its doom. A great number of people had assembled to see the dam filled, and the waters of the Connecticut arrested in their course. But from the first, imperfections were discovered in the work, and a breach, small at first, widened with great rapidity, until about three-fourths of the embankments burst away before the mighty mass of angry waters. The dam was constructed of immense timbers, fastened to the rocky bed of the river with iron bolts. Fault must be attributed to the principle of its construction.”

NEWS AND ANALYSIS

IN FOCUS

NOTHING BUT LIGHT

Hunger for bandwidth drives all-optical technology to market

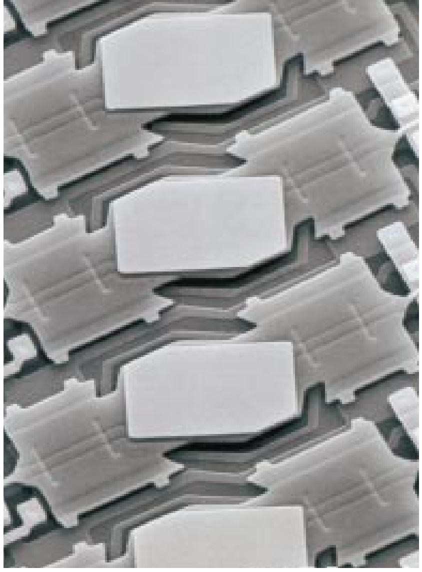
CHRIS USHER *Ciena Corporation*

OPTICAL COMPONENTS FOR TELECOMMUNICATIONS are assembled at Ciena, a multiplexer manufacturer.

The Internet-fueled boom in data communications has set off a grab for bandwidth—the additional network capacity needed to transmit Monica Lewinsky's grand jury testimony or the Taliban's Web page. Traffic on the Internet as much as quadruples every year, whereas plain old voice calls chug along at 8 to 13 percent annual growth. To sate the bandwidth crunch, long-distance telecommunications carriers have begun to demand optical communications technologies that had languished in university and industrial laboratories until the mid-1990s. "There's a useful place for the technology to go," notes Steve W. Chaddick, a senior vice president at Maryland-based Ciena, a leading optical network equipment manufacturer. "That wasn't true just a few years back."

Five years ago networks that incorporated what is called a dense wavelength division multiplexer (DWDM) were to be found in U.S. and European government-industry research consortia that were showcasing new technologies. This heavy-handed engineering term describes networking equipment that has, in the interim, rescued long-distance carriers such as the telecommunications provider Sprint from a bandwidth drought. The multiplexer sends laser light of different wavelengths down a single optical fiber. Meanwhile components of the transmission system in the path of the fiber reflect individual information-carrying wavelengths, allowing them to be diverted onto or off a high-capacity link. DWDM systems work in concert with optical amplifiers that can boost the strength of many wavelengths at once without having to convert the wave back into an electrical signal.

With this technology, the capacity of in-the-ground fiber can be expanded by simply adding wavelengths. For Sprint, deploying the multiplexers costs roughly 40 percent of the $77,000-per-mile expense of adding new fiber. "We would have had serious problems without this technology," remarks Frederick J. Harris, Sprint's director of network planning and design, whose company uses DWDM on 90 percent of its 30,000 miles of fiber networks.



LUCENT TECHNOLOGIES, BELL LABORATORIES

MICROSCOPIC MIRRORS
are one candidate for switching large numbers of optical wavelengths.

The U.S. market for this technology grew from nothing in 1994 to $1.5 billion last year and is expected to reach more than $4 billion in size by 2001. "Supply for bandwidth still has not crossed demand, so the market for the technology continues to grow," says Mathew H. Steinberg of the market analysis firm RHK in South San Francisco. (Before 1994, a small market existed for wavelength division multiplexers with only two channels.)

To meet new growth, multiplexers will flirt with or break the terabit (trillion-bit) barrier on a single fiber; a trillion bits per second exceeds all the traffic on the Internet. Most current equipment tops out at about a tenth of a terabit. But several firms—including Pirelli Cables and Systems North America in Lexington, S.C., and Lucent Technologies in Murray Hill, N.J., as well as Ciena—are either shipping or readying delivery of equipment that can support from 80 to 128 wavelengths on a fiber, each wavelength carrying up to 10 gigabits of information. Lucent Technologies's Bell Laboratories will attempt an experiment next year that would transmit 1,000 wavelengths on a fiber, in an effort to test the maximum capacity an individual fiber can accommodate.

Multiplexers create the lanes on optical superhighways. But these pathways move only from point A to point B. To channel traffic from New York to either Los Angeles or Seattle, a switching interchange may be needed in Chicago. So companies have dusted off 1980s-era research on switching optical signals.

Light-wave switches would avoid the costly burden telecommunications carriers now face—converting the multiple gigabit stream running on each wavelength into dozens or hundreds of lower-speed electronic signals, switching them and then reaggregating them into a single light channel. Huge telecommunications equipment companies and start-ups alike are now racing to develop all-optical switching products. Photonics has even become a basis for regional economic development. In late October a group that combines the University of Texas at Dallas, several venture capitalists and major telecommunications equipment suppliers and carriers announced the establishment of a photonics development center based in Richardson, Tex., intended to attract new companies to the region.

Optical switching elements, expected in 1999, will be incorporated into the next generation of DWDM products. They will allow any wavelength in a fiber to be diverted onto or off a network on command, unlike current multiplexers, which cannot be reconfigured without a technician first disabling a fiber circuit. Tellium, a New Jersey start-up that was spun off from Bellcore, the former research arm of the regional phone companies, is one of several firms laboring on the technology. It has developed an optical switching multiplexer that uses the polarization state of liquid crystals to add or drop up to 64 wavelengths from a fiber.

Telecommunications suppliers such as Sprint and MCI want more than a souped-up multiplexer. They hanker for the photonic equivalent of an electronic switch called a digital cross-connect, which switches hundreds of incoming signals to an equal number of outgoing channels. Today's digital cross-connects, however, require that the multigigabit light waves that are channeled along fiber networks be converted to lower-rate electronic signals.

MCI Worldcom in Jackson, Miss., has purchased an early version of an optical cross-connect switch to protect against "backhoe losses": the catastrophic curtailment of phone service that occurs when a fiber is cut. The 24 deployed switches, which were manufactured by Astarté Fiber Networks in Boulder, Colo., use a piezoelectric material that steers the light from any of 72 incoming to any of 72 outgoing fibers. This system allows immediate restoration of service if a fiber goes down.

A hand-me-down from a technology used in classified military networks, the switch is very much a first-generation product. Astarté and others are working on switching elements for optical cross-connects that will provide more capacity and reduce the cost and size of the products. Some companies are considering arrays of thousands of microscopic mirrors that can tilt individually to send a wavelength down a chosen pathway. Alternatively, an electric field applied to certain materials may change the way light is routed. With yet another approach, called thermo-optics, application of heat to a polymer blocks light from proceeding down one pathway but not another. "In the next couple of years, you're going to see a shoot-out, and some practical devices will come out of this competition," notes Alastair M. Glass, director of photonics research at Lucent.

Despite the photonic revival, the difficulties of switching signals optically have caused some companies to opt for the development of new electronic switches that can accommodate high-bandwidth pipes. And even if optical cross-connects become ubiquitous, telecommunications specialists see a continuing role for electrons, which may be needed to reshape light pulses that have attenuated over long distances and in monitoring networks. "There's no way anyone knows to determine optically the number of bits with errors on an all-optical signal," says Tellium chief technology officer Charles A. Brackett.

The prospect of terabit networking, however, has begun to prompt further rethinking of how networks operate. In the laboratory, work continues on the speculative idea of switching not just wavelengths of light but the individual packets of data transmitted over fiber networks, all of which are now processed with relatively slow electronic switches. A European consortium, ACTS, has demonstrated an optical router that performs this function. "This type of device might handle routing and forwarding of data with multiple terabit inputs without slowing down traffic," says Daniel J. Blumenthal, associate professor of electrical and computer engineering at the University of California at Santa Barbara. Blumenthal is attempting to build a prototype optical router that forwards packets using the Internet Protocol.

For the moment, optical packet switching is still a dream. But the pull from a marketplace that is warming to the idea of a trillion bits per second may help turn laboratory oddities into commercial realities. *—Gary Stix*

SPORTS PHYSIOLOGY

ANDRO ANGST

Should the U.S. regulate over-the-counter sports supplements as anabolic steroids?

The cloud that hovered briefly over Mark McGwire's sunny march to baseball immortality this past summer was the revelation that he was taking androstenedione, a hormonally based supplement reputed to help weight lifters add muscle. Writers wagged their fingers and raised questions about whether performances achieved with the substance are somehow tarnished or less valid. (Major League Baseball and some other athletic organizations permit its use; most others ban it.) But the editorial sputtering did little to elucidate the central question: Are such compounds merely dietary supplements, as the U.S. Food and Drug Administration classifies them, or are they just another form of muscle-building (anabolic) steroid?

Many endocrinologists insist that the differences between supplements like androstenedione and traditional anabolic steroids (which are legal only for certain medical conditions) are trivial. "They are all steroid hormones," says Charles E. Yesalis, professor of health and human development at Pennsylvania State University. "The only debate is whether they are anabolic or not."

Moreover, though it was somehow overlooked in the hundreds of articles written about androstenedione in the wake of the McGwire admission, 4-androstenedione, as it is technically known, is just one of a growing family of over-the-counter steroids. In fact, many fitness buffs do not even consider androstenedione to be particularly potent. "4-androstenedione has really been left in the dust," says Timothy N. Ziegenfuss, an assistant professor of physiology at Eastern Michigan University who is researching several of the steroid compounds. The five newer products are 5-androstenedione, 4-androstenediol, 5-androstenediol, 19-4-norandrostenedione and 19-5-norandrostenediol. (The *Merck Index* classifies 5-androstenediol and 19-5-norandrostenediol as anabolic steroids.)

CHRIS TROTMAN *Duomo*

***SLUGGER MARK McGWIRE'S** remarkable season coincided with his use of androstenedione, an over-the-counter steroid.*

The argument about whether such nonprescription steroids are anabolic or not is more than an academic curiosity because, should the U.S. ever officially decide that they are—as most other countries have already done—they would fall under the Anabolic Steroids Control Act of 1990, which directed the government to restrict the substances the same way it regulates marijuana. Currently over-the-counter steroids are not regulated by the FDA, because their makers "don't claim to treat, cure, mitigate, diagnose or prevent a disease," notes Judith Foulke, an FDA spokesperson.

Traditional anabolic steroids have long been recognized as giving athletes an unfair advantage, especially in sprinting, shot-putting and other activities demanding short bursts of power. All of them are basically either esters of testosterone or synthetic versions of testosterone that have been altered to enhance certain physiological effects and to minimize others. (Testosterone is the primary male sex hormone and has many functions in the body, including muscle-building.)

According to Ziegenfuss, the over-the-counter steroids work in a different way. The substances, which are supposed to be taken orally and typically in 100-milligram doses, make it into the liver, which destroys all but a few percent of the amount ingested. The few milligrams that survive, however, combine with various enzymes there and temporarily boost testosterone levels. But whether they do so significantly enough to make a difference for muscle-building (anabolism) or athletics is now hotly disputed.

Scientific research on the extent to which the substances boost testosterone levels is scant and conflicting. In a 1962 study some women showed a 300 percent testosterone increase an hour after taking androstenedione. But Ziegenfuss's initial research with 4-androstenediol, the results of which were to be presented at a meeting in November, showed only a meager 45 percent testosterone increase 90 minutes after ingestion. A different mode of administration, though, which he would not identify, resulted in a 100 percent increase in blood testosterone levels.

"Whether it's large enough to impact performance, we don't really know," Ziegenfuss cautions. He also notes that no studies have evaluated the efficacy and physiological effects of taking more than one steroid supplement at once, as many bodybuilders are now doing. Anecdotal evidence suggests that "stacking" certain supplements in this manner can be more effective than taking a single one.

Although the physiological mechanisms underlying over-the-counter steroids may not be exactly the same as those of traditional anabolic steroids, the differences do not impress some experts. "I want them taken off the market," remarks Yesalis, the author of two books on performance-enhancing drugs.

Derek W. Cornelius, whose company, Syntrax Innovations, manufactures and markets all of the steroid supplements,

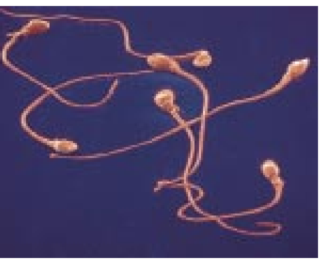
IN BRIEF

Mini-Mammal

When the Society of Vertebrate Paleontology met in October, Jonathan Bloch of the University of Michigan presented a very small find—in size, at least: a fossil jaw from the tiniest mammal ever discovered. A distant relative of shrews , the creature, named *Batodonoides*, weighed no more than 1.3 grams. Its existence challenges earlier theories about the smallest body that can be supported by a warm-blooded physiology (small bodies generally do not retain body heat as well as large ones); for its size, *Batodonoides* must have been extremely active. Bloch came across the remains within limestone that was taken from the badlands in Wyoming and dates to some 65 to 37 million years ago.

His Pill

Male contraceptives may one day be based on a discovery reported this past fall in *Science*. Postdoctoral fellow Chunghee Cho and his colleagues at the University of California at Davis found that sperm lacking the protein fertilin-beta can rarely get near an egg, let alone penetrate it, even though these sperm look and move like any other. The group studied mice lacking the gene for fertilin-beta, a binding protein found on cell surfaces. As it turned out, the fertility rate in these animals was 98 percent less than that in normal mice.



DAVID PHILLIPS *Photo Researchers, Inc.*

Falling Thermosphere

Chicken Little had a point: part of the sky *is* falling. According to a recent paper in the *Journal of Geophysical Research*, the height of the earth's upper atmosphere—the thermosphere, 300 kilometers above the earth, and the ionosphere, 70 kilometers above—has dropped eight kilometers in the past 38 years. The finding is based on more than 600,000 echo-sounding signatures taken by researchers at the British Antarctic Survey (BAS) and Rutherford Appleton Laboratory. As the thermosphere cools, atmospheric pressure drops, which in turn lowers the level of the ionosphere. BAS attributes the cooling to increased greenhouse gas emissions, which trap heat in the lower atmosphere but help to radiate it away in the upper atmosphere.

More "In Brief" on page 28

insists that "the abuse potential of these supplements is low," noting that they are all intended to be taken orally and that much of the product is therefore destroyed in the liver. For comparison, some traditional anabolic steroids are injected intravenously or taken through the skin via a patch.

Ziegenfuss, however, notes that "many of the deleterious effects you see from [anabolic steroids] are related to the use of some synthetic oral compounds, which have harmful effects on the liver." He adds that "although there's no reason at this point to expect androstenedione or androstenediol to have toxic effects on the liver, I wouldn't call these compounds abuse-proof." —*Glenn Zorpette*

PHYSICS

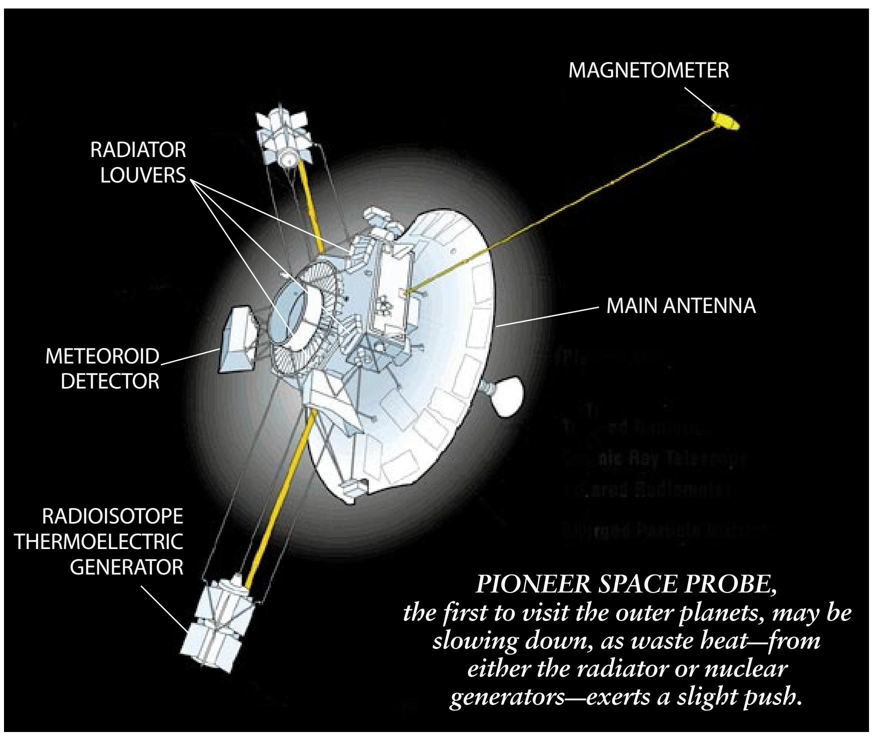
PIONEERING GAS LEAK?

The strange motions of two space probes have mundane explanations—probably

Scientists are victims of their own success: as theories improve, it becomes harder to distinguish genuinely new phenomena from boring experimental errors. The recent announcement of discrepancies in the motions of distant space probes is a case in point. When Pioneer 10 and 11—launched in 1972 and 1973 to visit Jupiter and Saturn—ventured beyond the realm of the nine planets in the early 1980s, researchers began monitoring their orbits for evidence of the long-hypothesized Planet X. They found no such planet, in accordance with later observations, but they did notice that the Pioneers have been slowing down faster than predicted by Einstein's general theory of relativity. Some extra tiny force—equivalent to a ten-billionth of the gravity at Earth's surface—must be acting on the probes, braking their outward motion.

"I started out looking for Planet X but stumbled on this instead," says John D. Anderson of the Jet Propulsion Laboratory in Pasadena, Calif. In 1994 Michael Martin Nieto of Los Alamos National Laboratory and his colleagues suggested that the anomaly was a sign that relativity itself had to be modified.

This past August Anderson and his team reported its refined analysis, which rules out a variety of less seditious interpretations, such as instrumental error, interplanetary gas, the gentle push exerted by sunlight and the gravity of planets, comets and distant stars. They also found hints of the anomaly in the two other deep-space missions that would feel such a force, Galileo and Ulysses. (The successors to the Pioneers, Voyager 1 and 2, would not be sensitive to the effect, because



PIONEER SPACE PROBE, *the first to visit the outer planets, may be slowing down, as waste heat—from either the radiator or nuclear generators—exerts a slight push.*

LAWRENCE E. LASHER/NASA AMES RESEARCH CENTER

In Brief, *continued from page 26*

Water World

Good news from the U.S. Geological Survey: despite a growing population, Americans are using 2 percent less water than they did in 1990 and 10 percent less than in 1980. Indeed, freshwater per-capita use dropped from 1,340 gallons a day in 1990 to 1,280 gallons a day in 1995. Before 1980, U.S. water use had steadily increased since 1950. The USGS reports that enhanced citizen awareness, improved irrigation techniques and heightened efficiency have helped turn the trend around.

PHOTO RESEARCHERS, INC.

Zapped by a Magnetar

On August 27 a burst of gamma rays and x-rays struck the earth's upper atmosphere, disrupting radio signals and high-flying spacecraft for about five minutes. Umran Inan of Stanford University and his colleagues observed the pulse and based on its intensity—which sparked as much electrical activity in the ionosphere as our neighborhood sun—believe its source was a rare type of neutron star, a magnetar, which has a powerful magnetic field. Kevin Hurley of the University of California at Berkeley calculated that such a magnetar must have released enough energy to power all of human civilization for a billion billion years to have created the August event.

HIV Insight

Two recent discoveries regarding HIV strains could have a significant impact on treatment strategies. First, researchers from the St. Gall Cantonal Hospital in Switzerland and the University of North Carolina have found that the HIV strains manufactured in an infected man's blood rarely match those in his reproductive organs—nor do they respond to the same drugs. Thus, therapies must attack both. And a second group from the National Cancer Institute and the Food and Drug Administration has found how cytokines—chemical messengers in the immune system—can switch the HIV virus from an M-tropic strain, prevalent during early infections, to a T-tropic strain, which is most common during full-blown AIDS. Blocking the switch might help stall the onset of symptoms.

More "In Brief" on page 34

they frequently fired their rockets; the compounded imprecision of these maneuvers would conceal any anomaly.)

Within two months after Anderson's paper appeared on the Internet (xxx.lanl.gov/abs/gr-qc/9808081) and made the front pages, three scientists responded with possible explanations. Two invoke waste heat. As the spacecraft radiate excess infrared radiation out into space, they should recoil ever so slightly. An infrared power of 85 watts, if beamed away from the sun, would suffice to impart the tiny anomalous force. Jonathan I. Katz of Washington University proposes that this power could arise from slight asymmetries in how the onboard nuclear generators dispose of heat. The radiation might reflect off the back of the radio dish and stream away from the sun.

Edward M. Murphy of Johns Hopkins University notes that the 85-watt figure roughly equals the power consumption of the Pioneer instrumentation. As electricity courses through the circuitry, most of its energy is dissipated as heat and dumped into space by a radiator on the side of the spacecraft opposite from the sun.

Finally, Philip A. Laing of Aerospace Corporation near Los Angeles, who is a member of Anderson's team, argues that the spacecraft are venting fuel into space. A leak of just two grams per year, less than 0.01 percent of the total fuel supply, would do the trick. Laing says Pioneer shuddered unexpectedly in 1990 and 1992, a sign that a valve in the propulsion system was stuck.

Unfortunately, Anderson responds, each explanation has its own shortcomings. Waste heat reflected off the back of the antenna would be too unfocused. Dissipated electrical power is not the answer, either, because the acceleration did not diminish as the power consumption dropped over the years. And gas leaks had already been observed in the tracking data and accounted for. Even so, Anderson agrees that these explanations—perhaps acting in combination—are more palatable than refuting Einstein. Indeed, if relativity were wrong, similar anomalies should appear in the motions of the planets. They do not.

Yet one thing gives researchers pause. The value of the anomaly matches the critical acceleration in a new law of motion devised 15 years ago by Mordehai Milgrom of the Weizmann Institute of Science in Rehovot, Israel. The scheme, known as MOND, has steadily gained adherents because it explains galactic motions without recourse to "dark matter," material inferred by traditional laws of motion but never actually seen. MOND modifies Newton's second law (force equals mass times acceleration) for accelerations less than a critical value.

At these low accelerations—which scientists have seldom studied—weird quantum or cosmological effects may reduce the inertia of objects. A given gravitational force would then have a stronger effect on bodies. In one version of MOND, bodies within the solar system receive a constant boost, as seen in the Pioneer data. Moreover, objects in elongated orbits, such as these probes, could indeed be affected differently from those in nearly circular orbits, such as the planets.

Anderson is analyzing the latest velocity data for Pioneer 10, which is currently 71 times as far from the sun as Earth is. (The tracking system on Pioneer 11 failed eight years ago.) Meanwhile Murphy is working with Pioneer project manager Lawrence E. Lasher of the National Aeronautics and Space Administration Ames Research Center to dust off the old engineering manuals and reconstruct what happened on board the probes. At the very least, the anomalous acceleration has proved how sensitive scientists, as well as their spacecraft, are to the most modest irregularity.

—George Musser

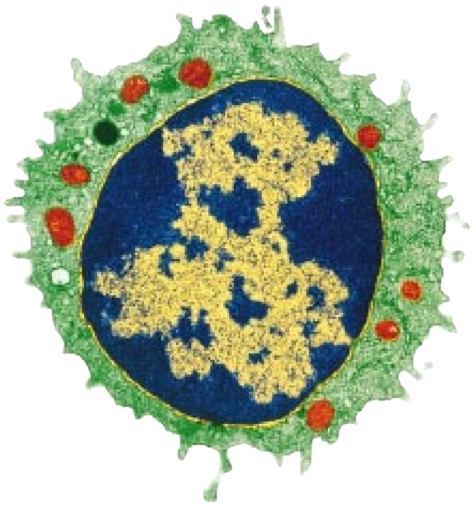
ENDOCRINOLOGY

LEAPING LEPTIN

Evidence of the fat-regulating hormone is turning up in immune system cells and blood vessel linings

What do body weight, the immune response and the growth of new blood vessels have in common? The answer, according to several recent studies, is a hormone called leptin.

Within the past few months, researchers have discovered receptors for leptin—which was originally identified because of its link to obesity in mice—in newly sprouting capillaries and in the T cells of the immune system. The findings are changing scientists' views of the hormone and are suggesting that leptin might be involved in conditions as diverse as compromised immunity and cancer.



DON FAWCETT *Photo Researchers, Inc.*

WHAT'S A FAT HORMONE DOING HERE? *Receptors for leptin found on T cells may explain why malnourished people have suppressed immunity.*

Leptin caused a media flurry in 1995, when Jeffrey M. Friedman of the Rockefeller University and his colleagues showed that injections of leptin could shrink mice that were bloated with fat because they lacked the gene for the hormone. The researchers suggested that fat cells normally produce leptin to tell the brain how fat the body is and, therefore, whether an organism should eat more or stop eating.

In the September 11 issue of *Science,* M. Rocío Sierra-Honigmann of the Yale University School of Medicine and her co-workers reported running across receptors for leptin while studying the endothelial cells that line human blood vessels. As part of exploring what the function of leptin might be in the vasculature, the researchers implanted pellets containing leptin into the corneas of rats—a common test to determine whether a substance causes blood vessel growth, or angiogenesis. To their surprise, new blood vessels infiltrated the corneas of rats with leptin implants. In contrast, the corneas of rats that received implants containing a saline solution remained clear.

Two weeks earlier, in the August 27 issue of *Nature,* Graham M. Lord and his associates at the Imperial College School of Medicine in London had reported another odd finding concerning leptin. In seeking an explanation for why underweight, malnourished people have an increased susceptibility to infectious diseases, the researchers added leptin to cultures of white blood cells called T helper, or CD4, cells. By secreting various chemicals called cytokines, CD4 cells prompt other cells of the immune system either to produce antibodies or to become specialized killer cells in response to an infection.

Lord and his co-workers found that mice that had been starved for 48 hours had an impaired immune response: when injected with an irritant, the starved animals' ears swelled to only one third the size of the ears of fed mice. But when the starved mice were given leptin, they reacted as strongly as the fed mice.

What do these two studies mean? Lord says they are evidence that leptin is a multipurpose hormone and that its role in weight regulation might be simply the tip of the iceberg. Sierra-Honigmann agrees. "Focusing on leptin as just a hormone that regulates appetite is not the full story," she asserts.

Lord claims that it makes sense for the body to rein in its ability to generate a specific immune response—which requires extra energy—when it is starving. On a practical level, he suggests that his group's results might help explain why vaccines are ineffective in people experiencing a famine.

Sierra-Honigmann emphasizes that the findings of her group could indicate how fat deposits gain a blood supply when someone puts on weight. She speculates that the results might also yield clues to why people with cancer sometimes become dangerously thin, a condition known as cachexia. Cancer cells are known to secrete other factors that foster angiogenesis. If they also produce leptin, it could have the secondary effect of reducing a person's weight. "It's a very exciting possibility," she says.

But Jeffrey S. Flier of Beth Israel Deaconess Medical Center in Boston urges caution in interpreting the new studies. He suggests that they might reflect incidental functions of leptin that do not play an important role in the body. "In each case, the question is whether the activity [of leptin] is biologically relevant," he comments. "It's unclear whether it's an adaptive response to damp down your immune response when you're undernourished, for example."

In the meantime, early results are in from the ongoing clinical trials of leptin as a treatment for obesity. In June, Amgen in Thousand Oaks, Calif., reported at an American Diabetes Association conference that eight moderately obese people who took the highest dose of leptin lost an average of 16 pounds during a six-month study. But 37 others taking lower doses lost much less weight—some as little as 1.5 pounds—even though all were also on a calorie-restricted diet. *—Carol Ezzell*

BY THE NUMBERS

Two fifths of the world's people live under tyranny, while another two fifths live under governments that often act arbitrarily and unaccountably. The remaining one fifth live in Western-style democracies, in which their political and civil rights are generally respected, although minorities are sometimes not accorded the full protection of the law.

The worst countries—those in which basic rights were denied in 1997—are coded on the map as "poor." These countries have been designated as "not free" by Freedom House, a Washington, D.C.–based group that has been tracking human rights since 1941. Among the worst are Saudi Arabia, which denies suspects the right to counsel, and Afghanistan, where women cannot leave their homes without a male relative. For sheer, arbitrary violence, few rival Algeria, where Islamic groups are pitted against the army, with both sides periodically committing mass murders of adults, children and infants. Not shown on the map separately but in the same poor group are Freedom House's worst-rated territories: East Timor and West Papua (Indonesia), Kashmir (India), Kosovo (Yugoslavia) and Tibet (China).

Human rights in the three most populous countries in the poor group may be improving: in Iran the moderate Mohammed Khatami was elected president in 1997; in Indonesia the authoritarian government of President Suharto was replaced this year by the possibly more tolerant government of B. J. Habibie; and in Nigeria the despotic Sani Abacha was replaced by Abdulsalam Abubakar, who released political prisoners and promised that an elected government would take over in May 1999.

In the "intermediate" group of countries, citizens have limited political rights and civil liberties under regimes that are often weak and corrupt. The governments in these countries typically use their power to violate citizens' rights by, for example, detaining suspects for extended periods without charge or trial or holding so-called prisoners of conscience. Governments that do not (or cannot) prevent widespread ex-

Human Rights throughout the World

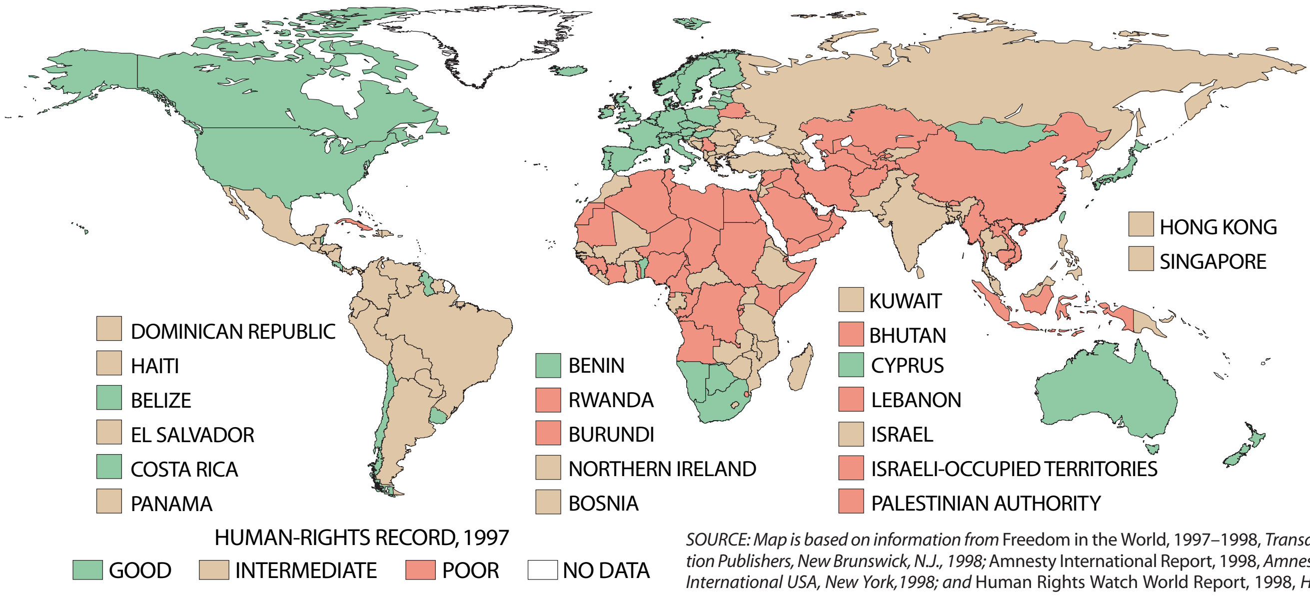
trajudicial executions by police or security forces also qualify a country for inclusion in the intermediate category. Russia is included because it held prisoners of conscience and because provincial authorities harassed human-rights activists in 1997. In India thousands of political prisoners, including prisoners of conscience, were held, and the police, army and paramilitary organizations were responsible for a number of extrajudicial executions. In Brazil police and death squads linked to the security forces conducted hundreds of extrajudicial executions. In Hong Kong, also in the intermediate category, residents retained some rights after the handover to China: trials remained fair, and there was no overt press censorship, although self-censorship was common.

Israel is an unusual case. Citizens have substantial rights, but because they can be detained without charge, and because journalists must submit articles on security issues to military censors, Israel is classified as intermediate. In the Israeli-occupied territories, however, the military regime is harshly repressive; therefore, these areas are classified as poor. Human rights in the area administered by the Palestinian Authority are also poor.

The classification of "good" encompasses all Western-style democracies. In these countries, human rights are secure, except in some cases for minorities and immigrants. Among the latter groups that suffer from police brutality and inadequate protection under the law are Arabs in France; Turks in Germany; Albanians in Italy; blacks, Pakistanis, Indians and Gypsies in the U.K.; Gypsies in the Czech Republic and Hungary; Aborigines in Australia; and blacks, Hispanics and Native Americans in the U.S.

A recent study by Human Rights Watch of 14 major American cities found that none had adequate accountability for police misbehavior—a widespread problem among democracies. Among the industrial democracies, the U.S. and Japan are the only countries enforcing the death penalty for ordinary crimes (crimes other than treason). In the past 25 years, 467 people were executed in the U.S, and as of mid-1998, there were 3,474 on death row, more than half of them minorities. According to one count, 23 innocent people were executed in the 70-year period ending in 1974.

On December 10, 1948, the U.N. General Assembly adopted the Universal Declaration of Human Rights. Conditions have improved in the 50 years since then: most people of the former Soviet empire are freer than before, the states of southern Africa are now democratic, and racial oppression has been legally banished from the American South. But of the world's 10 most populous countries, only two—the U.S. and Japan—have good human-rights records. —*Rodger Doyle (rdoyle2@aol.com)*



SOURCE: Map is based on information from Freedom in the World, 1997–1998, *Transaction Publishers, New Brunswick, N.J., 1998;* Amnesty International Report, 1998, *Amnesty International USA, New York, 1998; and* Human Rights Watch World Report, 1998, *Human Rights Watch, New York, 1997. Data from all three organizations are for 1997.*

RODGER DOYLE

POPULATION

THE POPULATION SLIDE

Fertility in some poor countries is taking a nosedive

In 1975 a typical Bangladeshi woman would have had seven children in her lifetime; today she would probably have three. This sudden decline, known as a fertility transition, is the most extreme case in a pattern that has emerged throughout South Asia. It occurred first in Sri Lanka, then in India and most recently in Bangladesh and Nepal.

The drop has demographers baffled. In the West, fertility started falling after an advanced stage of development had been reached. But the new declines are not directly correlated with such commonly cited factors as increased literacy or alleviation of poverty: Bangladesh remains one of the 20 poorest countries in the world.

Some observers, such as Sajeda Amin of the Population Council in New York City, credit the Bangladeshi success to the government's intensive family-planning program. It includes a cadre of 24,000 women, often covered from head to toe in traditional Islamic robes, who penetrate the innermost sanctums of rural homes with supplies of contraceptives and advice about health.

But although such efforts have provided essential access to contraception, they are working because Bangladeshis have also decided to have fewer children. In 1975, when asked how many children she wanted, a typical woman would reply four. Today she would say two. And back then, she was four times more likely to offer a fatalistic response, such as, "It is up to God." Now she is confident that it is up to her.

(If her two children are both girls, however, a woman is likely to have another child. Under Islamic law, she gets no inheritance from her husband unless she has borne him a male child, and without one she will most likely end up impoverished and homeless.)

Demographers agree that the fertility transition is ultimately caused by a drop in mortality. Once a couple realizes that their children are likely to survive, they can give birth to fewer infants and still be sure of being cared for in their old age. But according to Sonalde Desai of the University of Maryland, it used to be 50 years before a mortality drop led to the fertility transition; now it is taking barely 10. And in Bangladesh, the connection is especially weak: infant mortality had remained at the rather high level of about 14 per 100 live births for two decades preceding the fertility transition.

Another oft-cited trigger for the transition is microcredit, an idea pioneered by Bangladeshi economist Muhammed Yunus. Since the 1970s, his Grameen Bank of Bangladesh and another private organization, the Bangladesh Rural Advancement Committee (BRAC), have been making small loans to poor rural men and women. Monitoring by peers replaces collateral, leading to a repayment rate of more than 90 percent. Currently three million Bangladeshis, mostly women, have access to such credit, which they use to set up small ventures.

Although the programs have clearly been beneficial, their impact on fertility is hard to decipher. Both Grameen and BRAC require grantees to take a set of resolutions, one of which is to have small families. Women do use contraceptives more consistently when they belong to Grameen. More curiously,

SHEHZAD NOORANI *Still Pictures*

LESSONS IN FAMILY PLANNING, provided by female workers of the Bangladesh government, have contributed to a fertility drop.

women in villages where Grameen operates are more likely to use contraceptives than women in other villages, even if they are not Grameen members.

Such an effect may come from an unconscious bias in Grameen's choice of villages. On the other hand, it could be that the bank's messages are diffusing throughout the community. Amin points out that microcredit programs were too small in the late 1970s, when the fertility transition began, to have been directly responsible for it. They might, she concedes, have had a catalytic effect.

Another factor for the transition, cited by Moni Nag of Columbia University, is less pleasant. The early 1970s were traumatic for Bangladesh. A bloody war with Pakistan led to the nation's birth, which was followed by severe floods, crop failures and famines. These events highlighted the vulnerability of women: many were raped in the war, and many more women than men died in the floods and famines. The resulting upheaval in the social order—large numbers of women left their homes to become manual laborers—may, in a bizarre twist, have forced women to take more control of their fates.

But Adrienne Germain of the International Women's Health Coalition in New York City takes issue with such poverty-driven reasoning for the drop. Bangladesh, she points out, is no longer the "basket case" it was once labeled by former U.S. secretary of state Henry Kissinger: it has seen quite a bit of development. "Even though demographers can't seem to measure it," Germain adds, "there's been an enormous change in the status of women." She holds that such empowerment, combined with better health care and education, will be essential to Bangladesh's maintaining its momentum.

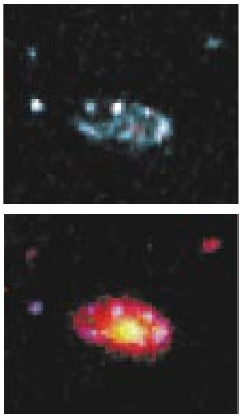
The final explanation for the population puzzle may lie in the information age. Bangladeshi radio provides six hours of health and family-planning programming a day. "People seem to think it is irresponsible to have large numbers of children because of overpopulation," Amin remarks. Such awareness, remarkable in a people that cannot be sure of getting two square meals a day, suggests that media messages can on occasion replace literacy. Across the border in the Indian state of West Bengal, fertility has also dropped, in a radial pattern around the city of Calcutta. Evidently, urban centers serve to somehow disseminate the idea that small families are better.

Ultimately, Bangladesh offers few lessons that policy makers can apply to other regions of the world; everything seems to have played a role. Perhaps the good news is that even the simplest ideas are worth trying. —*Madhusree Mukerjee*

In Brief, continued from page 28

Deeper Deep Field

Three years ago the Earth-orbiting Hubble Space Telescope aimed its Wide Field Planetary Camera 2 (WFPC2) at what was thought to be an empty patch of sky, dubbed the Hubble Deep Field. The results revealed scores of far-off galaxies and strange, lumpy blue knots of light.



NASA AND RODGER I. THOMPSON *University of Arizona*

Now the craft has reexamined the region using the Near-Infrared Camera and Multi-Object Spectrometer (NICMOS), which has a greater viewing range. In comparison, the infrared pictures show many more distant galaxies—some of which are probably 12 billion years old. Also, the NICMOS pictures suggest that the mysterious blue clumps in the optical set are simply areas of intense star formation within otherwise ordinary galaxies. See our Web site at www. sciam.com/exhibit/101998hubble/index.html for more information.

Sliming Around

Egbert Hoiczyk and Wolfgang Baumeister of the Max Planck Institute for Biochemistry in Martinsried, Germany, have at last figured out how gliding bacteria get around—and in doing so, they've discovered a new, unusual organelle. Using modern microscopy and image analysis, the pair found that gliding bacteria propel themselves by continually secreting slime fibrils, which attach at one end to the cell and at the other to the surface it is on. The fibrils are shot out as a slime jet of sorts from a porelike structure that spans the entire bacterial cell wall.

Golden Harvest

It sounds too good to be true, but scientists in New Zealand have found a way to coax plants into collecting gold from ore in the soil. Robert R. Brooks of Massey University and his co-workers treated the soil around *Brassica juncea*, or Chinese mustard plants, with ammonium thiocyanate, a compound often used in mining operations to make gold soluble. The plants then accumulated gold in their tissues. The researchers think that if they use soil rich with gold ore—and gold prices remain steady—their biomining technique might prove financially viable. *—Kristin Leutwyler*

SA

ANTI GRAVITY

A Leg to Stand On

A very old, very bad story talks about this guy who happens onto a farm where he notices a pig with a wooden leg. Naturally, he asks the farmer about his asymmetrical companion and gets told that this pig is indeed some special porker. (The correct telling of this joke takes about 12 minutes, so we'll just summarize.) Turns out the pig saved the farmer's family by running through the house and waking them up during a fire. So, the guy asks, he lost his leg in the blaze? No, the farmer explains. A pig that great, you don't eat him all at once.

A very new, very good story is the one about Primrose, a burro in Colorado, which, like the limping pig in the joke, happens to have an artificial leg. At the age of three weeks, Primrose was attacked by dogs, which bit her legs severely. A resulting infection led to bone damage that under most circumstances would have led to the burro being destroyed. But this particular region of Colorado, near the state university at Fort Collins, happens to be home to Carl and Theresa Conrath. This husband-and-wife team have combined their backgrounds in human prosthetics and veterinary science to create an unusual specialty and family business: Veterinary Brace and Limb Technologies, which literally helps animals get a leg up once again.

The couple had designed braces for horses, which despite leg injuries still had value. They also had created artificial limbs for dogs. But an amputation on a larger animal was virtually a death sentence.

"With a small animal," Theresa Conrath explains, "you can amputate a leg, and it can get around on three." (This is definitely true. In what would have been one of the more embarrassing moments in the history of bicycling, a three-legged sheepdog almost chased me down once on a rural road. My initial sympathy for his paucity of limbs turned to outrage at his excess of cheek.) Bigger beasts, however, have different issues. "With a large animal, the way it transfers its weight, you can't do that," she says. If the animal compensates at all for the missing limb, joint and other health problems could arise. So amputations and prostheses for large animals simply haven't been considered. The Conraths' attitude about that was basically the same as my ambitious sheepdog's: hey, it's worth a try.

University veterinarians were familiar with the Conraths, thanks to their previous collaborations on dogs and some birds of prey. So when the amputation recently was performed, by a surgeon ironically named Trotter, the Conraths were ready. Animal prosthetics is old-fashioned trial-and-error stuff, and the Conraths burro-sat Primrose for two weeks so they could make minor adjustments to the false leg and administer some physical therapy.

Now life's a holiday on Primrose's lane. "Oh, yeah," Theresa says, "she's running and playing and bucking and kicking."

Were anyone to be on the wrong side of a Primrose prosthetic kick, he or she would feel the sting of two pounds of nylon, fiberglass, carbon fiber and acrylic resin. And it's the development of these incredibly strong, lightweight materials that makes the Conraths think that prosthetics for large animals may have more of a place in veterinary practice. Will the future, in a boon to the manufacturers of umbrella stands, see elephants tromping around on false legs? "I'm less experienced with elephants," Theresa admits, "but with the materials we have now, we can realistically do a horse."

Given the alternative to false legs, horses everywhere will no doubt greet this news by finally getting rid of those long faces. *—Steve Mirsky*

MICHAEL CRAWFORD

Smashing through Science's Glass Ceiling

As the new head of the National Science Foundation, Rita R. Colwell seeks to bring environmental research into the information age

Rita R. Colwell knows all about the "glass ceiling" in science—an unsubtle sexism that denies important positions to women. When she was still in high school in the 1950s, her chemistry teacher announced that chemistry was not a profession for women. And after Colwell gained a bachelor's degree in bacteriology (with distinction) at Purdue University, her department chairman denied her request for a fellowship to earn a master's degree, explaining that the department did not waste them on women. "Of course, you wouldn't hear that now," adds Colwell, who is 64. "What would happen is that they'd simply say, 'Well, they've all been given out.'" And gender discrimination in science, she declares, "gets worse the higher you go."

Despite the career-thwarting efforts of some academics, Colwell has gone just about as high as you can go in science. After making pivotal discoveries about *Vibrio cholerae*, the bacterium that causes cholera, she became in 1987 head of the University of Maryland's Biotechnology Institute and in 1995 began a one-year stint as president of the American Association for the Advancement of Science. Recently Colwell assumed a post that makes her one of the most powerful scientists in the federal government. As director since August of the National Science Foundation (NSF), she is responsible for a $3.5-billion budget that supports most of the nonbiomedical civilian research in the U.S. The first woman to head the agency and the first biologist in 25 years, she brings to the job a radical agenda to support an expansion of funding for information technology, enhanced efforts in science and math education, and a new focus on what she terms "biocomplexity."

Biocomplexity is Colwell's name for an interdisciplinary approach to biodiversity, sustainability and ecosystem studies that puts a heavy emphasis on hard-nosed quantitative modeling. She gives as an example how it is now possible to extract DNA from soil, analyze it and learn about biological processes in the sample without even culturing whatever bacteria are present.

Work on chaos theory and fractals points to recurrent themes in biological organization that researchers are now equipped to analyze, she suggests. Colwell, who seems to wear a perpetual slightly worried expression, declares that her goal is to build up from the ecological interactions in a crumb of soil "to see how the planetary system works." She told a gathering of science writers in September that "our survival depends" on being willing to take on such grand challenges. She added that the attitude of some scientists that educating the public is not their responsibility "really has to change."

SAM KITTNER

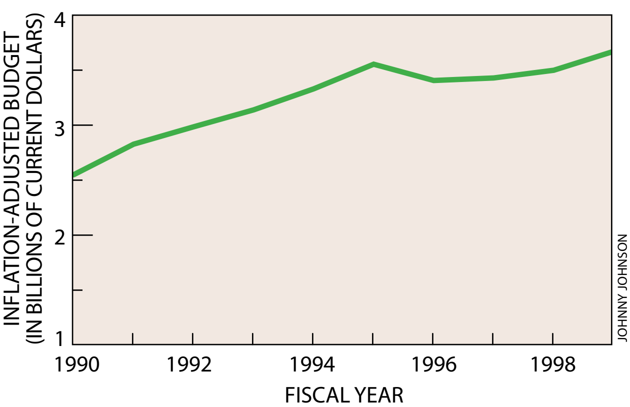
***FASTER COMPUTER NETWORKS** and better software will open up new domains of biological science and reveal unrecognized patterns in medical and climatic databases, Rita R. Colwell says.*

Colwell's ambitions to further ecosystem modeling will only be realized with advances in computing power. She thinks important scientific and medical findings lie today unnoticed in archives of climatic and medical and census data. And she is not alone in rooting for faster computers.

An interagency advisory committee concluded earlier this year that the U.S. is "gravely underinvesting" in long-term research in information technology. The panel recommended that the federal government spend $1 billion over the next five years to ensure that the U.S. stays at the forefront of developments, with top priority for software development. "I think it's the most important thing the United States can do," says Colwell, whose agency will most likely be responsible for a large part of the response.

Scientific passion notwithstanding, Colwell has a diplomat's deftness at sidestepping awkward questions and a politician's skill at reaching out to a constituency. At the meeting in September, she ably deflected a complaint about how meetings of the National Science Board, which advises the NSF, are now less accessible to the press than they were a few years ago. Colwell answered by talking about the increasing use of teleconferencing. After a riff on biocomplexity she takes care to point out that she also wants to nurture the NSF's traditional disciplines of physics and, especially, mathematics.

Discerning the influences that have shaped Colwell's distinctive vision of future science is not hard. In the 1960s she was the first researcher in the U.S. to develop a computer program to analyze bacteriological taxonomic data, an effort that led her to the then radical conclusion that the strain of cholera found in outbreaks of disease belong to the same species as harmless strains do. Like them, the harmful strain is, she discovered, widely distributed in estuaries and coastal waters, although it passes through a dormant phase that makes it hard to detect. Disease occurs only when people drink water containing more than a million or so of the bacteria per teaspoonful.



GROWTH OF THE NSF BUDGET
would make many agencies envious (1999 is estimated).

Now, Colwell says, scientists can track the pathogenic strain of cholera in the environment quite precisely. The bacterium, which has caused thousands of deaths in Asia in the past decade, is found in the guts of common zooplankton called copepods. If the sea becomes unusually warm, one consequence may be a bloom of phytoplankton, which in turn leads to an increase in the number of copepods feeding on them. The result is that humans are more exposed to *V. cholerae*. By analyzing satellite data, Colwell has linked cholera in Bangladesh to phytoplankton blooms. She and her colleagues at the University of Maryland are now investigating whether outbreaks can be prevented by straining the copepods out of drinking water with sari cloth. (After floods, inhabitants of poor countries often have no means of boiling water, she points out.)

Colwell's interest in bacteria was stimulated by a gifted teacher at Purdue. After her rebuff by the bacteriology department, she earned a master's degree in genetics before moving with her husband, Jack Colwell (now a physicist at the National Institute of Standards and Technology), to the University of Washington to do research for a Ph.D. Her first academic adviser there, a prominent geneticist, gave her "no support," although "time was taken" with male graduate students. Colwell eventually found a more "nurturing" adviser.

The difficulties of being the wrong sex were not yet over. In 1961 Colwell was offered a postgraduate position with Canada's National Research Council in Ottawa, where her husband had a fellowship. But the Canadian agency decided that its antinepotism rule forbade it from offering fellowships to husbands and wives simultaneously, so it withdrew its offer of financial support to Rita Colwell. She made an end run by obtaining funds to work there from the U.S. agency she now heads.

Later, at Georgetown University as an associate professor (and the first faculty woman in science), Colwell realized that although her department chairman was a supporter, she might have a long wait to become a full professor. Things "work slower for women," she says. Colwell's husband was criticized by some of his colleagues for letting his wife work, and the wife of one of those colleagues passed on the unsolicited advice that Colwell's two daughters would not succeed in life because of their mother's career.

The concern was misplaced. During what she describes as the feel-good era of education in the 1970s, Colwell and her husband spent hours teaching their children spelling and arithmetic. When one daughter had difficulty with math, her father realized the textbook was wrong and spoke to the girl's teacher. The teacher told him not to worry because "she's attractive, and girls aren't good at math."

Ignoring the teacher's advice, Colwell and her husband prevailed on their daughters to stick with math as far as calculus and chemistry as far as organic. Colwell says that if parents encourage their children to study science at least to that level, they will "have the opportunity to do everything they want to." One daughter now has a Ph.D. in biology; the other has an M.D. and is working toward a Ph.D.

Colwell was recruited to the University of Maryland as a full professor in 1972. She believes that "every child can be educated in basic science and math" and holds that "if we undermine and leave behind a part of our population, we leave behind every other goal."

Although the NSF spends about $600 million a year on education, Colwell suspects its current programs focus too much on the most common learning strategies. She is convinced that children employ a variety of ways to acquire knowledge: some benefit from visual aids, some learn by rote and some think in abstract, mathematical ways. Colwell plans to ensure that the NSF's efforts employ more varied approaches to learning.

The thrust will involve drawing on the latest findings of neuroscientists and might include a partnership with the National Institutes of Health. The NSF is already developing a program that would require graduate students to teach not in their university but in elementary, middle and high schools, under the guidance of qualified teachers.

The NSF has done reasonably well in the annual battle for federal funds in recent years, gaining an annualized inflation-adjusted increase of 44 percent since 1990. But it has not done as well as the NIH, so Colwell will have to fight for the NSF's share of the research pie.

Her Maryland colleagues say she is well qualified for the task. Her political nous was responsible for obtaining $52 million in federal funds for the university's biotechnology institute. Gaylen Bradley, the institute's vice president for academic affairs, says that Colwell has a "unique ability to present to audiences ranging from Brownies to congressmen and their aides to fellow scientists." She is also likely to bring an internationalist perspective to the NSF, Bradley believes. Christopher D'Elia of the Biotechnology Institute says that Colwell "is a workaholic, in the best sense" and that she is able to get the best out of people. Basic research seems to have a strong new champion in Washington, and male chauvinists had better take refuge.

—Tim Beardsley in Washington, D.C.

OPTICS

SHADING THE TWINKLE

Telescope that shuts out starlight could spy new planets

Astronomers have surmised the existence of a dozen or so planets outside the solar system by the "wobble" in light received by telescopes as a planet orbits around a nearby star and exerts its gravitational pull on the gaseous body. A real picture of an extrasolar planet, however, is worth a thousand wobbles. But these images are not often there for the taking. A parent star, millions of times brighter than a planet, simply washes out the lesser image.

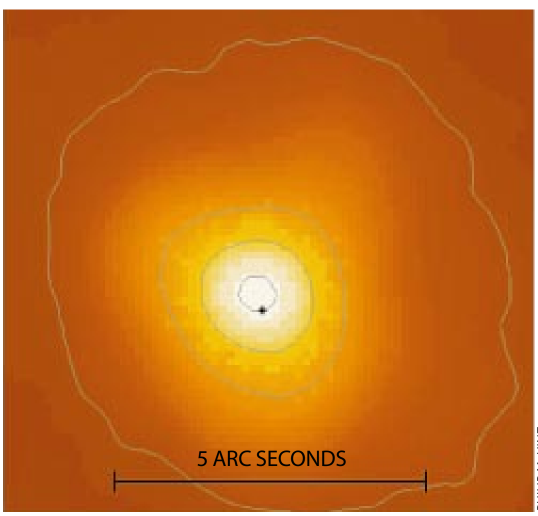
An experiment reported in a recent issue of *Nature* by the Center for Astronomical Adaptive Optics at the University of Arizona at Tucson marked an important step toward building an instrument capable of taking planetary snapshots. Philip M. Hinz and his collaborators demonstrated a starlight-shading device, called a nulling interferometer, that was fitted to the Multiple Mirror Telescope on Mount Hopkins in Arizona.

Nulling interferometry, which was first proposed by Ronald N. Bracewell of Stanford University in 1978, has generated increasing interest in recent years. J. Roger P. Angel and Neville J. Woolf, two researchers from the University of Arizona's Steward Observatory who are co-authors on the paper, have led efforts to refine the technique.

The experiment on the Multiple Mirror Telescope marked the first time a nulling interferometer had actually been mounted on a telescope. The interferometer canceled out light from Betelgeuse, a star in the constellation Orion. Astronomers could then discern a dust cloud, or nebula, around the star. The image was the first direct one of the Betelgeuse dust cloud ever produced. "The star just plain disappeared, and they were able to see something that was vaguely known about—an infrared-emitting cloud," Bracewell remarks.

The Multiple Mirror Telescope experiment used two mirrors mounted five meters (16 feet) apart on a rigid frame. When the star is at an exact right angle to the frame connecting the two mirrors, its light is canceled out. The light waves hitting one of the mirrors are inverted: wave peaks become troughs. The inverted light then interferes with the waveforms from the other mirror, darkening both the core area of the star and its surrounding halo.

At the same time, the light from a planet even a short distance away from the star is not in perfect alignment with the interferometer. So the light waves reaching the mirrors interfere constructively: the crest and troughs coincide, enhancing the planet's illumination. The experiment demonstrated that a nulling interferometer could detect an object as little as 0.2 arc second from a star—an arc second being $^1/_{3,600}$ of a degree. This distance is farther from the star than the range for the method that looks for a star's wobble but is far less than the minimum for any other direct technique that tries to blot out starlight.



PHILIP M. HINZ

***DUST CLOUD AROUND BETELGEUSE** can be seen with nulling interferometry. The plus sign denotes the star's position.*

The work will help further projects to build telescopes that incorporate nulling interferometry. "It was a good starting point to refine the technology and figure out what is needed to make a more precise interferometer," Hinz says.

Beginning in 2003, the Large Binocular Telescope, which is under construction on Mount Graham in Arizona, will use nulling interferometry and should be able to image Jupiter-size planets close to nearby stars. This telescope will boast improved resolution because of its larger size and its ability to employ adaptive optics: minute adjustments to the surface of the mirror will correct for distortions in the received light caused by turbulence in Earth's atmosphere.

Just over a decade from now, the National Aeronautics and Space Administration plans to launch a space-based nulling interferometer, called the Terrestrial Planet Finder, that may be able to spot extrasolar planets no bigger than Earth. If an Earth-size planet is discovered, the observations of the infrared light will be subjected to spectroscopic analysis to determine whether it harbors an atmosphere and whether that atmosphere contains the ozone, carbon dioxide and water that suggest that life might be present. So blotting out starlight may eventually provide a glimpse of other worlds like our own. —*Gary Stix*

BIOCHEMICAL ENGINEERING

WHERE NO BRUSH CAN REACH

Scientists engineer bacteria to prevent corrosion in pipes

Medical researchers have long known that not all of the bacteria in dental plaque fosters tooth decay. And years ago some investigators began working to create vaccines against the destructive ones, in hopes that eliminating them might prevent more cavities than trying to kill all microbes present would. Now materials scientists have started thinking in similar terms about the bacterial films that coat the inside of water-carrying metal pipes. They plan to use genetically engineered strains of bacteria to prevent corrosion of such conduits, a problem that affects many industrial settings, from cooling systems to electric power stations and sewage treatment plants.

Researchers are going to such extremes because biologically induced corrosion of metal pipes is hard to prevent. Paint invariably wears off, and dosing the water with biocides is costly and can threaten the environment when released. Substituting a tougher metal (say, stainless steel for iron) can help a great deal but is often prohibitively expensive. So why not attack the bacteria responsible for speeding corrosion?

The plaquelike "biofilm" that gets established inside metal piping is largely composed of oxygen-loving bacteria, which themselves do little damage. "It's the sulfate-reducing bacteria that are the principal villains," explains David C. White, a microbial ecologist at the University of Tennessee. These oxygen-hating bacteria reside where the biofilm meets the metal. As they carry out their normal metabolic reactions, the sulfate reducers cause the metal atoms to lose electrons and hence to float away. This dissolution forms small pits in the metal, which can grow into cracks and ultimately cause a pipe to fail.

"Initially, we thought we'd put down protozoa and have them eat the sulfate-reducing bacteria," explains Thomas K. Wood, a biochemist at the University of Connecticut, who with James C. Earthman of the University of California at Irvine pioneered the idea of using beneficial microbes to protect pipes. The two researchers then hit on a more promising strategy: to have the oxygen-loving bacteria secrete a poisonous peptide molecule to destroy the sulfate reducers. "The real goal here is to insert the gene [for the peptide] into a bacterium that is already thriving," Wood says. That capability would allow engineers to take whatever harmless strain is already living inside a particular industrial facility, modify that microbe and then put it back so it can kill the deleterious sulfate-reducing bacteria.

"If they could do that—the yogurt treatment of a cooling tower—that would be terrific," remarks White, referring to the common home remedy of replacing pathogenic organisms in a patient with the benign ones from yogurt. Although a patent for the process was filed last May, the researchers are still a long way from demonstrating that the scheme truly works. "We've only tested in laboratory-prepared media," Earthman freely admits. But with the help of the people who manage the physical plant on his campus, he has recently set up a realistic arrangement for examining the effect of the engineered bacteria in pipes carrying cooling water.

The test piping is isolated from the main circulation, so Earthman has not had to grapple with regulatory requirements involved in releasing genetically engineered bacteria into the environment. Yet he and the other researchers promoting this approach expect to face that hurdle soon.

Even if environmental regulators allow these genetically engineered organisms to be used in industrial facilities, there is no guarantee that the bacteria already living there will permit the interlopers to prosper. The engineered organisms might be so much less fit than the "wild" ones that they die off. The researchers are well aware that bacterial competition may ultimately prove to be an insurmountable problem. Nonetheless, they are optimistic. As Wood notes, "We still think this has a fighting chance." —*David Schneider*

SOFTWARE

BEATING THE TEMPEST

Software to defeat electronic eavesdropping of computer monitors

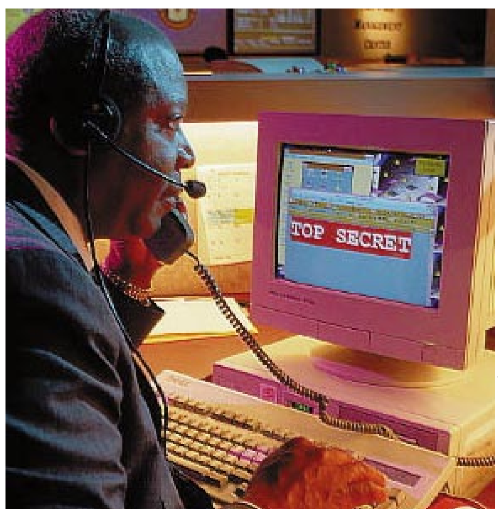
Just because you're paranoid doesn't mean they aren't out to get you. Most computer users would be startled to realize that somebody parked outside their home with the right kind of (very expensive) receiving equipment can read the data that appear on their computer screens. The receiver uses the monitor's radio emanations to reconstruct the screen's contents. The U.S. Department of State and other organizations spend a fortune buying shielded hardware to defeat these signals, known as Tempest radiation, after the code name for a government program aimed at tackling it.

Now Ross Anderson, a computer scientist at the University of Cambridge, and graduate student Markus G. Kuhn say they have developed methods for controlling Tempest radiation. What's different about their techniques is that they run in software, making them much cheaper and easier to deploy.

The story began, Anderson says, when Microsoft made its $20-million investment in Cambridge's computer science lab and said the company was particularly interested in ways to control software piracy. Most approaches call for some kind of copy protection; Anderson's idea was to design something that would enable detection of offenders rather than prohibit copying, which is a nuisance loathed by consumers. Their concept was to make computer screens broadcast the serial number of the software in use. In principle, properly equipped vans could patrol business districts looking for copyright infringements. In researching the broadcast idea, Anderson and Kuhn came up with fundamental discoveries about Tempest.

In particular, they observed that emissions relating to screen content are mostly found in the higher bands—above 30 megahertz, in the UHF and VHF bands. So altering those frequencies could change the Tempest radiation.

Anderson and his colleagues have fashioned a couple of prototypes that rely on different frequency-alteration methods. One of the lab's prototypes, built using a black-and-white video display capable of monitoring and receiving Tempest radiation, filters the top frequencies. As a result, the fonts become unreadable to the eavesdropping receiver. On-screen, the fonts look comfortably legible and nearly normal. Filtering text requires display software that supports grayscale representation of fonts, but most computers have this ability. Therefore, Anderson believes this technology could be easily built into existing machines, although the fonts' interference with graphics makes it more likely they would be included in a security product than in, say, a general operating system.



ROGER RESSMEYER *Corbis*

***I KNOW WHAT YOU TYPED LAST SUMMER:* new programs can foil electronic spies.**

The second prototype takes advantage of the display technique known as dithering, a method of mixing extra colors from a limited palette based on the principle that if the dots that make up the display are small enough, the human eye will perceive the mix as a solid color. Given a monitor of today's high resolutions, the human eye cannot distinguish between a solid medium gray and a pattern of black-and-white pixels that adds up to the same gray. But the pattern of black and white is much easier for the snooping receiver to detect, one consequence being that the computer could be programmed to broadcast a different signal from the one that actually appears on the screen. The demonstration on display at Anderson's lab serves as a nice example, in which the word "Oxford" on the display appears as "Cambridge" on the receiver.

Aside from stemming electronic eavesdropping, these prototypes could open the way to new types of security attacks on computers, Anderson and Kuhn suggest. A virus could be designed to find and then broadcast information stored on a machine without a user's knowledge. The game of spy versus spy goes on.—*Wendy M. Grossman*

WENDY M. GROSSMAN is a freelance writer based in London.

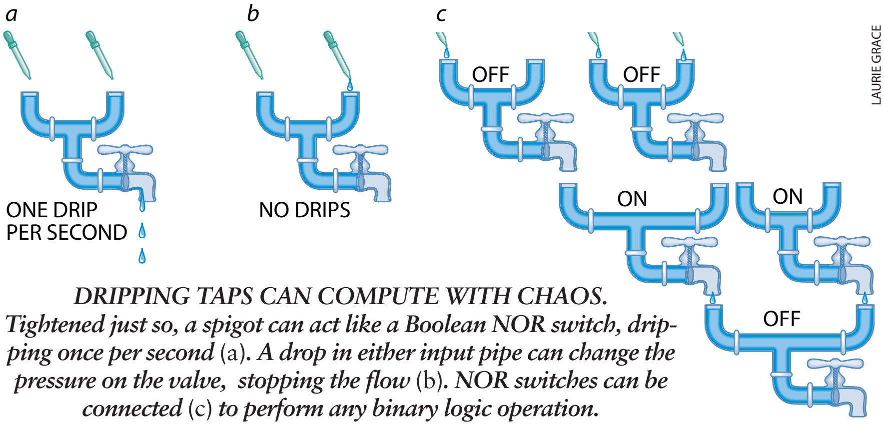
COMPUTER SCIENCE

COMPUTING WITH CHAOS

In the heart of a new machine lies the flakiness of nature

It is a sure sign that a physical science has reached maturity when it yields a new kind of computer. Charles Babbage's brass-geared difference engine crowned 19th-century mechanics, ENIAC's vacuum tubes put atomic theory to a tough test, and microchips proved the power of early materials science. More recently, geneticists have coaxed DNA to do math, and physicists have dodged the uncertainty principle to build simple quantum computers.

Now it appears that chaos theory, the scientific debutante of the 1980s, has grown up as well. In September, William L. Ditto of the Georgia Institute of Technology and Sudeshna Sinha of the Institute of Mathematical Sci-



DRIPPING TAPS CAN COMPUTE WITH CHAOS. Tightened just so, a spigot can act like a Boolean NOR switch, dripping once per second (a). *A drop in either input pipe can change the pressure on the valve, stopping the flow* (b). *NOR switches can be connected* (c) *to perform any binary logic operation.*

ence in Madras, India, published the first design for a chaotic computer. Their novel species of machine would exploit the very instabilities that other kinds of computers do their utmost to squelch.

So far the machines have been only simulated mathematically; it will take several months to actually build one. Daniel J. Gauthier, a chaos researcher at Duke University, says the design is "very interesting" nonetheless because chaotic machines appear able to add and multiply numbers, handle Boolean logic and even perform more specialized calculations. Together, Ditto says, such operations provide the bare necessities needed to make a general-purpose machine. Whereas quantum computers and DNA seem suited to only certain problems, such as code breaking or complex mathematics, chaotic computers might be able to do nearly everything current computers do and more.

Whether they can do so better is an open question. "Better means faster or cheaper, and semiconductors have a huge head start," Gauthier points out. But devices with a heart of chaos will certainly be different.

They will come in many forms. The first machines will probably be assembled out of lasers or analog electronic circuits. But in principle, Ditto says, chaotic computers could be made by connecting a bunch of almost any devices that slip easily into chaos—not randomness, but cyclic behavior that cannot be predicted very far in advance because it is so sensitive to tiny perturbations. The "processors" could theoretically be something as simple as dripping faucets.

Building a computer out of leaky spigots is easier than you might think, and it illustrates well how a chaotic computer would work. If a faucet is very leaky, its drips fall in a chaotic rhythm that varies wildly depending on the water pressure. Slightly leaky faucets, however, drip steadily. So the tap handle can control both the rate of dripping and whether it is regular or chaotic.

To add three numbers—x, y and z—simply place a funnel under three faucets, adjust them to drip x, y and z times a minute, respectively, and then measure how many drops of water leave the funnel after a minute. Boolean logic, the foundation of all digital computing, is only slightly harder. The trick is to set the water pressure and handle position to just the right point at which the spigot drips exactly once per minute if left alone but not at all if a single extra drop of water is added to the pipe behind it. Almost all chaotic systems will have such critical points, and chaos theory tells you how to find them. By arranging many faucets on a wall so that the drips of higher taps start or stop lower faucets leaking, one can program with plumbing.

Of course, Ditto and his colleagues plan to use considerably faster components: advanced lasers that, instead of dripping, send out femtosecond pulses, trillions of which can fit comfortably into one second. "Coupling them together, so that each leaks light into the next, might allow us to perform billions or trillions of calculations per second," he says, giddy at the prospect.

"We're also working on using silicon chips to control living neurons," which behave chaotically, Ditto reports. A web of such cybercells could work on many different parts of a problem at the same time. "This really is a whole new paradigm for computers," Ditto says.

New computing paradigms are claimed entirely too often and too cavalierly. But now that chaos theory has matured from naive science to fulsome technology, perhaps this particular spinster is worth a long, thoughtful look. —*W. Wayt Gibbs in San Francisco*

Hello, Is This the Web?

Every year must have its wildly overhyped computer "breakthrough"; the award for 1998 clearly goes to dictation software—or, as its promoters grandly call it, "speech-recognition technology." Dictation programs rival SaladShooters for the title of all-time champion in the unwieldy-solution-to-an-insignificant-problem category. But this year also saw a truly new approach to polishing computers' conversational skills, an invention that might just do for the telephone what the World Wide Web did for computers.

The contrast between the two technologies is instructive. On one hand, we have a brute-force method that, ever since Apple first introduced voice control of its operating system in 1993, has sucked up every last processor cycle and bit of memory available as it attempts to match your utterances to words in its dictionary. Every year, as computers have grown in power, programmers have added a little grammar checking here, a touch of learning ability there—always just enough smarts to bring your computer to its knees.

Now half a dozen competing software packages claim to boost the efficiency and even the creativity of your writing by cutting out the keyboard. They are selling briskly because they are new and because most reviewers, awed by the sight of a computer doing its own typing, have played down the systems' frequent errors as mere stumbles on a march to greatness.

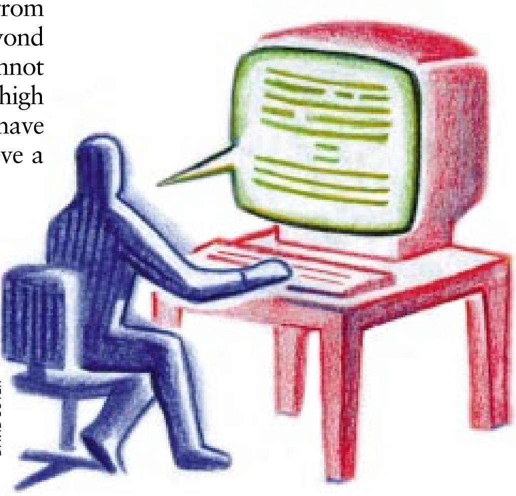
But the pundits tend to overlook three fundamental problems that will most likely prevent dictation software from ever serving an audience much beyond the small fraction of people who cannot use keyboards. The first obstacle is high expectations. Even those of us who have never been privileged enough to have a personal secretary know how dictation is supposed to work. It's easy: you press a button, you say, "Margie, take a letter," and then you talk, and Margie types. Secretaries understand English, so they stick commas and periods in (roughly) the right places. And they don't make inane mistakes, such as writing "pickled pumpkins" when you say, "Pick a number in."

Even the best dictation programs, however, know less about the meaning of words than the average kindergartner. They cannot punctuate, and their errors, which are alarmingly easy to miss when proofreading because they are always correctly spelled, can make you look either stupid or insane.

A second problem is that even when dictation software works perfectly, it saves many keystrokes but little time. The laborious part of writing is the thinking and the editing, not the typing. And proofreading the computer's shoddy work can easily fritter away the few minutes saved by automation.

Journalists have created most of the hype surrounding dictation software, so it makes sense to look to them for evidence of its utility. After all, if any large profession could get a serious productivity boost from the speech-recognition "breakthrough," it ought to be journalism. We reporters are constantly writing dispatches and taking dictation, in the form of interview notes. The ability to plug a tape recorder into the computer, walk away and return to a verbatim transcript could shave hours, not mere minutes, from our work.

But when I contacted several journalists who had recently written glowing reviews of dictation products, I discovered that not one was using the software in his daily writing. In my experience, even the most highly acclaimed package—the $700 professional version of Dragon Systems' NaturallySpeaking software—is paralyzed with confusion when presented with the recorded speech of a stranger. And that is the third flaw of brute-force dictation: it only recognizes voices that it has been trained to understand. It will be many years before that limitation will fall.


DAVID SUTER

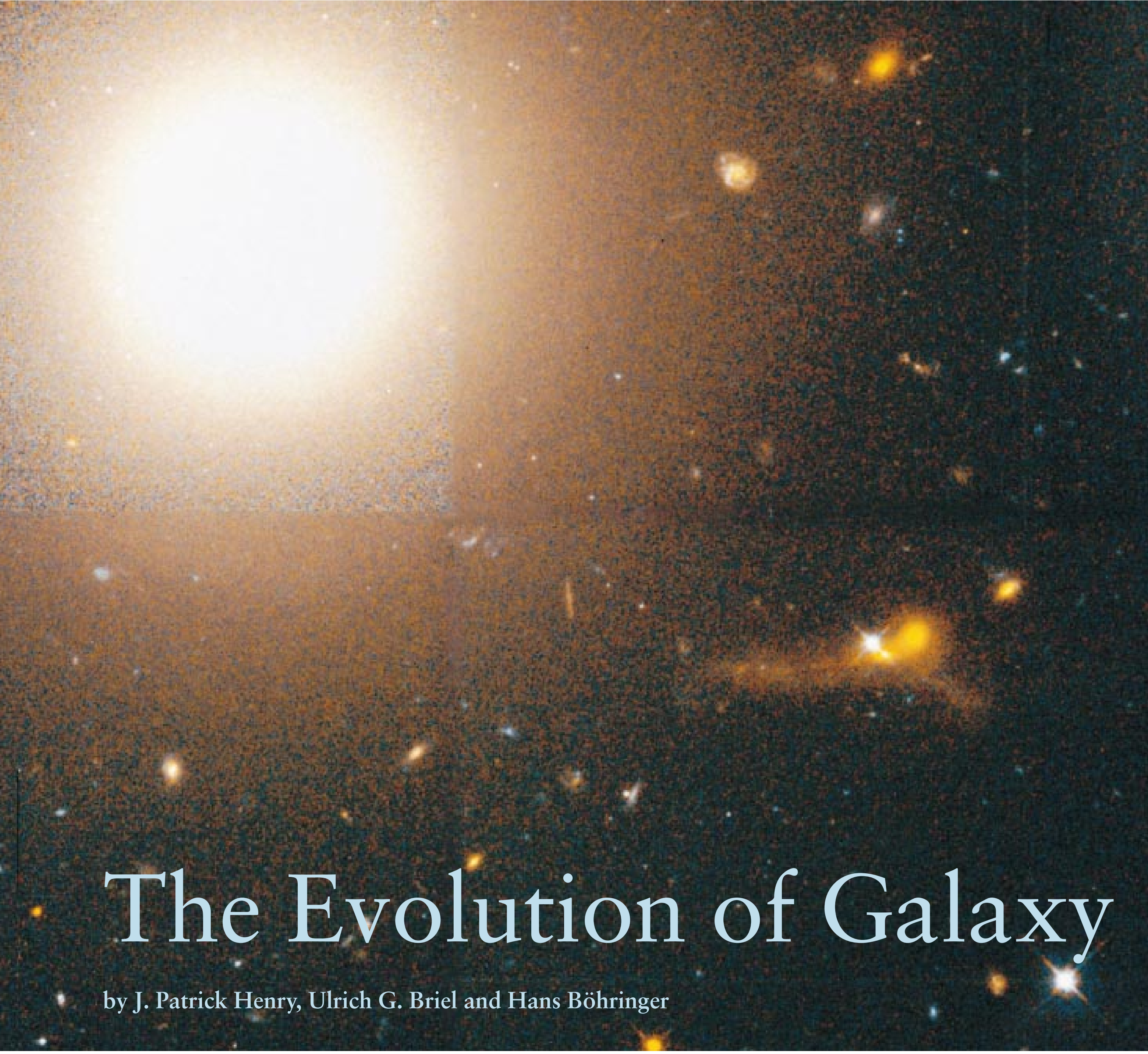
In the meantime, however, a much simpler approach may soon have us all talking to computers. In October, Motorola unveiled a computer language called VoxML that is designed to let people use the Internet via telephone. It works in a way analogous to the hypertext markup language (HTML) pages on the Web. The difference is that the information is formatted not for display by a Web browser but for a conversation between a user and a "voice browser"—a program that can interpret spoken commands and can speak itself. Users will call a central voice service provider (such as Motorola or perhaps America Online) and talk to the voice browser software there.

The first pilot applications of the new technology are all fairly obvious ones. The Weather Channel built a VoxML site that allows callers to request forecasts for several major cities; the company plans to extend the service to include all the forecasts in its database. CBS MarketWatch is serving up stock quotes. Biztravel.com offers flight status information.

None of that is very new: there have long been numbers that you can call to press one for weather, two for stock quotes and so on. What is significant about VoxML is not that it makes such services less annoying by replacing "press one" with "say 'weather' " but that it makes it relatively cheap and easy for anyone to offer them. With just a few days' work, Mark J. Wladika, chief software engineer for KnowledgeWeb, Inc., adapted the daily horoscope database on his firm's Astrology.Net Web site to work under voice control. "I didn't need to know anything about speech recognition or speech synthesis; the voice browser does all the hard work," he says.

How useful would it be for a driver to pick up a cell phone, dial the Internet and tap into the Yellow Pages to find the nearest gas station or Italian restaurant? For a traveler to use an airport pay phone to check e-mail or to pull up a sales figure from the company database? For a poor single parent to call up the CIA's *World Factbook* to help her child with a homework question? A lot more useful than a $3,000 dictation machine.

—*W. Wayt Gibbs in San Francisco*



The Evolution of Galaxy

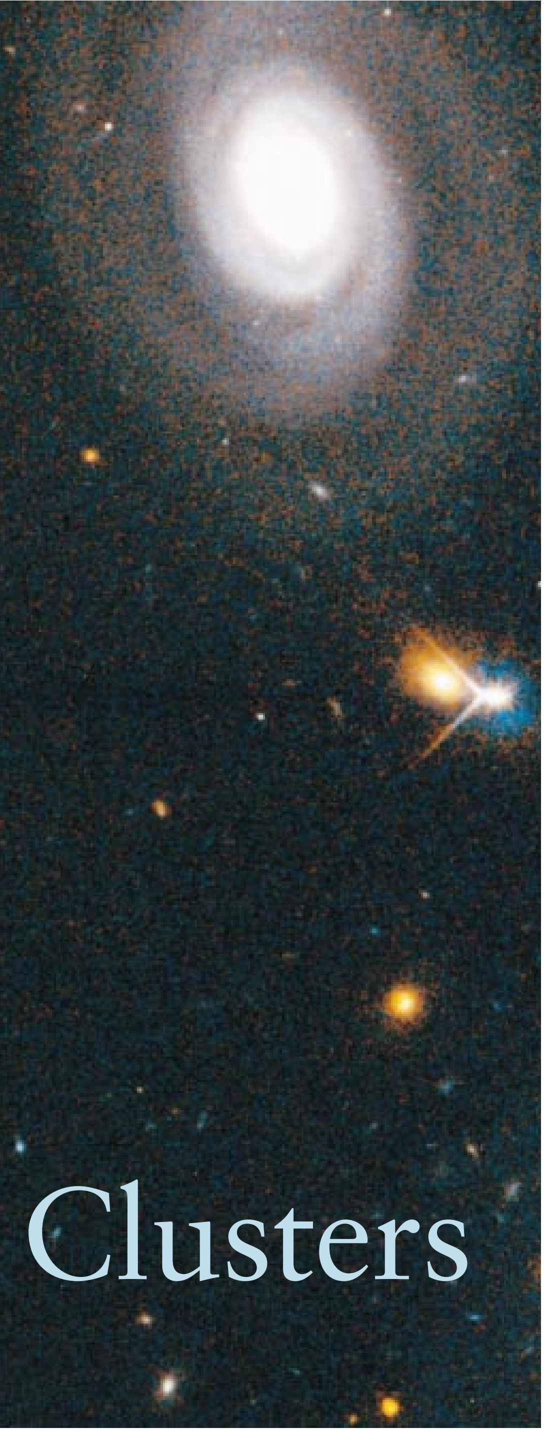
by J. Patrick Henry, Ulrich G. Briel and Hans Böhringer

The royal Ferret of Comets was busy tracking his prey. On the night of April 15, 1779, Charles Messier watched from his Paris observatory as the Comet of 1779 slowly passed between the Virgo and Coma Berenices constellations on its long journey through the solar system. Messier's renown in comet spotting had inspired the furry moniker from King Louis XV, but on this night he took his place in astronomy history books for a different reason. He noticed three fuzzy patches that looked like comets yet did not move from night to night; he added them to his list of such impostors so as not to be misled by them during his real work, the search for comets. Later he commented that a small region on the Virgo-Coma border contained 13 of the 109 stationary splotches that he, with the aid of Pierre Mechain, eventually identified—the Messier objects well known to amateur and professional astronomers today.

As so often happens in astronomy, Messier found something completely different from what he was seeking. He had discovered the first example of the most massive things in the universe held together by their own gravity: clusters of galaxies. Clusters are assemblages of galaxies in roughly the same way that galaxies are assemblages of stars. On the cosmic organizational chart, they are the vice presidents—only one level below the universe itself. In fact, they are more massive relative to a human being than a human being is relative to a subatomic particle.

In many ways, clusters are the closest that astronomers can get to studying the universe from the outside. Because a cluster contains stars and galaxies of every age and type, it represents an average sample of cosmic material—including the dark matter that choreographs the movements of celestial objects yet

The most massive objects in the universe are huge clusters of galaxies and gas that have slowly congregated over billions of years. The process of agglomeration may now be ending



Clusters

WILLIAM A. BAUM *University of Washington*, HUBBLE SPACE TELESCOPE WFPC TEAM AND SPACE TELESCOPE SCIENCE INSTITUTE

TWO BRIGHT GALAXIES in the Coma cluster, one elliptical (*top left*) and the other spiral (*top right*), appear in this composite Hubble Space Telescope image taken in 1994. The Coma cluster, located some 300 million light-years away, was one of the first galaxy clusters identified by astronomers. Most of the other splotches in the image are galaxies at even greater distances.

cannot be seen by human eyes. And because a cluster is the result of gravity acting on immense scales, its structure and evolution are tied to the structure and evolution of the universe itself. Thus, the study of clusters offers clues to three of the most fundamental issues in cosmology: the composition, organization and ultimate fate of the universe.

A few years after Messier's observations in Paris, William Herschel and his sister, Caroline, began to examine the Messier objects from their garden in England. Intrigued, they decided to search for others. Using substantially better telescopes than their French predecessor had, they found more than 2,000 fuzzy spots—including 300 in the Virgo cluster alone. Both William and his son, John, noticed the lumpy arrangement of these objects on the sky. What organized these objects (which we now know to be galaxies) into the patterns they saw?

A second question emerged in the mid-1930s, when astronomers Fritz Zwicky and Sinclair Smith measured the speeds of galaxies in the Virgo cluster and in a slightly more distant cluster in Coma. Just as the planets orbit about the center of mass of the solar system, galaxies orbit about the center of mass of their cluster. But the galaxies were orbiting so fast that their collective mass could not provide enough gravity to hold them all together. The clusters had to be nearly 100 times as heavy as the visible galaxies, or else the galaxies would have torn out of the clusters long ago. The inescapable conclusion was that the clusters were mostly made of unseen, or "dark," matter. But what was this matter?

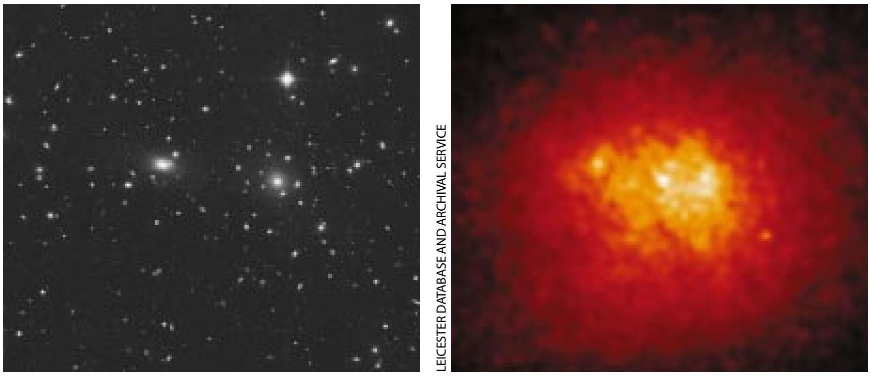
These two mysteries—the uneven distribution of galaxies in space and the unknown nature of dark matter—continue to confound astronomers. The former became especially puzzling after the discovery in the mid-1960s of the cosmic microwave background radiation. The radiation, a snapshot of the universe after the big bang and before the formation of stars and galaxies, is almost perfectly smooth. Its tiny imperfections somehow grew to the structures that exist today, but the process is still not clear [see "Very Large Structures in the Universe," by Jack O. Burns; SCIENTIFIC AMERICAN, July 1986]. As for dark matter, astronomers have learned a bit more about it since the days of Zwicky. But they are still in the uncomfortable position of not knowing what most of the universe is made of [see "Dark Matter in the Universe," by Lawrence M. Krauss; SCIENTIFIC AMERICAN, December 1986].

Light from Dark Matter

Impelled by these mysteries, the pace of discovery in the study of clusters has accelerated over the past 40 years. Astronomers now know of some 10,000 of them. American astronomer George Abell compiled the first large list in the early 1950s, based on photographs of the entire northern sky taken at Palomar Observatory in California. By the 1970s astronomers felt they at least understood the basic properties of clusters: They consisted of speeding galaxies bound together by huge amounts of dark matter. They were stable and immutable objects.

Then came 1970. In that year a new satellite, named Uhuru ("freedom" in Swahili) in honor of its launch from Kenya, began observing a form of radiation hitherto nearly inaccessible to astronomers: x-rays. Edwin M. Kellogg, Herbert Gursky and their colleagues at American Science and Engineering, a small company in Massachusetts, pointed Uhuru at the Virgo and Coma clusters. They found that the clusters consist not only of galaxies but also of huge amounts of gas threading the space between the galaxies. The gas is too tenuous to be seen in visible light, but it is so hot—more than 25 million degrees Celsius—that it pours out x-rays.

In short, astronomers had found some of the dark matter—20 percent of it by mass. Although the gas is not enough to solve the dark matter mystery completely, it does account for more mass than all the galaxies put together. In a way, the term "clusters of galaxies" is inaccurate. These objects are balls of gas in which galaxies are embedded like seeds in a watermelon



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COMA CLUSTER looks different in visible light (*left*) and in x-rays (*right*). In visible light, it appears to be just an assemblage of galaxies. But in x-rays, it is a gargantuan ball of hot gas some five million light-years across.

[see "Rich Clusters of Galaxies," by Paul Gorenstein and Wallace Tucker; Scientific American, November 1978].

Since the early 1970s, the x-ray emission has been scrutinized by other satellites, such as the Einstein X-Ray Observatory, the Roentgen Satellite (ROSAT) and the Advanced Satellite for Cosmology and Astrophysics (ASCA). Our own research mainly uses ROSAT. The first x-ray telescope to record images of the entire sky, ROSAT is well suited for observations of large diffuse objects such as clusters and is now engaged in making detailed images of these regions. With this new technology, astronomers have extended the discoveries of Messier, Zwicky and the other pioneers.

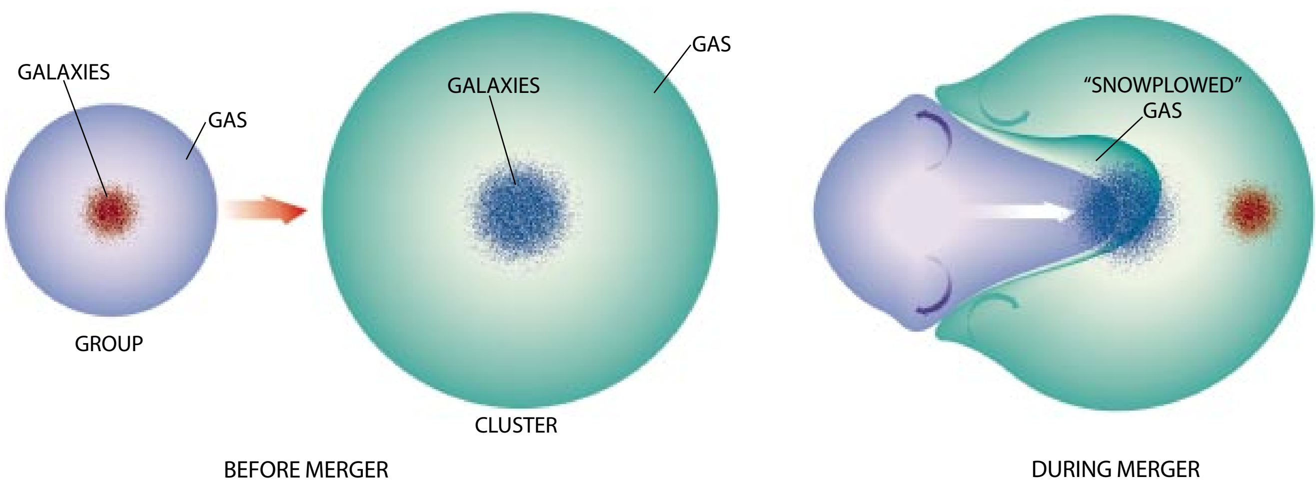
When viewed in x-rays, the Coma cluster has a mostly regular shape with a few lumps [*see left illustration on page 56*]. These lumps appear to be groups of galaxies—that is, miniature clusters. One lump to the southwest is moving into the main body of the cluster, where other lumps already reside. Virgo, by comparison, has an amorphous shape. Although it has regions of extra x-ray emission, these bright spots are coming from some of the Messier galaxies rather than from clumps of gas [*see right illustration on page 56*]. Only the core region in the northern part of Virgo has a nearly symmetrical structure.

Such x-ray images have led astronomers to conclude that clusters form from the merger of groups. The lumps in the main body of the Coma cluster presumably represent groups that have already been drawn in but have not yet been fully assimilated. Virgo seems to be in an even earlier stage of formation. It is still pulling in surrounding material and, at the current rate of progress, will look like Coma after a few billion years. This dynamic view of clusters gobbling up and digesting nearby matter is in stark contrast to the static view that astronomers held just a few years ago.

Taking Their Temperature

Ever since astronomers obtained the first good x-ray images in the early 1980s, they have wanted to measure the variation of gas temperature across clusters. But making these measurements is substantially more difficult than making images, because it requires an analysis of the x-ray spectrum for each point in the cluster. Only in 1994 did the first temperature maps appear.

The maps have proved that the formation of clusters is a violent process. Images of the cluster Abell 2256, for example, show that x-ray emission has not one but rather two peaks. The western peak is slightly flattened, suggesting that a group slamming into the main cluster has swept up material just as a snowplow does. A temperature map supports this interpretation [*see illustration on opposite page*]. The western peak, it turns out, is comparatively cool; its temperature is characteristic of the gas in a group of galaxies. Because groups are smaller than clusters, the gravitational forces within them are weaker; therefore, the speed of the gas molecules within them—that is, their temperature—is lower. A typical group is 50 trillion times as massive as the sun and has a temperature of 10 million degrees C. By comparison, a typical cluster weighs 1,000 trillion suns and registers a temperature of 75 million degrees C; the heaviest known cluster is five



SLIM FILMS

ABSORPTION OF GALAXY GROUP allows a cluster to grow to colossal size. Pulled in by gravity, the group slams into the cluster, pushing gas out the sides. The galaxies themselves pass through the cluster, their progress unimpeded by the tenuous gas. Eventually the galaxies and gas mix together, forming a unified cluster that continues to draw in other groups until no more are to be found.

times as massive and nearly three times as hot.

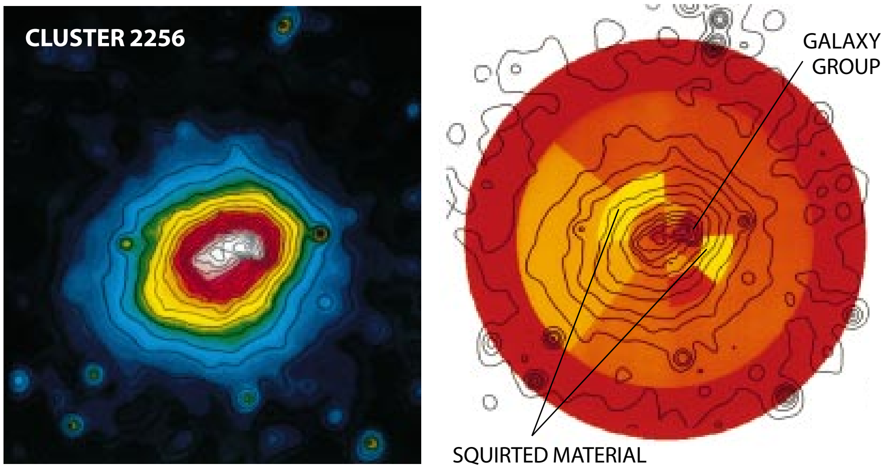
Two hot regions in Abell 2256 appear along a line perpendicular to the presumed motion of the group. The heat seems to be generated as snowplowed material squirts out the sides and smashes into the gas of the main cluster. In fact, these observations match computer simulations of merging groups. The group should penetrate to the center of the cluster in several hundred million years. Thus, Abell 2256 is still in the early stages of the merger.

The late stages of a merger are apparent in another cluster, Abell 754. This cluster has two distinguishing features. First, optical photographs show that its galaxies reside in two clumps. Second, x-ray observations reveal a bar-shaped feature from which the hot cluster gas fans out. One of the galaxy clumps is in the bar region, and the other is at the edge of the high-temperature region to the west.

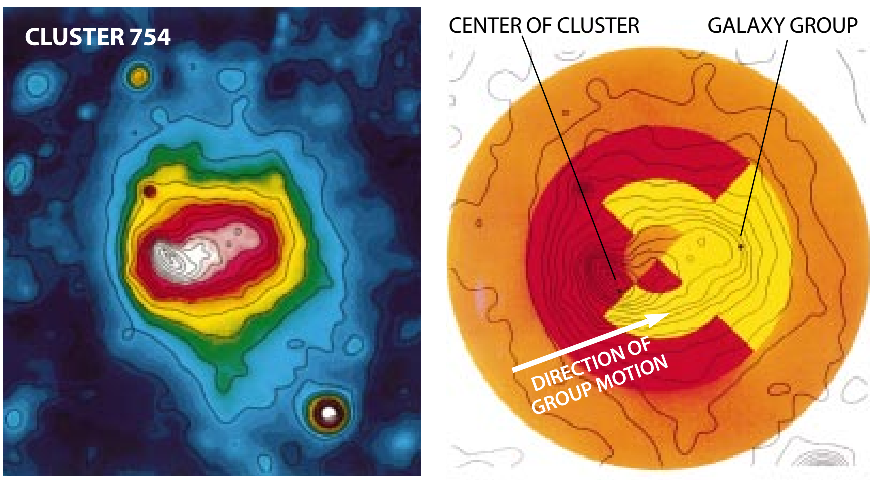
Theorists can explain this structure with an analogy. Imagine throwing a water balloon, which also contains some pebbles, into a swimming pool. The balloon represents the merging group: the water is gas, and the pebbles are galaxies. The swimming pool is the main cluster. When the balloon hits the water in the pool, it ruptures. Its own water stays at the surface and mixes very slowly, but the pebbles can travel to the other side of the pool. A similar process apparently took place in Abell 754. The gas from the merging group was suddenly stopped by the gas of the cluster, while the group galaxies passed right through the cluster to its far edge.

A third cluster, Abell 1795, shows what a cluster looks like billions of years after a merger. The outline of this cluster is perfectly smooth, and its temperature is nearly uniform, indicating that the cluster has assimilated all its groups and settled into equilibrium. The exception is the cool region at the very center. The lower temperatures occur because gas at the center is dense, and dense gas emits x-rays more efficiently than tenuous gas. If left undisturbed for two or three billion years, dense gas can radiate away much of its original energy, thereby cooling down.

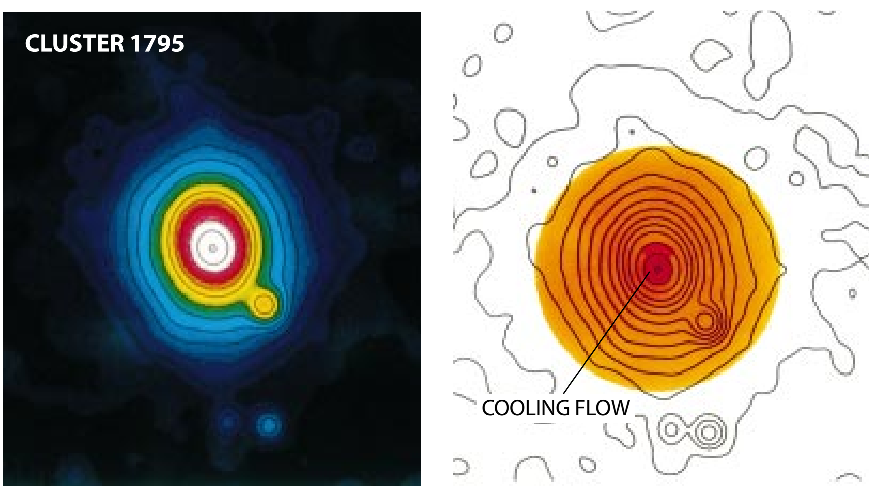
As the gas cools, substantial amounts of lukewarm material build up—enough for a whole new galaxy. So where has all this material gone? Despite exhaustive searches, astronomers have yet to locate conclusively any pockets of tepid gas. That the cluster gas is now losing



THREE GALAXY CLUSTERS are at different stages in their evolution, as shown in these x-ray images (*left column*) and temperature maps (*right column*). The first cluster, Abell 2256, is busily swallowing a small group of galaxies, which is identified by its relatively low temperature. On the map red is comparatively cool, orange intermediate and yellow hot.



The second cluster, Abell 754, is several hundred million years further along in its digestion of a galaxy group. The hapless group probably entered from the southeast, because the cluster is elongated in that direction. The galaxies of the group have separated from their gas and passed through the cluster.



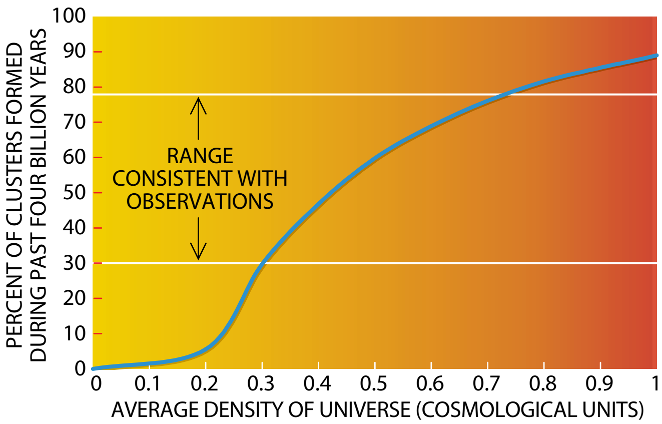
J. PATRICK HENRY, ULRICH G. BRIEL AND HANS BÖHRINGER

The third cluster, Abell 1795, has gone several billion years since its last meal. Both its x-ray brightness and gas temperature are symmetrical. At the core of the cluster is a cool spot, a region of dense gas that has radiated away much of its heat.

From Cluster Evolution to Cosmic Evolution

Ever since the big bang, the universe has been expanding. All objects not bound to one another by gravity or some other force are being pulled apart. But will the cosmic expansion continue forever, or will the gravity of all the matter in the universe be sufficient to halt it? Traditional attempts to answer the question have foundered because they require a careful census of the total amount of matter in the universe—and that is difficult, because most of it is invisible dark matter.

Now there is a new approach made possible by studying the evolution of galaxy clusters. Over time, clusters grow as they accrete matter, until the matter within their gravitational reach is exhausted. The more matter there is, the faster and bigger they can grow (*right*). If the universe has enough matter to come to a halt, then fewer than 10 percent of the massive clusters that exist today were in place four billion years ago—and new clusters should still be forming and growing today. But if the universe has only one quarter of the matter needed to stop its expansion, then all the massive clusters were in place four billion years ago—and no further growth has taken place since then.



SLIM FILMS

The observed cluster evolution rate favors the latter scenario: because galaxy clusters have essentially stopped growing, there must be comparatively little matter in the universe. Therefore, the cosmos will expand forever (unless there exists material with exotic physical properties, such as a gravitational repulsion that varies with time). Other recent measurements of cosmic expansion, using distant supernovae and other markers, agree. Although the case is not closed, several independent pieces of evidence now make it more likely that astronomers do know the ultimate fate of the cosmos. *—J.P.H.*

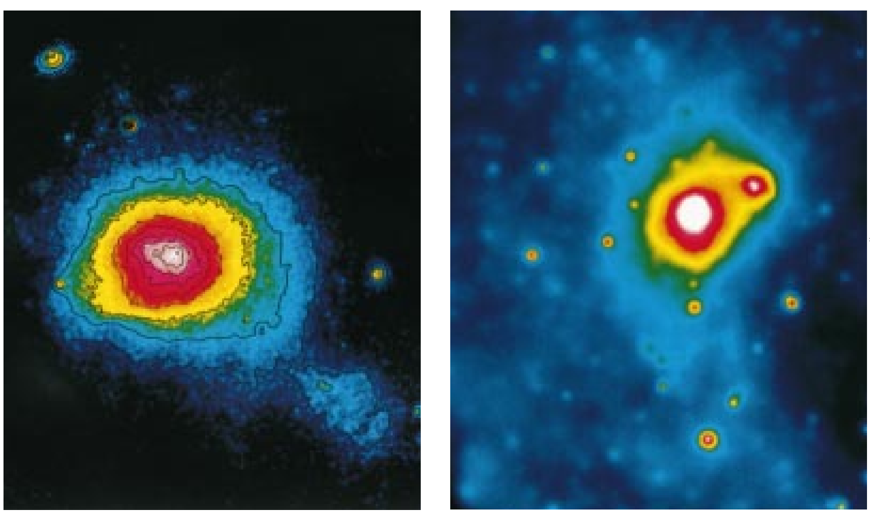
heat is obvious from the temperature maps. Perhaps the heat loss started only fairly recently, or perhaps the collision of galaxy groups prevents cool gas from collecting in one spot. These so-called cooling flows remain yet another unsolved mystery.

Bottoms Up

The sequence represented by these three Abell clusters is probably undergone by every cluster as it grows. Galaxy groups occasionally join the cluster; with each, the cluster gains hot gas, bright galaxies and dark matter. The extra mass creates stronger gravitational forces, which heat the gas and accelerate the galaxies. Most astronomers believe that almost all cosmic structures agglomerated in this bottom-up way. Star clusters merged to form galaxies, which in turn merged to form groups of galaxies, which are now merging to form clusters of galaxies. In the future it will be the clusters' turn to merge to form still larger structures. There is, however, a limit set by the expansion of the universe. Eventually, clusters will be too far apart to merge. Indeed, the cosmos may be approaching this point already.

By cosmological standards, all the above-mentioned clusters (Coma, Virgo, and Abell 2256, 754 and 1795) are nearby objects. Astronomers' efforts to understand their growth are analogous to understanding human growth from a single photograph of a crowd of people. With a little care, you could sort the people in the picture into the proper age sequence. You could then deduce that as people age, they generally get taller, among other visible changes.

You could also study human growth by examining a set of photographs, each containing only people of a certain age—for example, class pictures from grade school, high school and college. Similarly, astronomers can observe clusters at ever increasing distances, which correspond to ever earlier times. On average, the clusters in a more distant sample are younger than those in a nearby one. Therefore, researchers can piece together "class photos" of clusters of different ages. The advantage of this approach is



J. PATRICK HENRY, ULRICH G. BRIEL AND HANS BÖHRINGER

X-RAY IMAGES of Coma (*left*) and Virgo (*right*) clusters show the hot intergalactic gas that dominates the luminous part of these structures. The gas in Coma has a more regular shape than that in Virgo, suggesting that the cluster has reached a more advanced stage of formation. Both clusters are surrounded by infalling material.

that it lets astronomers work with a whole sample of clusters, rather than just a few individual clusters. The disadvantage is that the younger objects are too far away to study in detail; only their average properties can be discerned.

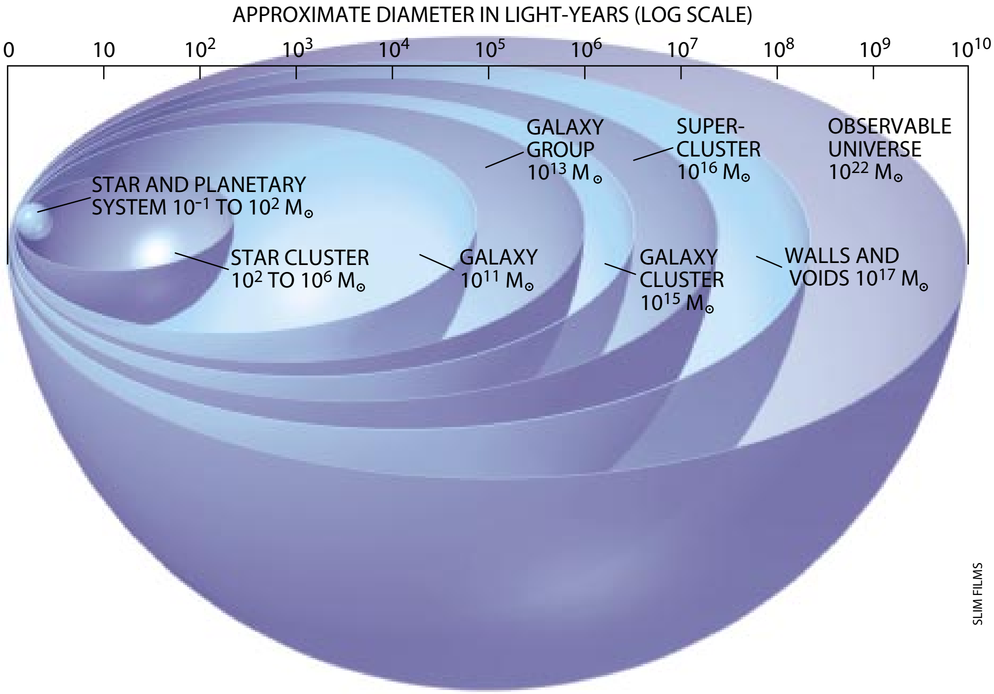
One of us (Henry) applied this method to observations from the ASCA x-ray satellite. He found that distant, younger clusters are cooler than nearby, older ones. Such a temperature change shows that clusters become hotter and hence more massive over time—further proof of the bottom-up model. From these observations researchers have estimated the average rate of cluster evolution in the universe. The rate, which is related to the overall evolution of the universe and to the nature of the dark matter, implies that the universe will expand forever [*see box on opposite page*].

New x-ray observations may shed light on the remaining dark matter in clusters. By the end of 2000 there will be three advanced x-ray observatories in orbit: the Advanced X-Ray Astrophysics Facility from the U.S., the X-ray Multi-mirror Mission from Europe and ASTRO-E from Japan.

In the meantime, observations of another form of radiation, known as extreme ultraviolet light, are yielding mysteries of their own. The extreme ultraviolet has an energy that is only slightly lower than that of x-rays. It is heavily absorbed by material in our galaxy, so astronomers assumed that most clusters are not visible in this wavelength band. But recently Richard Lieu of the University of Alabama at Huntsville, C. Stuart Bowyer of the University of California at Berkeley and their colleagues studied five clusters using the sensitive Extreme Ultraviolet Explorer satellite.

These clusters, they discovered, shine brightly in the extreme ultraviolet. In some ways, this discovery was as unexpected as the first detection of x-rays from clusters in the early 1970s. Although some of the radiation comes from the same gas that generates the x-rays, there appears to be an additional source in at least some of the clusters. This finding is very new and has not yet been explained. Perhaps astronomers are seeing another component of the clusters' dark matter for the first time. The upcoming x-ray facilities may identify this new component.

Those of us involved in this work feel a special bond with Charles Messier as he strained to glimpse those faint patches of light in Virgo, not knowing their true significance. As advanced as our technology has become, we still strain to understand these clusters. We feel a bond with future observers as well, for science advances in a continuous process of small increments. We have been helped by those who preceded us; we share our new understanding with those who follow. SA



HIERARCHY OF COSMIC STRUCTURES ranges from stars and planets to the universe itself. The largest objects held together by gravity are galaxy clusters with masses up to 10^{15} times that of the sun (denoted as $M_\odot$). Although there is a higher level of organization consisting of superclusters and great walls, these patterns are not bound gravitationally. On even larger scales, the universe is featureless. Astronomers think most of these structures form from the progressive agglomeration of smaller units.

The Authors

J. PATRICK HENRY, ULRICH G. BRIEL and HANS BÖHRINGER are x-ray astronomers who study clusters of galaxies. The first two met in the late 1970s while working at the Smithsonian Astrophysical Observatory on one of the instruments on the Einstein X-ray Observatory satellite. Henry is now an astronomy professor at the University of Hawaii. He says he enjoys sitting on his lanai and thinking about large-scale structure while watching the sailboats off Diamond Head. Briel and Böhringer are staff members of the Max Planck Institute for Extraterrestrial Physics in Garching. Briel is an observer who tested and calibrated the ROSAT instrument that made the temperature maps discussed in this article. Böhringer is a theorist who studies galaxy clusters, cosmology and the interstellar medium.

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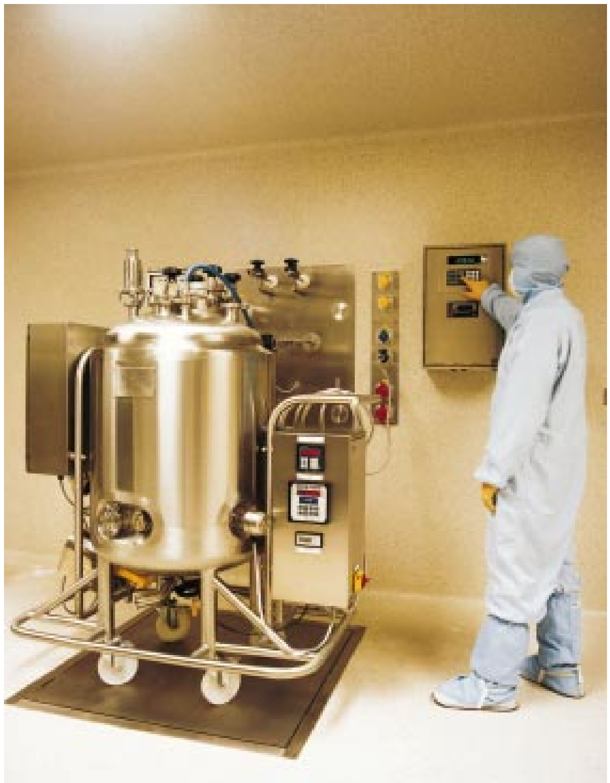
Cloning

Now that genetically modified and copied mammals are a reality, biomedical researchers are starting to develop imaginative ways to use this technology



JOHN CHADWICK PHOTOGRAPHIC AND PPL THERAPEUTICS

RODDY FIELD *Roslin Institute*

In the summer of 1995 the birth of two lambs at my institution, the Roslin Institute near Edinburgh in Midlothian, Scotland, heralded what many scientists believe will be a period of revolutionary opportunities in biology and medicine. Megan and Morag, both carried to term by a surrogate mother, were not produced from the union of a sperm and an egg. Rather their genetic material came from cultured cells originally derived from a nine-day-old embryo. That made Megan and Morag genetic copies, or clones, of the embryo.

Before the arrival of the lambs, researchers had already learned how to produce sheep, cattle and other animals by genetically copying cells painstakingly isolated from early-stage embryos. Our work promised to make cloning vastly more practical, because cultured cells are relatively easy to work with. Megan and Morag proved that even though such cells are partially specialized, or differentiated, they can be genetically reprogrammed to function like those in an early embryo. Most biologists had believed that this would be impossible.

We went on to clone animals from cultured cells taken from a 26-day-old fetus and from a mature ewe. The ewe's cells gave rise to Dolly, the first mammal to be cloned from an adult. Our announcement of Dolly's birth in February 1997 attracted enormous press interest, perhaps because Dolly drew attention to the theoretical possibility of cloning humans. This is an outcome I hope never comes to pass. But the ability to make clones from cultured cells derived from easily obtained tissue should bring numerous practical benefits in animal husbandry and medical science, as well as answer critical biological questions.

How to Clone

Cloning is based on nuclear transfer, the same technique scientists have used for some years to copy animals from embryonic cells. Nuclear transfer involves the use of two cells. The recipient cell is normally an unfertilized egg taken from an animal soon after ovulation. Such eggs are poised to begin developing once they are appropriately stimulated. The donor cell is the one to be copied. A researcher working under a high-power microscope holds the recipient egg cell by suction on the end of a fine pipette and uses an extremely fine micropipette to suck out the chromosomes, sausage-shaped bodies that incorporate the cell's DNA. (At this stage, chromosomes are not enclosed in a distinct nucleus.) Then, typically, the donor cell, complete with its nucleus, is fused with the recipient egg. Some fused cells start to develop like a normal embryo and produce offspring if implanted into the uterus of a surrogate mother.

In our experiments with cultured cells, we took special measures to make the donor and recipient cells compatible. In particular, we tried to coordinate the cycles of duplication of DNA and those of the production of messenger RNA, a molecule that is copied from DNA and guides the manufacture of proteins. We chose to use donor cells whose DNA was not being duplicated at the time of the transfer [*see box on page 60*]. To arrange this, we worked with cells that we forced to become quiescent by reducing the concentration of nutrients in their culture medium. In addition, we delivered pulses of electric current to the egg after the transfer, to encourage the cells to fuse and to mimic the stimulation normally provided by a sperm.

After the birth of Megan and Morag demonstrated that we could produce viable offspring from embryo-derived cultures, we filed for patents and started experiments to see whether offspring could be produced from more completely differentiated cultured cells. Working in collaboration with

for Medicine

by Ian Wilmut

MEGAN AND MORAG (*above*) were the first mammals cloned from cultured cells. That basic technique has allowed the creation of cloned sheep carrying human genes. Such animals produce milk that can be collected and processed (*left*) to yield therapeutic human proteins.

PPL Therapeutics, also near Edinburgh, we tested fetal fibroblasts (common cells found in connective tissue) and cells taken from the udder of a ewe that was three and a half months pregnant. We selected a pregnant adult because mammary cells grow vigorously at this stage of pregnancy, indicating that they might do well in culture. Moreover, they have stable chromosomes, suggesting that they retain all their genetic information. The successful cloning of Dolly from the mammary-derived culture and of other lambs from the cultured fibroblasts showed that the Roslin protocol was robust and repeatable.

All the cloned offspring in our experiments looked, as expected, like the breed of sheep that donated the originating nucleus, rather than like their surrogate mothers or the egg donors. Genetic tests prove beyond doubt that Dolly is indeed a clone of an adult. It is most likely that she was derived from a fully differentiated mammary cell, although it is impossible to be certain because the culture also contained some less differentiated cells found in small numbers in the mammary gland. Other laboratories have since used an essentially similar technique to create healthy clones of cattle and mice from cultured cells, including ones from nonpregnant animals.

Although cloning by nuclear transfer is repeatable, it has

Is Quiescence the Key to Cloning?

All the cells that we used as donors for our nuclear-transfer experiments were quiescent—that is, they were not making messenger RNA. Most cells spend much of their life cycle copying DNA sequences into messenger RNA, which guides the production of proteins. We chose to experiment with quiescent cells because they are easy to maintain for days in a uniform state. But Keith H. S. Campbell of our team recognized that they might be particularly suitable for cloning.

He conjectured that for a nuclear transfer to be successful, the natural production of RNA in the donor nucleus must first be inhibited. The reason is that cells in a very early stage embryo are controlled by proteins and RNA made in the precursor of the parent egg cell. Only about three days after fertilization does the embryo start making its own RNA. Because an egg cell's own chromosomes would normally not be making RNA, nuclei from quiescent cells may have a better chance of developing after transfer.

A related possibility is that the chromosomes in quiescent nuclei may be in an especially favorable physical state. We think regulatory molecules in the recipient egg act on the transferred nucleus to reprogram it. Although we do not know what these molecules are, the chromosomes of a quiescent cell may be more accessible to them. *—I.W.*

limitations. Some cloned cattle and sheep are unusually large, but this effect has also been seen when embryos are simply cultured before gestation. Perhaps more important, nuclear transfer is not yet efficient. John B. Gurdon, now at the University of Cambridge, found in nuclear-transfer experiments with frogs almost 30 years ago that the number of embryos surviving to become tadpoles was smaller when donor cells were taken from animals at a more advanced developmental stage. Our first results with mammals showed a similar pattern. All the cloning studies described so far show a consistent pattern of deaths during embryonic and fetal development, with laboratories reporting only 1 to 2 percent of embryos surviving to become live offspring. Sadly, even some clones that survive through birth die shortly afterward.

Clones with a Difference

The cause of these losses remains unknown, but it may reflect the complexity of the genetic reprogramming needed if a healthy offspring is to be born. If even one gene inappropriately expresses or fails to express a crucial protein at a sensitive point, the result might be fatal. Yet reprogramming might involve regulating thousands of genes in a process that could involve some randomness. Technical improvements, such as the use of different donor cells, might reduce the toll.

The ability to produce offspring from cultured cells opens up relatively easy ways to make genetically modified, or transgenic, animals. Such animals are important for research and can produce medically valuable human proteins.

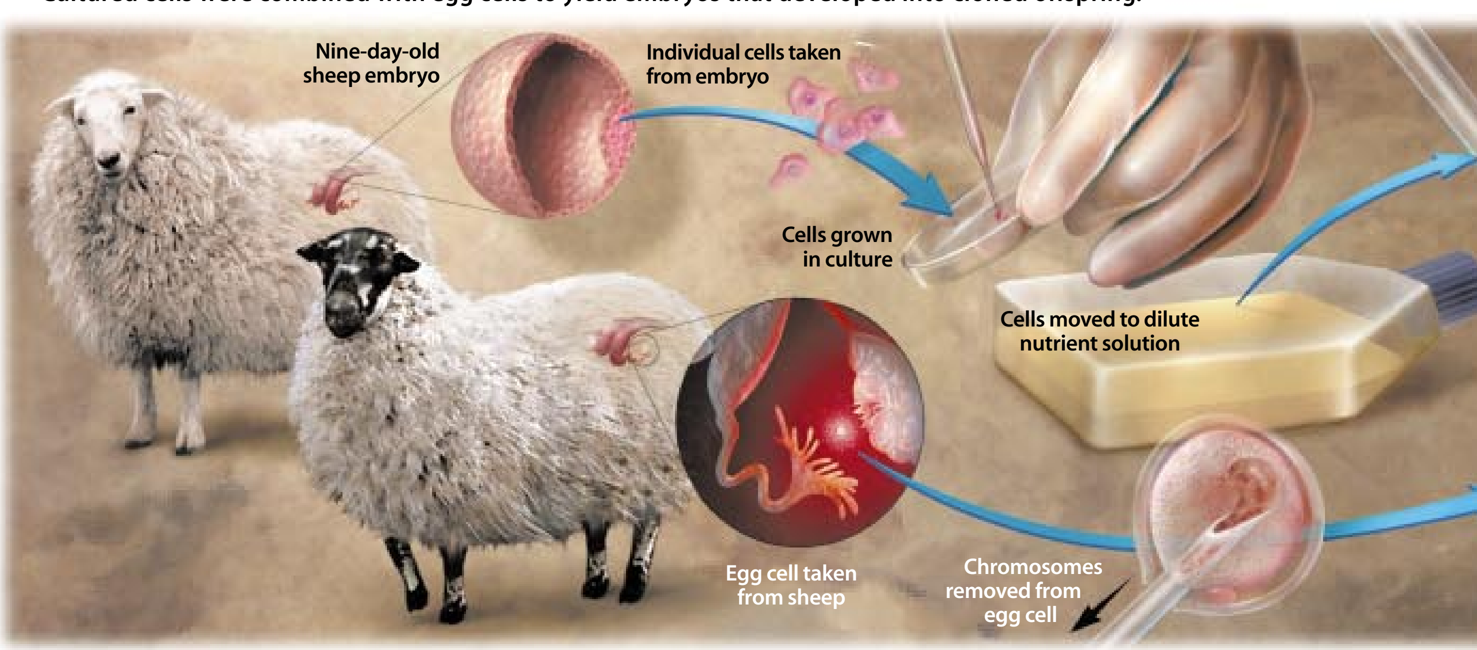
The standard technique for making transgenic animals is painfully slow and inefficient. It entails microinjecting a genetic construct—a DNA sequence incorporating a desired gene—into a large number of fertilized eggs. A few of them take up the introduced DNA so that the resulting offspring express it. These animals are then bred to pass on the construct [see "Transgenic Livestock as Drug Factories," by William H. Velander, Henryk Lubon and William N. Drohan; Scientific American, January 1997].

In contrast, a simple chemical treatment can persuade cultured cells to take up a DNA construct. If these cells are then used as donors for nuclear transfer, the resulting cloned offspring will all carry the construct. The Roslin Institute and PPL Therapeutics have already used this approach to produce transgenic animals more efficiently than is possible with microinjection.

We have incorporated into sheep the gene for human fac-

How Megan and Morag Were Made

Cultured cells were combined with egg cells to yield embryos that developed into cloned offspring.



KEITH KASNOT

tor IX, a blood-clotting protein used to treat hemophilia B. In this experiment we transferred an antibiotic-resistance gene to the donor cells along with the factor IX gene, so that by adding a toxic dose of the antibiotic neomycin to the culture, we could kill cells that had failed to take up the added DNA. Yet despite this genetic disruption, the proportion of embryos that developed to term after nuclear transfer was in line with our previous results.

The first transgenic sheep produced this way, Polly, was born in the summer of 1997. Polly and other transgenic clones secrete the human protein in their milk. These observations suggest that once techniques for the retrieval of egg cells in different species have been perfected, cloning will make it possible to introduce precise genetic changes into any mammal and to create multiple individuals bearing the alteration.


RODDY FIELD *Roslin Institute*

DOLLY
(*right*) shot to worldwide fame in 1997 as the first mammal cloned from an adult's cells. Now mature, Dolly has given birth to a healthy lamb, Bonnie (*left*), the product of a normal mating and gestation.

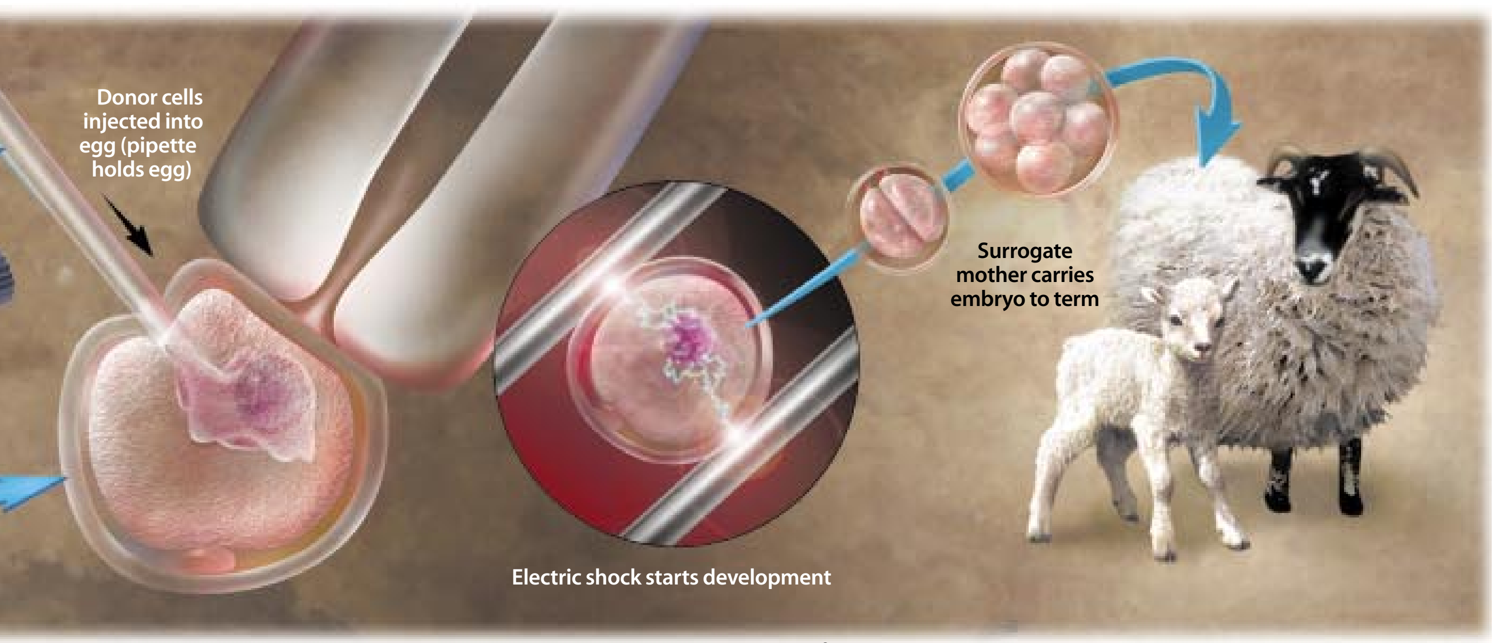
Cultures of mammary gland cells might have a particular advantage as donor material. Until recently, the only practical way to assess whether a DNA construct would cause a protein to be secreted in milk was to transfer it into female mice, then test their milk. It should be possible, however, to test mammary cells in culture directly. That will speed up the process of finding good constructs and cells that have incorporated them so as to give efficient secretion of the protein.

Cloning offers many other possibilities. One is the generation of genetically modified animal organs that are suitable for transplantation into humans. At present, thousands of patients die every year before a replacement heart, liver or kidney becomes available. A normal pig organ would be rapidly destroyed by a "hyperacute" immune reaction if transplanted into a human. This reaction is triggered by proteins on the pig cells that have been modified by an enzyme called alpha-galactosyl transferase. It stands to reason, then, that an organ from a pig that has been genetically altered so that it lacks this enzyme might be well tolerated if doctors gave the recipient drugs to suppress other, less extreme immune reactions.

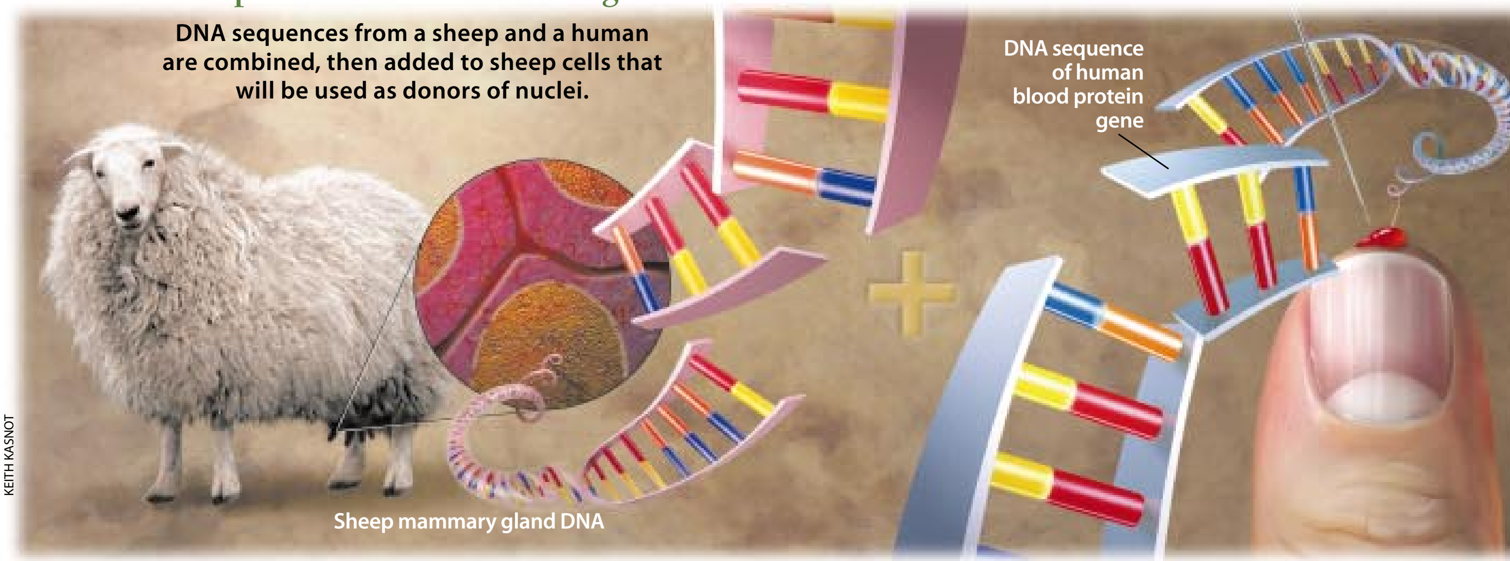
Another promising area is the rapid production of large animals carrying genetic defects that mimic human illnesses, such as cystic fibrosis. Although mice have provided some information, mice and humans have very different genes for cystic fibrosis. Sheep are expected to be more valuable for research into this condition, because their lungs resemble those of humans. Moreover, because sheep live for years, scientists can evaluate their long-term responses to treatments.

Creating animals with genetic defects raises challenging ethical questions. But it seems clear that society does in the main support research on animals, provided that the illnesses being studied are serious ones and that efforts are made to avoid unnecessary suffering.

The power to make animals with a precisely engineered genetic constitution could also be employed more directly in cell-based therapies for important illnesses, including Parkinson's disease, diabetes and muscular dystrophy. None of these conditions currently has any fully effective treatment. In each, some pathological process damages specific cell populations, which are unable to repair or replace themselves. Several novel approaches are now being explored that would provide



How to Prepare Cells to Make Transgenic Clones



new cells—ones taken from the patient and cultured, donated by other humans or taken from animals.

To be useful, transferred cells must be incapable of transmitting new disease and must match the patient's physiological need closely. Any immune response they produce must be manageable. Cloned animals with precise genetic modifications that minimize the human immune response might constitute a plentiful supply of suitable cells. Animals might even produce cells with special properties, although any modifications would risk a stronger immune reaction.

Cloning could also be a way to produce herds of cattle that lack the prion protein gene. This gene makes cattle susceptible to infection with prions, agents that cause bovine spongiform encephalitis (BSE), or mad cow disease. Because many medicines contain gelatin or other products derived from cattle, health officials are concerned that prions from infected animals could infect patients. Cloning could create herds that, lacking the prion protein gene, would be a source of ingredients for certifiable prion-free medicines.

The technique might in addition curtail the transmission of genetic disease. Many scientists are now working on therapies that would supplement or replace defective genes in cells, but even successfully treated patients will still pass on defective genes to their offspring. If a couple was willing to produce an embryo that could be treated by advanced forms of gene therapy, nuclei from modified embryonic cells could be transferred to eggs to create children who would be entirely free of a given disease.

Some of the most ambitious medical projects now being considered envision the production of universal human donor cells. Scientists know how to isolate from very early mouse embryos undifferentiated stem cells, which can contribute to all the different tissues of the adult. Equivalent cells can be obtained for some other species, and humans are probably no exception. Scientists are learning how to differentiate stem cells in culture, so it may be possible to manufacture cells to repair or replace tissue damaged by illness.

Making Human Stem Cells

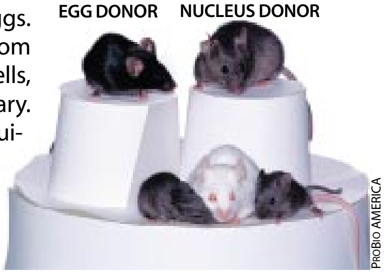
Stem cells matched to an individual patient could be made by creating an embryo by nuclear transfer just for that purpose, using one of the patient's cells as the donor and a human egg as the recipient. The embryo would be allowed to develop only to the stage needed to separate and culture stem cells from it. At that point, an embryo has only a few hundred cells, and they have not started to differentiate. In particular, the nervous system has not begun to develop, so the embryo has no means of feeling pain or sensing the environment. Embryo-derived cells might be used to treat a variety of serious diseases caused by damage to cells, perhaps including AIDS as well as Parkinson's, muscular dystrophy and diabetes.

Scenarios that involve growing human embryos for their cells are deeply disturbing to some people, because embryos have the potential to become people. The views of those who consider life sacred from conception should be respected, but I suggest a contrasting view. The embryo is a cluster of cells that does not become a sentient being until much later in development, so it is not yet a person. In the U.K., the Human Genetics Advisory Commission has initiated a major public consultation to assess attitudes toward this use of cloning.

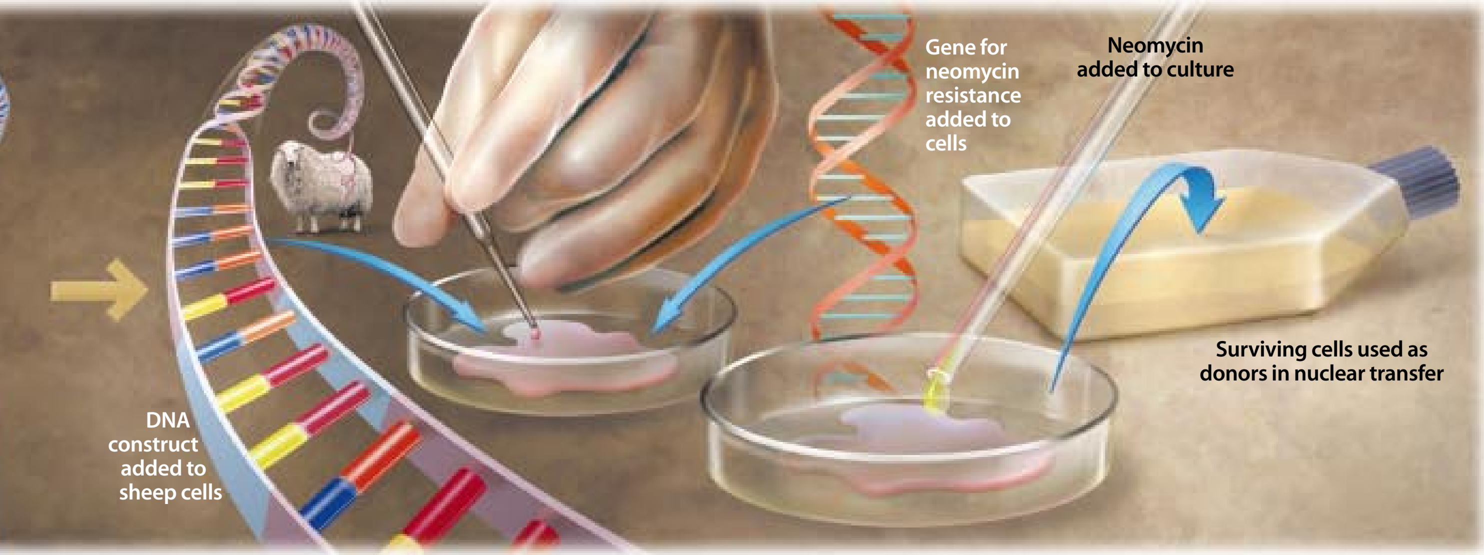
Creating an embryo to treat a specific patient is likely to be an expensive proposition, so it might be more practical to establish permanent, stable human embryonic stem-cell lines from cloned embryos. Cells could then be differentiated as needed. Implanted cells derived this way would not be genetically perfect matches, but the immune reaction would prob-

Now, Cloned Mice

Recently Ryuzo Yanagimachi of the University of Hawaii at Honolulu and his colleagues successfully cloned mice by transferring donor nuclei—not whole cells—into eggs. The group took nuclei from cells called cumulus cells, which surround the ovary. These cells are naturally quiescent. So far we believe that no one has shown that offspring can be produced from differentiated cells that are not quiescent. —*I.W.*



Surrogate mother (*center*) is flanked by cloned offspring of nucleus donor.



ably be controllable. In the longer term, scientists might be able to develop methods for manufacturing genetically matched stem cells for a patient by "dedifferentiating" them directly, without having to utilize an embryo to do it.

Several commentators and scientists have suggested that it might in some cases be ethically acceptable to clone existing people. One scenario envisages generating a replacement for a dying relative. All such possibilities, however, raise the concern that the clone would be treated as less than a complete individual, because he or she would likely be subjected to limitations and expectations based on the family's knowledge of the genetic "twin." Those expectations might be false, because human personality is only partly determined by genes. The clone of an extrovert could have a quite different demeanor. Clones of athletes, movie stars, entrepreneurs or scientists might well choose different careers because of chance events in early life.

Some pontificators have also put forward the notion that couples in which one member is infertile might choose to make a copy of one or the other partner. But society ought to be concerned that a couple might not treat naturally a child who is a copy of just one of them. Because other methods are available for the treatment of all known types of infertility, conventional therapeutic avenues seem more appropriate. None of the suggested uses of cloning for making copies of existing people is ethically acceptable to my way of thinking, because they are not in the interests of the resulting child. It should go without saying that I strongly oppose allowing cloned human embryos to develop so that they can be tissue donors.

It nonetheless seems clear that cloning from cultured cells will offer important medical opportunities. Predictions about new technologies are often wrong: societal attitudes change; unexpected developments occur. Time will tell. But biomedical researchers probing the potential of cloning now have a full agenda. SA

JOHN CHADWICK PHOTOGRAPHIC AND PPL THERAPEUTICS

POLLY (*left*) is a transgenic clone of a poll Dorset sheep. A gene for a human protein, factor IX, was added to the cell that provided the lamb's genetic heritage, so Polly has the human gene. The ewe that carried Polly (*right*) is a Scottish blackface.

The Author

IAN WILMUT pursues research on the genetic engineering of livestock at the Roslin Institute near Edinburgh in Midlothian, Scotland. After obtaining a Ph.D. from the University of Cambridge for research on methods of freezing boar semen, he did postdoctoral work at Cambridge on techniques for freezing animal embryos. Later Wilmut identified developmental and physiological causes of prenatal death in sheep and pigs, before turning to studies of ways to improve economically important animals.

Further Reading

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Genomic Potential of Differentiated Cells. Marie A. Di Berardino. Columbia University Press, 1997.

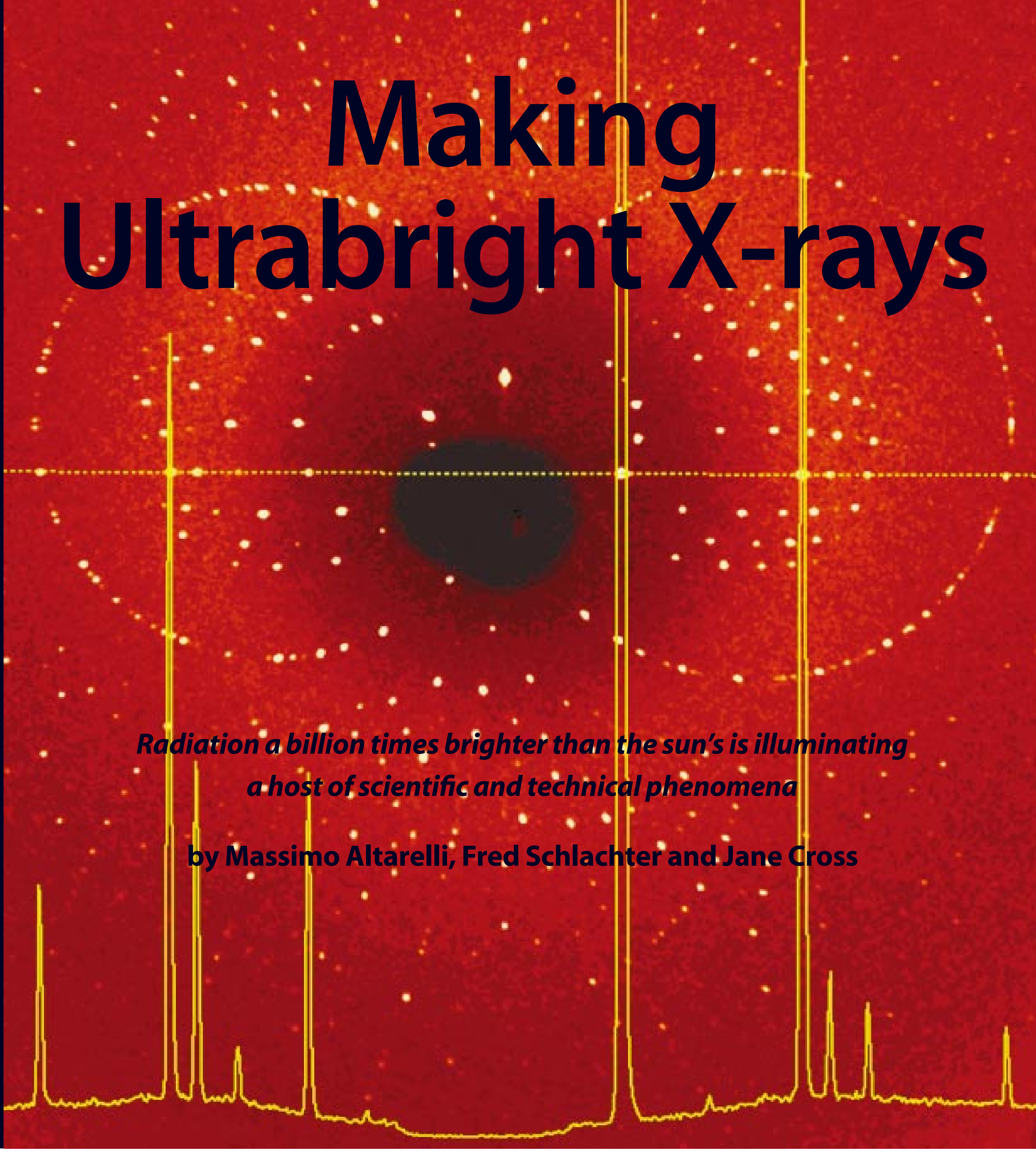
Sheep Cloned by Nuclear Transfer from a Cultured Cell Line. K.H.S. Campbell, J. McWhir, W. A. Ritchie and I. Wilmut in *Nature,* Vol. 385, pages 810–813; February 27, 1997.

Human Factor IX Transgenic Sheep Produced by Transfer of Nuclei from Transfected Fetal Fibroblasts. E. Schnieke et al. in *Science,* Vol. 278, pages 2130–2133; December 19, 1997.

Making Ultrabright X-rays

Radiation a billion times brighter than the sun's is illuminating a host of scientific and technical phenomena

by Massimo Altarelli, Fred Schlachter and Jane Cross



DIFFRACTION IMAGE shows how a brief pulse of extremely bright x-radiation was scattered as it went through a sample of myoglobin, a molecule found in muscle tissue responsible for the uptake and storage of oxygen. This image shows both the spots of diffracted radiation and also a plot of the intensity of just those spots that lay along the horizontal line at the center of the pattern.

MICHAEL WULFF *European Synchrotron Radiation Facility* AND KEITH MOFFATT *University of Chicago*

The construction of extremely bright sources of x-rays has been one of the great—and infrequently told—success stories of science and technology over the past few decades. These facilities, based on evacuated, circular tubes several hundred meters in diameter, carry electrons at nearly the speed of light, giving off brilliant bursts of radiation that enable experimenters to examine matter on a scale measured in atoms. Using this extraordinary light, scientists have gained invaluable insights into diverse objects and phenomena, including the structure of molecules, advanced semiconductors and magnetic materials, and the details of complex chemical reactions.

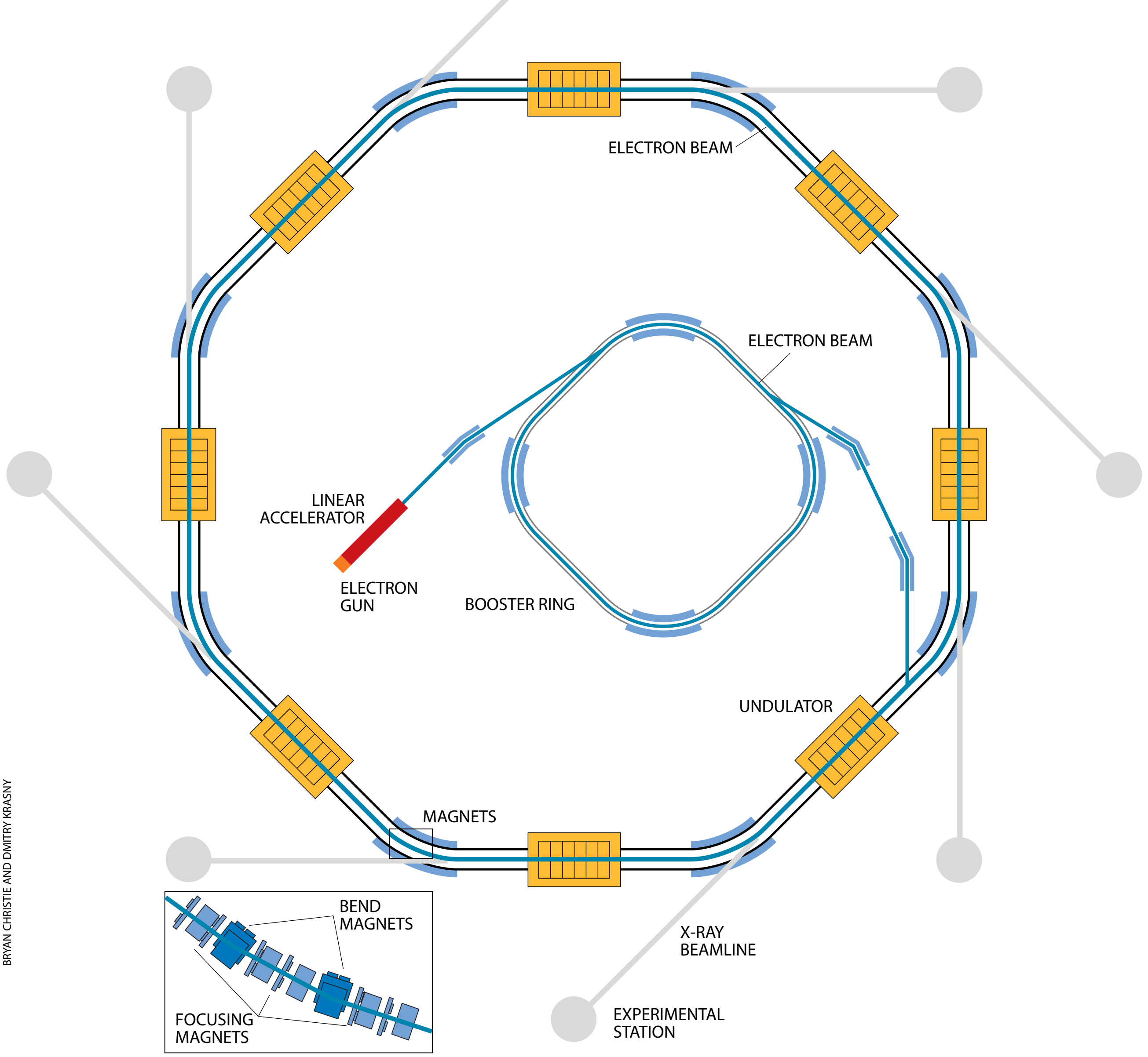
Such scientific achievements have been made possible by equally impressive engineering advances. Using the brightness of these x-ray sources as a yardstick, their rate of improvement since the early 1960s is matched by few other technologies. For example, the increase in computational speed available with the highest-performance computers is often cited as an example of the rapid pace of information-age progress. Yet the increase in brightness of the x-ray sources over the same period has occurred far faster.

The latest devices, examples of which have come on line over the past five years in various countries, are nearly 100 times brighter than anything built in the previous generation. In fact, these new sources are producing radiation a billion times brighter than that from the sun [*see box on page 72*]. Eight of these facilities are now operating, and another two are to begin operating in the near future [*see table on page 69*]. In addition, there are about 40 previous-generation sources operating around the world.

Fueling this surge in construction of new sources, despite price tags in the range of $100 million to $1 billion per site, is the promise of the most intimate look yet at the structure, composition and chemical bonding of crystals and molecules, in materials ranging from semiconductors to proteins.

Succinctly put, the astounding brightness of these devices means that their x-rays come from a source with an extremely small cross-sectional area and that they shine in a very narrow cone. The x-rays come from electrons traveling in a bunch with a diameter about the same as that of a human hair. The x-ray beams those electrons emit also have a small cross section and low angular divergence, which allows the radiation to remain concentrated. To have high brightness, a beam must also have high spectral intensity, meaning that it is made up of an extraordinarily large number of photons per unit of time in a given range of wavelengths.

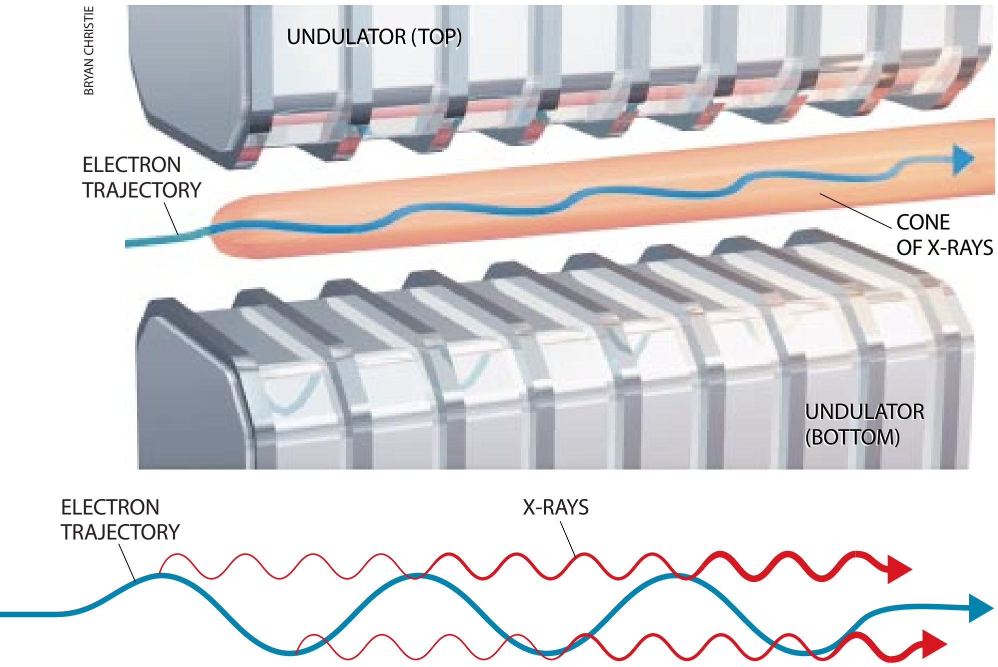
Brilliant x-ray beams are essential for many important classes of experiments, because in some situations the greater

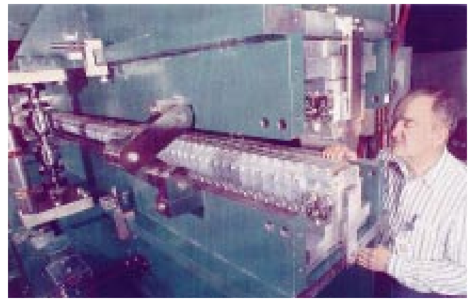


BRYAN CHRISTIE AND DMITRY KRASNY

STORAGE RING enables a current of electrons to circulate at nearly the speed of light for many hours. Electrons created in an electron gun are accelerated to nearly the speed of light by a linear accelerator. From there, they go into a small synchrotron, or booster ring, that increases the electrons' energy. Finally, the particles are injected into the storage ring, where they go around in hair-thin bunches, each of which causes a pulse of superbright electromagnetic radiation as it travels through any of the curved parts of the orbit. The main elements of the storage ring that control the circulating electron beam are magnets (*blue*) in an arrangement called a lattice. The focusing magnets (*detail at lower left*) keep the electrons in thin, concentrated bunches; the other magnets in the lattice bend the path of the electrons into a curve, causing radiation to be emitted. Radiation also comes from specially designed magnetic devices called undulators (*yellow*), which are installed in straight sections of the ring. Some of the radiation from the bend magnets, and most or all of the emissions from the undulators, leaves the ring through tangential ports into beamlines that allow the radiation to pass to experimental stations located around the ring (*gray circles*).

BRYAN CHRISTIE





COURTESY OF LAWRENCE BERKELEY NATIONAL LABORATORY

UNDULATOR creates a spatially alternating magnetic field that bends electrons back and forth many times to produce an x-ray beam of exceptional brightness. Waves from different points along the electron trajectory (*blue line*) overlap one another because x-rays are emitted in a narrow cone (*pink*). Only waves of certain frequencies overlap one another in such a way that all their peaks and troughs occur at the same positions—a condition known as constructive interference (*lower illustration at left*). These frequencies are determined by adjusting the size of the gap between the undulator's two rows of magnets (*above*).

the brightness, the smaller the objects that can be usefully probed. In addition, the brighter a source is, the narrower the range of wavelengths that can be selected in practice. Such fine selectivity is useful, for example, to excite a molecule that absorbs strongly at one resonant frequency.

Besides having desirable characteristics, the radiation from these facilities, which are more precisely known as storage rings, spans the wavelengths and energies needed to examine the atomic and electronic structure of matter. These two physical attributes determine nearly all of a material's key properties, such as its strength, magnetism and chemical reactivity, as well as its conduction of heat and electricity. The latest generation of x-ray sources is helping to advance our understanding of such important subjects as the malaria parasite, optical interferometry, catalysis and the manipulation of matter on an atomic scale.

Synchrotrons and Storage Rings

For roughly a century, scientists have known that charged particles give off electromagnetic radiation whenever they accelerate, decelerate or change direction. Thus, particles moving in a circle—even at constant speed—are accelerating and so emit radiation continuously as they follow the curved orbit. This radiation is known as synchrotron radiation because it was first observed about 50 years ago in an electron synchrotron, a kind of particle accelerator. Synchrotron radiation in fact occurs in nature, as in the Crab Nebula, which emits x-rays by the acceleration, in strong magnetic fields, of electrons whose speed approaches that of light.

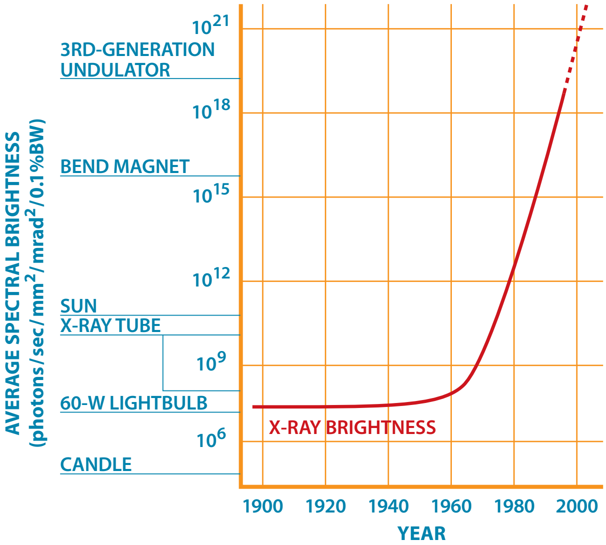
A synchrotron consists of a more or less doughnut-shaped vacuum chamber, which can be many kilometers in circumference, surrounded by magnets that bend and focus a beam of charged particles to keep them on the same path inside the vacuum chamber as they increase in energy. When the particles are circulating at speeds well below that of light, the radiation they emit is relatively weak, low frequency and omnidirectional. But as they approach the speed of light, the intensity, frequency and directionality of the emitted radiation increase dramatically. The radiation is emitted tangentially to the curving path of the particles. The emissions are particularly intense for particles that are not massive, such as electrons and positrons.

To create very bright beams of radiation for research, experimenters generally use storage rings, which are a specialized form of synchrotron. Storage rings circulate charged particles, typically electrons, at a constant speed—close to that of light—and in the same orbit for many hours. The particles must be brought to speed by a separate accelerator, often another synchrotron, before being injected into the storage ring. At the Advanced Light Source (ALS) at Lawrence Berkeley National Laboratory, the electrons orbit at 99.999996 percent of the speed of light, a rate at which the effects described by Einstein's special relativity theory give each electron a mass some 3,000 times greater than what it is at rest.

As the swiftly moving electrons in a storage ring emit synchrotron radiation, they lose energy. For this reason, specially designed components known as radio-frequency cavities are needed to make up for such losses. These devices establish an oscillating electromagnetic field (a radio wave) that speeds the electrons on their journey.

The crest of each wave provides energy to a bunch of electrons. This phenomenon occurs once for each cycle of the radio wave—or 500 million times per second at the Advanced Light Source—for a duration of about 50 picoseconds (50×10^{-12} second). Traveling at nearly the speed of light, each hair-thin packet of electrons is roughly a centimeter in length, and there are hundreds of them in the storage ring at the same time, like tiny pearls in a huge rotating necklace. Each bunch produces an extremely short burst of x-radiation when it deviates from a straight line. Thus, storage rings produce extremely short, frequent and bright pulses of x-radiation.

A storage ring emits radiation that spans the electromagnetic spectrum from infrared to x-rays. In practice, however, physicists do not use the visible light given off, because tunable lasers are available that have even brighter beams at



DMITRY KRASNY

X-RAY BRIGHTNESS has increased dramatically since the first exploitation of radiation from particle accelerators (also known as synchrotron radiation) in the 1960s. Although all synchrotron facilities are significantly brighter than conventional x-ray sources, the newest machines, which use magnetic devices called undulators, generate x-ray beams that are about 100 times brighter than those from previous sources.

those wavelengths. But for the ultraviolet light and x-ray regions of the spectrum, no other practical source matches the brightness of synchrotron radiation.

Storage rings are actually polygonally shaped, with up to 50 straight sections connected by gently curved ones [*see illustration on page 67*]. Two types of powerful electromagnets focus the beam; a third type bends the path of the electrons into a curve, thereby causing synchrotron radiation.

In the curved sections, synchrotron radiation emerges tangentially to the electron beam. Thus, for each of the curved sections of a storage ring there is one or more associated x-ray "beam lines" that are used by experimenters.

Several factors have combined to permit the leap in brightness for the latest generation of storage rings. One is the availability of powerful, low-cost microprocessors. The design tools and control systems based on these microprocessors have now made it possible to design, model, construct and operate the myriad components and subsystems of a storage ring so exquisite control can be exerted over the electron beam. Operators can position this hair-thin beam to within a few hundredths of its width. Such extremely precise control keeps the beam very steady; movement of the electron beam would cause a blurred x-ray beam of lower brightness.

Another key factor has been the use of devices called undulators. As this name implies, an undulator causes the electron beam to bend back and forth many times over a length of a few meters. Recall that a change in direction—a form of acceleration—causes the electrons to emit radiation. An undulator, by forcing a series of rapid changes in direction in the electron beam, in effect squeezes out of it as much radiation as possible.

The waves of light emitted at each bend overlap and either reinforce or cancel one another, depending on their wavelengths [*see illustration on opposite page*]. The end result is that certain wavelengths are strongly enhanced. Light at these wavelengths emerges in a narrow cone and typically is partially coherent—that is, the crests and troughs of the waves tend to coincide with one another—making it similar in some respects to laser light.

The heart of an undulator is a double array of high-strength permanent magnets, which creates alternately upward- and downward-directed magnetic fields perpendicular to the electron beam. By adjusting the gap between the upper and lower magnets, researchers can tune an undulator so that all the emission falls near a specific fundamental frequency and its harmonics (multiples of that frequency).

Shining Future

The short wavelengths, extreme brightness and partial coherence of the x-ray beams from the latest storage rings are allowing researchers to investigate objects and phenomena that because of their size or other characteristics would have been difficult if not impossible to study as recently as five or six years ago. Hundreds of projects are under way, providing invaluable details on such disparate subjects as the performance of optical assemblies and the relation between the structure and the biological function of key proteins in the body.

Many of these experiments have potentially significant technological implications; others promise to elucidate long-standing scientific enigmas. The examples we have chosen illustrate how scientists and engineers are using these rings to investigate malaria parasites, to study technologies to reduce the size of transistors in future integrated circuits, to understand the way catalysis occurs on the surface of a material, to make images of the interior of minute samples without destroying them and to illuminate the dynamic behavior of the myoglobin molecule.

Among diseases caused by a single organism, malaria is a killer second only to tuberculosis. The World Health Organization estimates that every year malaria kills up to 2.7 million people, mainly children. There is no effective vaccine, and resistance to the available prophylactic drugs is growing. At Lawrence Berkeley National Laboratory's Life Sciences Division, Cathleen Magowan, collaborating with Werner Meyer-Ilse, John T. Brown and other members of the lab's Center for X-ray Optics, is using the Advanced Light Source to study the life cycle in red blood cells of the deadliest malaria parasite, *Plasmo-*

STATE-OF-THE-ART SYNCHROTRON LIGHT SOURCES

NAME	LOCATION	ELECTRON ENERGY*	DATE OF OPERATION
European Synchrotron Radiation Facility (ESRF)	Grenoble, France	6 GeV	1993
Advanced Light Source (ALS)	Berkeley, Calif., U.S.	1.5–1.9 GeV	1993
Synchrotron Radiation Research Center (SRRC)	Hsinchu, Taiwan	1.5 GeV	1994
Elettra	Trieste, Italy	2.0–2.4 GeV	1995
Pohang Light Source (PLS)	Pohang, Korea	2–2.5 GeV	1995
Advanced Photon Source (APS)	Argonne, Ill., U.S.	7 GeV	1996
MAX II	Lund, Sweden	1.5 GeV	1997
SPring-8	Nishi-Harima, Japan	8 GeV	1997
BESSY II	Berlin, Germany	0.9–1.9 GeV	1998
Swiss Light Source (SLS)	Villigen, Switzerland	2.4 GeV	2001

*The electron energy determines the range of photon energies produced by the light source; higher electron energies lead to higher photon energies.

DMITRY KRASNY

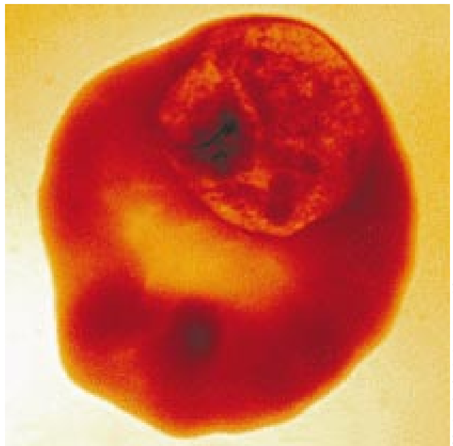
dium falciparum. This protozoan, which is carried by female *Anopheles* mosquitoes, invades the red blood cells of an infected host. Inside the host's cells, the parasites go through cycles of asexual division, insinuating their progeny into more and more red blood cells. Once inside a cell, the parasite digests hemoglobin in a food vacuole to produce most of the amino acids it needs to survive.

Magowan and her colleagues are using a transmission microscope in which an x-ray beam passes through infected red blood cells to make an enlarged image. They are studying various stages of the parasite's life cycle and viewing the effects of various drugs on it to see which are the most effective—and why. The researchers are using x-rays with a wavelength of 2.4 nanometers and get resolution five to 10 times better than would be possible with a visible-light microscope. In addition to the short wavelength of the illumination, the natural contrast from x-ray absorption lets the experimenters see minute structures within the infected cells and, in particular, inside the parasites themselves. This ability allows them to study the development of the parasite as it matures.

Moreover, the natural contrast from x-ray absorption allows precise and direct measurements of the redistribution of mass within the parasite, which is not possible with visible-light microscopes. Important examples of such features include abnormalities in the parasite's food vacuole, in which nutrients are accumulated. X-ray absorption provides the contrast that Magowan has used to follow redistribution of hemoglobin from the red-cell cytoplasm into the parasite food vacuole, both under normal conditions and under drug treatment. Drugs that inhibit parasite enzymes from digesting hemoglobin cause the food vacuole to swell with undigested hemoglobin and can thus kill the parasite. Magowan and her co-workers measured the increased mass in the parasite's food vacuole, which was not possible before on a microscopic scale. These x-ray studies, as well as others Magowan has done, could contribute to novel therapeutic approaches to the control of malaria.

Bright, partially coherent x-ray beams may also aid the electronics industry. The core business of this industry, which generates hundreds of billions of dollars in revenue every year, is the manufacture of integrated circuits ("chips"). Chips are manufactured in a multistep process that creates and interconnects millions of transistors to form complex electronic systems on a sliver of silicon. The heart of the fabrication process is based on a cycle of photolithographic steps, in which ultraviolet light is used to project the image of a stencillike mask onto the photosensitive coating on a silicon wafer.

The wavelength of the light used in the exposure determines the minimum feature size that can be projected and therefore the density of transistors on the silicon. At present, features of 0.25 micron are produced using ultraviolet light with a wavelength of 0.248 micron. The industry, however, is already planning for chips with features measuring 0.1 micron or less. Currently one promising option to produce feature sizes smaller than about 0.1 micron uses photolithographic systems based on extreme ultraviolet (EUV) radiation. These EUV rays, with a wavelength of about 13 nanometers, will probably come from a laser-produced plasma.



COURTESY OF BERKELEY LABS

MALARIA PARASITE is visible in unusual detail in this x-ray image (*above*) of an infected human red blood cell. The photograph at the right shows a healthy cell imaged using the same technique.

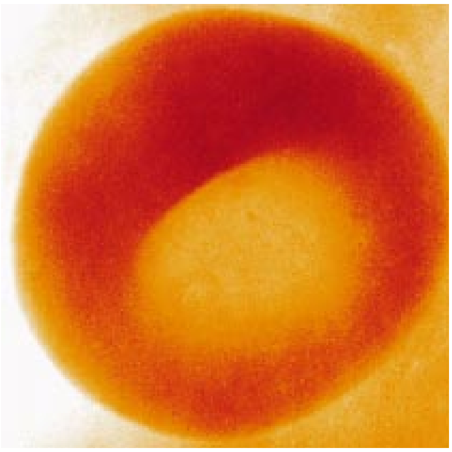
Extreme Interferometry

Nevertheless, storage rings are playing an important role in the development of technologies for the manufacture of these extremely dense integrated circuits. EUV projection lithography will require the use of mirrors with multilayer coatings to focus the radiation (without such a coating, the mirrors would not sufficiently reflect EUV radiation that hits the mirrors' surface nearly perpendicularly). Achieving the necessary accuracy in the pattern projected onto the silicon wafer demands high precision in the optical system that projects the pattern and a very flat wafer surface. This kind of precision, in turn, requires methods of testing optical systems that can detect imperfections with dimensions of less than one nanometer (a thickness of just five to 10 atoms). Such a requirement would be difficult to meet with optical testing techniques that use visible light—which, in any case, could not test the multilayer coating.

At the ALS, however, researchers from the Center for X-ray Optics and the University of California at Berkeley's department of electrical engineering and computer science are developing a new method of measuring the performance of an optical system. The procedure uses EUV radiation from the storage ring and is based on interferometry, a sensitive optical technique in which information is obtained by the recombination of two or more coherent beams generated by the same source. Only radiation from a new-generation storage ring can provide a narrow, very intense beam at the EUV wavelengths that are necessary for this application.

With interferometry, the beams propagate along different paths, or in different ways. One beam interacts with an object under study, shifting the phase of the waves in that beam. (A 180-degree phase shift, for example, would leave the crests where the troughs were, and vice versa.) The other beam, meanwhile, serves as a reference.

When the two beams are brought together, or recombined, any relative shift in phase—due to aberrations in the optics being tested—becomes apparent as a pattern of light and dark fringes where the waves are constructively or destructively interfering. Following this approach, the group of investigators, headed by Jeffrey Bokor, built an interferometer that divides coherent light from an undulator source into two beams. One is reflected through the optical system under test, acquiring phase information that reveals the quality of the optical system. The second beam radiates through a tiny pinhole, producing a spherical reference beam. The group's work with ultraviolet light has demonstrated the ability to fabricate mirrors of sufficient accuracy for projection lithography at EUV wavelengths. In so doing, these researchers surmounted a major challenge to packing more transistors into microcircuits.



Bright synchrotron radiation is also furthering our understanding of how atoms and molecules interact (bond) with a surface—and how their electronic structure changes as a result of that interaction. This insight is important in the study of corrosion and also of catalysis, in which two chemical agents are induced to react by the presence of a third. Both phenomena are of enormous practical significance; catalysis, for example, is used in industry to produce many different compounds.

Neither phenomenon can be well understood without a clear picture of how atoms or molecules bond to a surface. To study this subject, scientists need a probe that can see how the electrons that form a chemical bond are distributed on each of the atoms involved in the bond. Such an "atom-specific" view is now possible using a high-brightness source and a technique called x-ray fluorescence spectroscopy.

A research group working at the ALS led by Anders Nilsson and Nial Wassdahl of Uppsala University in Sweden, in collaboration with the IBM Almaden Research Center, was one of the first to demonstrate this capability. This study of the chemical bond between molecular nitrogen (N_2) and a nickel surface has revolutionized our conception of the surface bond.

The nitrogen molecule is known to "stand up" on the nickel surface rather than to lie flat. In other words, only one of the nitrogen atoms in the molecular pair bonds to the surface; the other nitrogen atom sticks up from it. Because the bond to the surface is much weaker than the internal bond between the nitrogen atoms, chemists had assumed that the presence of the surface hardly affects the molecule and that it could therefore be treated as a symmetrical unit of two essentially identical nitrogen atoms. Yet what the researchers found was that there are large changes in the nitrogen's electron orbitals on adsorption, leading to a very different local electronic structure for each of the two atoms and a weakening of the intramolecular (N-N) bond. Understanding how and why the dissociation takes place could be a key to increasing the efficiency of ammonia synthesis for fertilizer and other nitrogen-containing molecules, because the rate-limiting step in the current process is the dissociation of N_2 into two separate nitrogen atoms.

Using the ALS, the researchers probed the energy-level differences in the inner-shell electrons of the two nitrogen atoms (a difference in energy level means a difference in the energy required to remove an electron from the atom or molecule). By tuning the energy of the incoming photons, the experimenters could selectively excite electrons from one nitrogen atom or the other and not those from the nickel surface on which the molecule was adsorbed. Information about the structure of the atom's outer electron layers was contained in the fluorescence x-rays emitted as the excited atoms returned to their ground state.

The experiment required a high-intensity source because x-ray fluorescence spectroscopy yields only about one photon emitted per 1,000 photons absorbed. And it required the ability to produce x-rays in a very narrow spectrum to selectively excite only one nitrogen atom of the two in the N_2 molecule.

Seeing through a Mosquito's Knee

Another potentially important application of high-brightness beams is phase-contrast imaging, which was recently demonstrated for the first time with high-energy x-rays by Anatoly Snigirev and his co-workers at the European Synchrotron Radiation Facility (ESRF). Their achievement opens the way to nondestructive imaging of biological, mineralogical and certain metallurgical samples at micron resolution. For example, Snigirev's group recently used the technique to make stunning x-ray cross-sectional images of a mosquito's knee [*see illustration on page 73*].

X-ray imaging is normally based on absorption contrast, as in the familiar medical imaging. In this case, contrast, which distinguishes different constituents of the object under examination, exists in the image because certain materials (those composed chiefly of elements with low atomic numbers, such as carbon, nitrogen and oxygen) are more transparent to x-rays than others.

In general, items composed of heavier atoms, which have a higher density of electrons, are more likely to absorb x-rays. In a conventional medical x-ray image, for example, bones stand out because they project a more pronounced shadow on the film than the less dense tissue surrounding them. Absorption contrast, therefore, is not well suited for samples that are composed exclusively of atoms of low atomic number.

Phase-contrast imaging relies on a different effect. Instead of the variation in absorption, it uses the variations in refractive indexes of the different substances within the sample. The refractive index of a material determines the deviation in the direction of a ray as it enters the material. For x-rays, differences in refractive indexes between different media are very small, at most one part in 100,000, but they are big enough to be exploited for imaging.

The basic principle of phase-contrast imaging with short-wavelength x-rays is identical to that of in-line holography. A coherent beam from a very bright source passes through a low-density specimen. Segments of the x-ray wavefront are deflected to a different degree relating to small variations in indexes of refraction. Consider first what happens near the edges of the sample: the rays that pass just by the sample are undeflected, but those that go through it are slightly deflected and get a bit out of step with respect to the undeflected ones. At some distance behind the sample, the various sets of wavefronts superimpose and, because they originate from a coherent beam, interfere. Thus, the characteristic fringes in intensity of an interference pattern are set up. These fringes, when recorded on a detector, map the outer contour of the sample. The same kind of interference takes place at the internal interfaces between regions of the sample that have different indexes of refraction. An exciting feature of the technique is that it is possible to make tomographic "cuts" through the sample, similar to those of a medical CT scan, by reconstructing a series of images made as the sample is rotated to expose it from different angles.

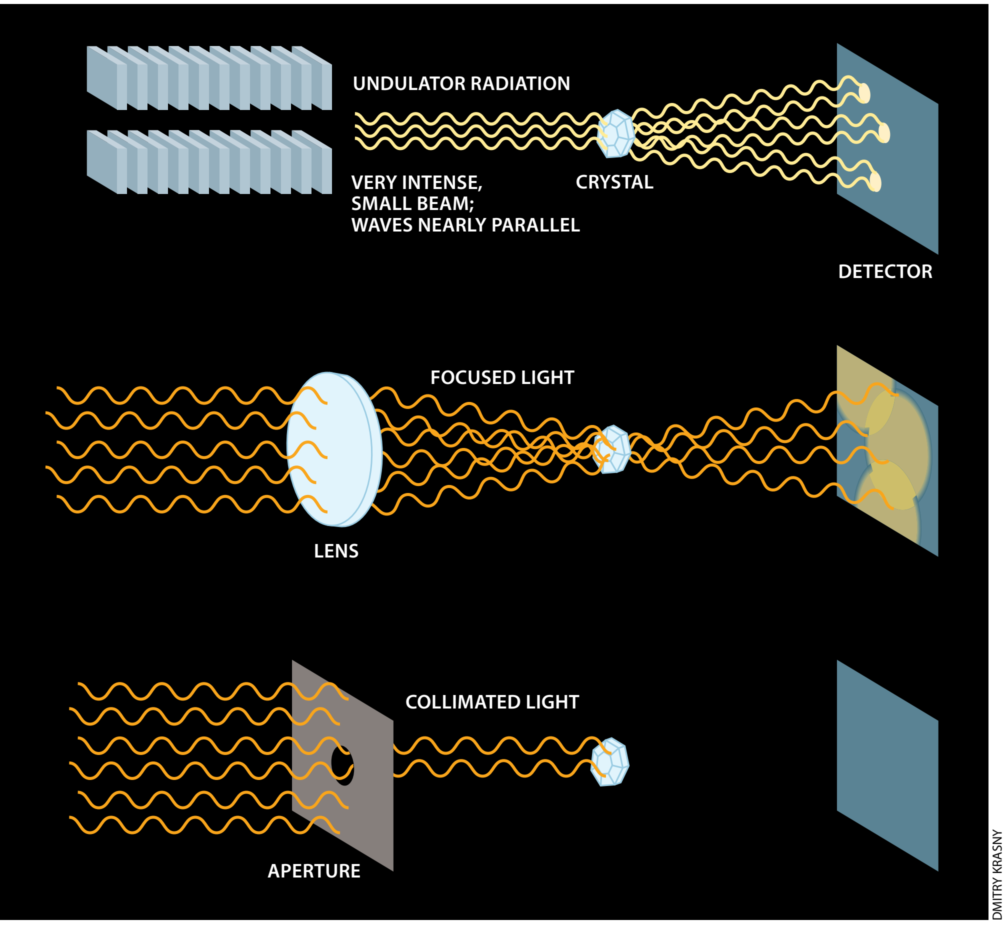
Bright x-ray beams are also illuminating long-standing scientific mysteries,

Brighter than the Brightest Star

Brightness is not simply the intensity of light but rather a measure of the degree of concentration of the light into a small emitting area and angle. Two sources may radiate the same amount of light, but the one in which the light comes from a small area and is collimated, meaning it shines in a narrow cone, is the brighter of the two. Thus, not only is a laser typically brighter than a lightbulb, but it can even be considerably brighter than the sun, which is large and radiates light equally in all directions.

Besides a source of small dimensions and a high degree of collimation, high brightness also demands high spectral flux, a technical term for the emission of many photons per second in a given range of wavelengths. A bright beam is also at least partially coherent, meaning that two separated but simultaneous waves can interfere with each other; this property is important for many scientific applications.

Brightness, called brilliance by European scientists, is an intrinsic property of a light source. It might seem plausible to increase brightness by focusing a beam to a small spot using a lens or a curved mirror. Yet by so doing, you would be increasing the divergence of the beam (making it less collimated)—and therefore not improving its brightness. Alternatively, you could decrease spot size without increasing angular divergence by using a tiny aperture; however, such a scheme would reduce the flux (the number of photons per second) on the sample and thus would not increase brightness either. *—M.A., F.S. and J.C.*



BRIGHTNESS of a beam cannot be improved. When a bright beam from, say, an undulator falls on a crystal, it creates a pattern of sharp, distinct diffraction spots (*top*). A lens may be used to focus a less bright beam (*middle*); however, this strategy trades beam size for divergence. The photons converge on the crystal and then diverge behind it, resulting in large, overlapping diffraction spots that contain much less information about the crystal. (In general, the beam can be magnified or demagnified, but the product of its cross-sectional size and the angle of divergence in each plane are constant.) An aperture can be used to make a smaller beam without increasing divergence (*bottom*). The problem in this case is dimness; the resulting diffraction spots are hard to detect and thus reveal little data.

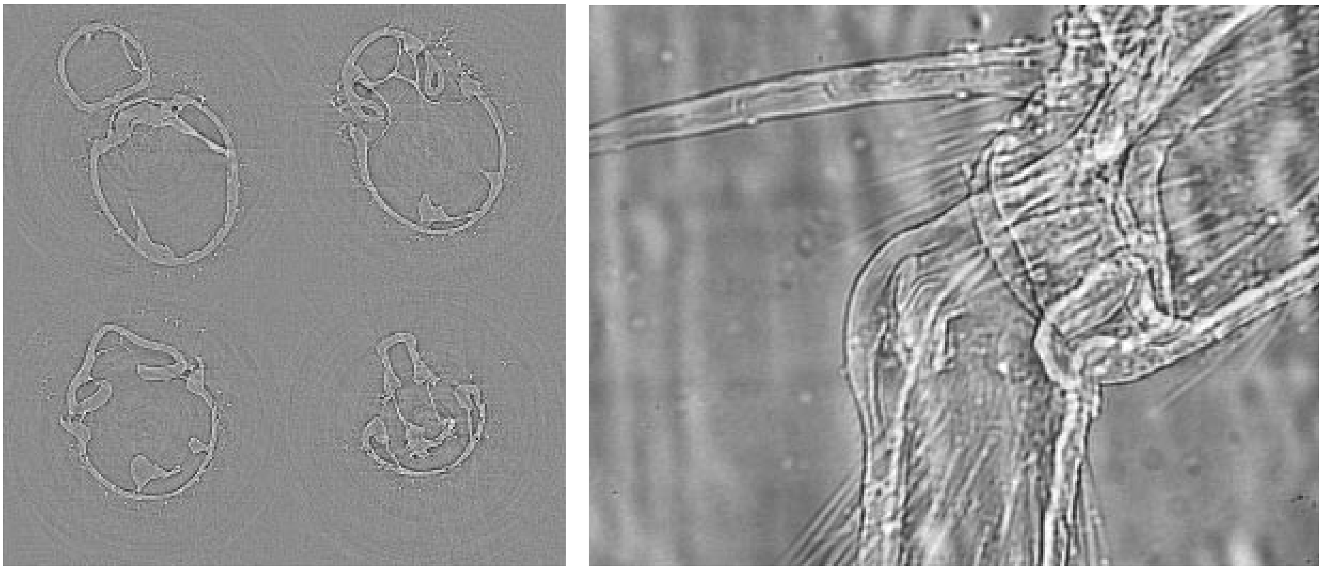
including the nanosecond-by-nanosecond behavior of biologically important molecules such as proteins. Biology researchers and the pharmaceutical industry are putting an ever increasing demand on light sources, given the significance of proteins for the understanding of life and of disease and for the development of new drugs. Protein molecules (which include enzymes, hormones and antibodies) are fundamental building blocks of living beings.

The effort to elucidate the behavior of protein molecules hinges on a technique called macromolecular crystallography, an important application of synchrotron radiation that enables researchers to map out the many thousands of atoms that make up large biological molecules such as proteins and viruses.

Basically, the information obtained in these studies is a static picture or "snapshot" of the atomic positions in the large molecules. But proteins are not at all static and rigid; they undergo complex structural rearrangements while carrying out their biological function. Today measuring and understanding these changes is largely unexplored territory, but there are clear indications that the new high-brightness facilities will allow progress in this direction.

For example, Michael Wulff of the ESRF, in collaboration with Keith Moffatt of the University of Chicago and others, has been able to follow the rapid structural rearrangements of myoglobin, a protein found in muscle tissue that is responsible for the uptake and storage of oxygen. Their work has resulted in a kind of movie, with each frame captured by a nanosecond-long x-ray pulse, which depicts the changes in the myoglobin molecule over a period of about one millisecond. The researchers are trying to discover the specific structural changes that allow an oxygen molecule to enter or leave a cagelike enclosure within the myoglobin molecule.

The intensity of current-generation light sources is such that a single pulse contains enough photons to take an x-ray "picture" (actually, a diffraction pattern) sufficient to reconstruct the configuration of the protein. To follow the structural rearrangements of the myoglobin protein during the release and rebinding of carbon monoxide, a sophisticated electronic setup controls the arrival of a laser pulse that lasts less than a nanosecond. This pulse breaks the chemical bond between the oxygen molecule and the heme site, which is the



ANATOLY SNIGIREV *European Synchrotron Radiation Facility*

MOSQUITO'S KNEE, imaged by a phase-contrast x-ray microscope, reveals anatomical detail on the scale of a few microns—despite the absence of any material as dense as the bones of vertebrates. Tomographic views of various cross sections of the mosquito knee were reconstructed by computer from images taken at different angles (*left*).

iron-containing part of the myoglobin molecule. In the experiments the researcher substituted carbon monoxide for oxygen, because CO has a higher probability of being detached from the heme site when it absorbs a laser photon.

After the laser pulse triggered the photochemical release of the CO from the myoglobin, there was a short interval before the x-ray snapshot was made. The researchers repeated the experiment many times, in each case with a slightly longer time interval between the laser pulse and the x-ray snapshot. By putting together all the snapshots, the investigators made a movie of structural changes on a nanosecond-by-nanosecond timescale. The movie showed that a few nanoseconds after the start of the reaction, the CO molecule is four angstroms away from the iron atom, which sits at the center of the iron-containing part of a myoglobin molecule and to which it was originally bound. Furthermore, at that instant the CO is rotated by 90 degrees with respect to its original orientation. In this "hold" position, the CO can wait hundreds of nanoseconds for a configuration of the environment that allows it to leave the protein and become available for participation in the chemical reactions that provide the energy necessary for muscle contraction.

Most important, researchers have for the first time been literally able to watch the time behavior of a dynamic molecular-biological process. This achievement opens the way to an understanding—in atomic detail—of the kinetics and dynamics of other important reactions involving proteins.

Such uses are just a few of the ones that are collectively advancing and in some cases even revolutionizing entire fields of technology and science. In time, such achievements will lead to demand for a yet more advanced generation of light sources. These ultrabright sources may be based on free-electron lasers, which are built around very long and complex undulators. (In these undulators, photons generated upstream react further downstream with electron pulses. This reaction reinforces the emission of more photons in step with the ones emitted upstream.)

This technology will yield beams many orders of magnitude brighter than those from today's storage rings, sustaining the remarkable rate of advancement in this area. More important, these future facilities will deepen our understanding of increasingly complex systems, extending the set of phenomena illuminated by this extraordinary light. SA

The Authors

MASSIMO ALTARELLI, FRED SCHLACHTER and JANE CROSS share an interest in describing the results achieved at large, government-funded research facilities to the general public. Altarelli is the newly appointed director of the Elettra light source in Trieste, Italy. He is leaving the European Synchrotron Radiation Facility in Grenoble, France, where he was head of the theoretical physics group and, prior to that, scientific director for physics and materials science. His research activity has been concerned with the investigation of magnetism and phase transitions by x-ray scattering and absorption. Schlachter joined the staff of the Advanced Light Source in 1989, while it was being constructed, and has held a number of positions there. His current interests include quantum chaos as it is exhibited by atoms in highly excited states. Cross is a writer, editor and former science teacher whose numerous technical and scientific publications span a variety of subjects. From 1993 until 1997, she worked as a scientific communications specialist at Lawrence Berkeley National Laboratory.

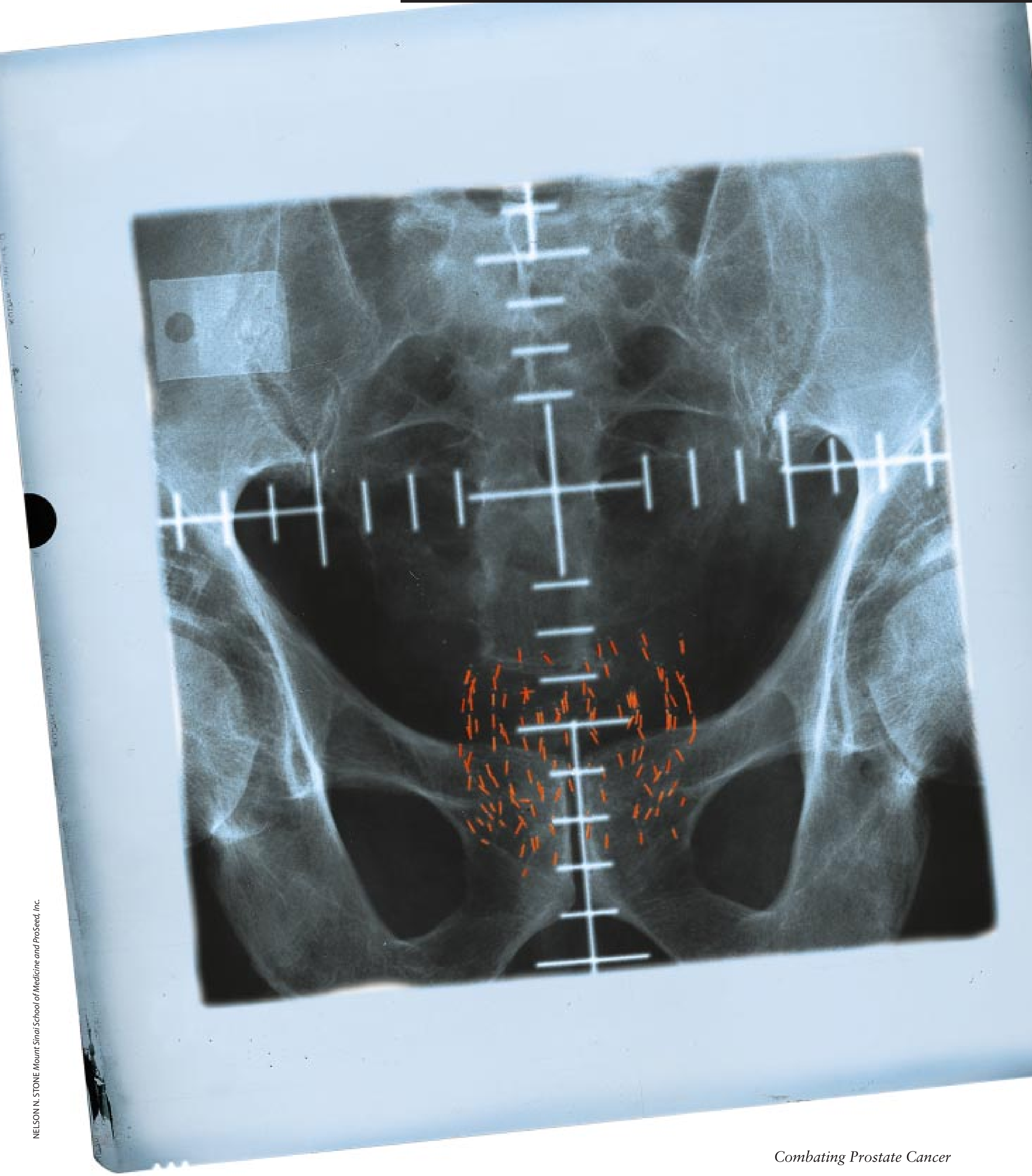
Further Reading

SYNCHROTRON RADIATION. Herman Winick in *Scientific American,* Vol. 257, No. 5, pages 88–99; November 1987.

X-RAY MICROSCOPES. Malcolm R. Howells, Janos Kirz and David Sayre in *Scientific American,* Vol. 264, No. 2, pages 88–94; February 1991.

Information on light sources around the world is available on the World Wide Web sites of the Advanced Light Source and the European Synchrotron Radiation Facility: www-als.lbl.gov and www.esrf.fr, respectively. The ALS also maintains an interactive site for exploring the structure of materials. The site, which is oriented to teachers and high school students, can be reached at www.lbl.gov/MicroWorlds

COMBATING



NELSON N. STONE *Mount Sinai School of Medicine and ProSeed, Inc.*

PROSTATE CANCER

by Marc B. Garnick and William R. Fair

Recent advances in diagnosis and treatment promise to extend survival time and improve the quality of life for many patients

RADIOACTIVE PELLETS (*red*), or "seeds," have been inserted into the prostate gland in an attempt to destroy a cancer within it. At one time, seed implantation, also known as brachytherapy, produced disappointing results. The seeds were often distributed unevenly, leaving some parts of the gland untreated. Today templates placed on the patient, combined with real-time ultrasound imaging of the prostate, enable physicians to achieve a uniform distribution and, according to recent findings, a much improved success rate.

The death rate from prostate cancer in the U.S. has been declining for several years, but the disease still claims too many lives. It will strike an estimated 184,500 men this year and prove fatal in 39,200, making it the second leading cancer killer of men, behind lung cancer. For such reasons, we and others continue to seek ever better ways to manage this disorder, which is especially prevalent in those older than 65. We cannot claim the ideal solution for every patient is at hand, but a spate of exciting recent discoveries deserves notice.

Some of the newer findings address a vexing flaw in the sole noninvasive screening test for detecting microscopic prostate cancer, the form most amenable to a cure. The test measures the level in the blood of prostate-specific antigen (PSA), a protein released by prostate cells. Both normal and malignant prostate cells secrete this substance, but when cancer is present, the levels in the circulation often rise. Elevated PSA levels can thus warn that the prostate gland harbors cancer even if the tumor is too minute for a doctor to feel. The other main screening test, the digital rectal exam, can identify only tumors that are no longer microscopic. In that procedure, a doctor inserts a finger into the rectum and, through its wall, feels the prostate for hardness or lumps.

Unfortunately, the PSA test is not particularly specific. As many as 25 percent of men with cancer will have normal PSA levels—usually defined as those equal to or below four nanograms per milliliter (ng/mL) of blood. At the same time, more than half of men with higher PSA levels are, in reality, cancer-free.

Before discussing the leading ideas for minimizing that error rate, we should acknowledge that use of PSA testing for mass screening has long been, and remains, controversial [see "The Dilemmas of Prostate Cancer," by Marc B. Garnick; Scientific American, April 1994]. In essence, some physicians, especially in Europe, doubt the need for identifying microscopic prostate cancers, which develop after a once normal prostate cell becomes unresponsive to the usual controls on proliferation and migration. Microscopic tumors, they point out, often grow too slowly to cause symptoms in a man's lifetime or to affect how long he lives. Consequently, doctors may do more harm than good by exposing large numbers of men to PSA testing, to follow-up tests (such as ultrasound imaging and biopsy) in response to elevated scores and then, if a hidden spot of cancer is found, to the side effects of therapy.

Other physicians, we among them, counter that the PSA test generally finds malignancies that will, in fact, affect survival time (become "clinically significant"). Moreover, scientists cannot yet distinguish conclusively between microscopic tumors that will become lethal and those that will not; hence, denying treatment to men with such cancers would certainly doom an unpredictable group of them to a premature death.

Improving Detection

Even investigators who favor PSA screening are unhappy about its lack of specificity. One scheme that may better distinguish patients who have cancer from those who do not relies on a sliding scale of acceptable PSA levels, with the top limits for normal starting low and rising with age [*see illustration on page 77*]. The approach is based on the observation that as men grow older their PSA concentrations tend to climb, even if the prostate contains no cancer. Ideally, such sliding scales should lower the threshold of suspicion for men in their 40s and 50s, in whom prostate cancer tends to be most aggressive. And they should spare more men in their 60s and 70s from unnecessary follow-up tests. Some doctors worry, however, that age-adjusted scales will miss malignancies in the older groups.

When two or more consecutive PSA results are available, the rate of change from one year to the next, otherwise known as PSA velocity, can help single out patients who have cancer, regardless of whether their raw PSA scores are in the normal range. Increases of greater than 0.75 ng/mL may signify that a biopsy is warranted.

A third manipulation can be especially helpful when a PSA score falls in the gray zone between clearly normal and clearly abnormal, such as between 4 and 10 ng/mL. Along with considering age to decide whether a given patient probably has cancer, physicians can take a blood sample and look at the relative levels of free PSA molecules (those not complexed to other proteins) and protein-bound versions. Men with prostate cancer tend to have an abnormally low ratio of free to bound PSA.

Aside from PSA, other molecules released into the circulation may undergo changes in structure or amount when cancer arises. Scientists are attempting to develop screening tools based on such changes. Certain tests may even identify men who do not yet have prostate cancer but are likely to acquire it; such individuals need extra monitoring and may benefit from promising ideas for prevention. Researchers, for instance, are investigating whether high levels in the blood of a molecule called insulinlike growth factor-1 can serve as a warning that a man has prostate cancer or is at increased risk for its development.

Pathologists have identified a rather different sign of cancer risk, one found only if a PSA test has prompted a biopsy or if a man has had prostate tissue removed for other reasons. Tissue excised from the prostate is always examined under a microscope for cancer, which is marked by misshapen or fused cells and by their loosened or disorganized packing. At times, pathologists who review prostate specimens see no cancer but do find areas displaying less dramatic abnormalities, such as a condition known as high-grade prostatic intraepithelial neoplasia (PIN). The jury is still out on whether high-grade PIN is a precursor of prostate cancer or merely a fellow traveler, but one thing is now clear: it warns that prostate cancer may be developing or is already hiding somewhere in the gland. Indeed, cancer shows up within five years in about half of patients with PIN who submit to subsequent biopsies.

Geneticists, too, are searching for indicators of an increased propensity for prostate cancer. Brothers and sons of women who have breast cancer or who carry a mutant form of the *BRCA1* gene (which has been linked to breast cancer) have a somewhat elevated risk. In addition, inheritance of an abnormal form of the *HPC1* (human prostate cancer 1) gene seems to contribute to some prostate cancers. Genetic screening tests for susceptibility to prostate cancer have not yet been perfected, however.

Who Can Be Cured?

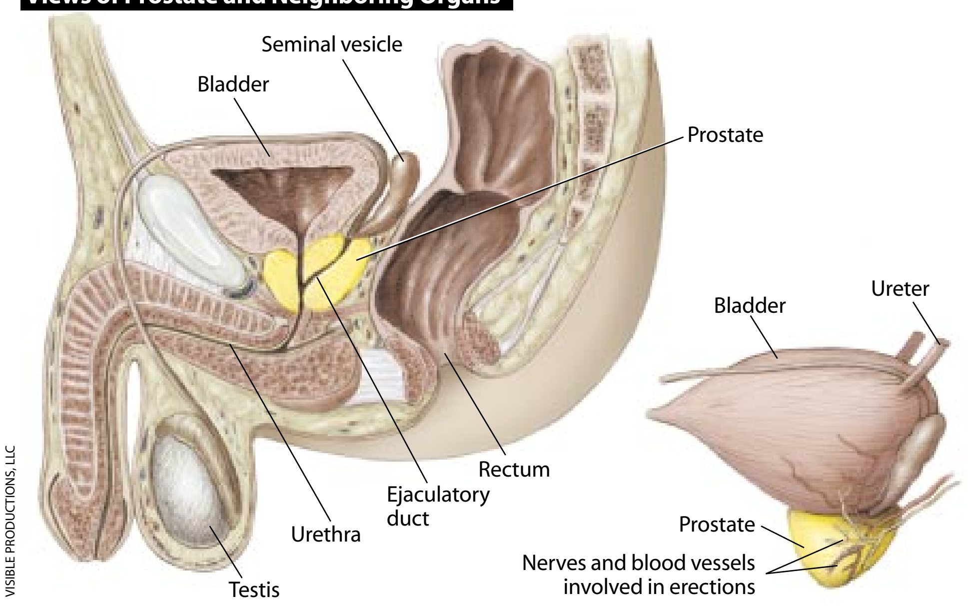
If a man is ultimately found to have prostate cancer, doctors will assess its stage, or extent of spread. Accurate evaluations are critical, because the stage determines the type of therapy a patient should receive. Existing diagnostic methods often produce an inaccurate picture of tumor progression, but new tools are helping to remedy this serious problem.

The value of these tools becomes most apparent when the logic that links stage to treatment is clear. Of the available staging systems, the so-called TNM approach has recently become most popular. It assigns the original, primary tumor (T) to one of four stages (and to substages within those categories). In general, a T1 designation indicates the tumor is microscopic and cannot be felt on rectal examination. T2 refers to tumors that are palpable but appear to be fully contained within the gland. T3 cancers have pushed beyond the prostate into surrounding connective tissue or have invaded the seminal vesicles (semen-storing structures) adjacent to the prostate. T4 tumors have extended still farther.

The system also assesses whether the cancer has metastasized to the pelvic lymph nodes (N) or beyond (M). Metastases are tumors that result when cancer cells break away from the original tumor, travel through the blood or lymphatic circulation to distant sites and proliferate at those sites.

As a rule, a tumor confined to the prostate gland, in stage T1 or T2, should be curable by prostatectomy (surgery to re-

Views of Prostate and Neighboring Organs



PROSTATE GLAND (*yellow*), which helps to maintain the viability of sperm and participates in semen production, lies close to several structures involved in bladder, bowel and sexual function. As prostate tumors grow, they often impinge on the bladder or urethra, causing such urinary problems as frequency and urgency. Treatments for prostate cancer can likewise affect surrounding tissues, causing incontinence, rectal inflammation, impotence or other effects.

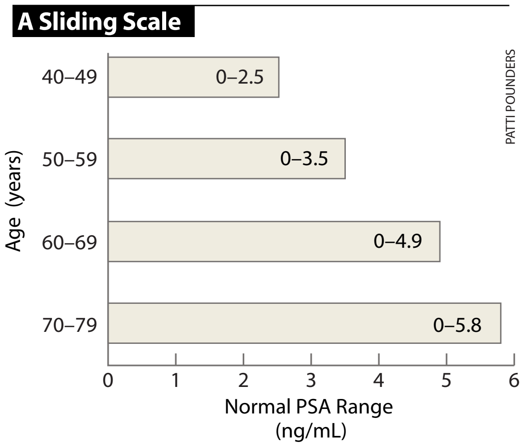
move the prostate, not an essential organ). It might also be cured by local radiation to destroy the tumor or by surgery or radiation combined with systemic hormonal therapy. Hormonal therapy is based on the fact that androgens—testosterone and related “male” hormones—fuel the growth of prostate tumors. It aims to stop the body from making androgens or to block androgen action in prostate cells, or both. In the absence of androgen stimulation, malignant prostate cells will often die. Hence, hormonal therapy can help shrink cancers and destroy malignant cells left behind by the other treatments, although it is unlikely on its own to eliminate prostate cancers that are no longer microscopic.

Surgery is still considered the “gold standard” for treating organ-confined disease, because it has produced the best survival times in long-term studies. As will be seen, however, advanced forms of radiation therapy and other new approaches to care promise to achieve comparable success in many instances.

When a malignancy has penetrated past the outer surface of the prostate (progressed to stage T3 or T4), surgical removal of the gland usually cannot eradicate the entire tumor. Radiation thus becomes the treatment of choice, again possibly combined with hormonal therapy. Some fraction of these protruding, later-stage tumors may be eradicable, but the odds of a cure tend to be much lower than for organ-confined disease. The odds decline because the masses are often large; big tumors frequently are resistant to the effects of radiation and drugs. Moreover, a high percentage of these tumors have already established as yet undetectable (microscopic) metastases by the time cancer is diagnosed.

Regrettably, existing therapies rarely cure metastatic disease. When a tumor has clearly metastasized or seems highly likely to have done so, physicians and patients usually switch their focus from achieving a cure to prolonging life and easing symptoms. Because hormonal therapy shrinks prostate tumors, it has long been a mainstay for these purposes. Radiation and sometimes chemotherapy (nonhormonal drugs) can also be delivered to relieve discomfort.

Deducing the correct stage is so important because the risks of intensive, curative therapies are justified only if the treatment has a reasonable chance of success. For surgery and radiation, the complications can include damage to the urinary tract and to nerves needed for an erection and thus can lead to incontinence and impotence, among other effects. Hormonal therapy can result in impotence, feminization, hot flashes and loss of libido, energy and bone density.



LEVELS OF PSA (prostate-specific antigen) in the blood can indicate whether a man is likely to have prostate cancer and thus needs diagnostic testing. One scale adjusts the definition of an acceptable PSA value as a man ages, instead of using four nanograms per milliliter of blood (ng/mL) as the top normal level for everyone. Doctors are still debating the best cutoffs, however.

Physicians determine the stage by examining the cancer from various perspectives and combining the results. They palpate and image the gland to assess tumor volume and positioning. They analyze any available prostate tissue (such as biopsy material) in a microscope, to gain a sense of the cancer’s aggressiveness. A high degree of cellular and tissue disorganization, represented by a high Gleason score, signifies that a tumor probably is fast-growing and may have already metastasized. Gleason scores range from an encouraging 2 to a worrisome 10.

Doctors can also employ a number of tools to spot metastases directly. Because prostate cancer usually spreads initially to the lymph nodes of the pelvis, the search often involves microscopic analysis of tissue from those nodes. Computed tomography (CT) scans may also reveal macroscopic abnormalities suggestive of metastases in pelvic or abdominal nodes. In this procedure, a rotating beam of x-rays produces cross-sectional images of a selected region of the body. Given that prostate cancer often spreads to the skeleton as well as to the lymph nodes, a radionuclide bone scan, performed with a different device, may also be done.

More Accurate Staging

Regardless of doctors’ best efforts, men are understaged—initially deemed to have less advanced cancer than they actually harbor—with astonishing frequency. This misassessment is true of so-called clinical staging, which is based on tests completed before a patient has therapy. To a lesser extent, it also plagues “surgical” or “pathological” staging, which usually provides a truer picture of a patient’s status. In surgical staging, pathologists examine any tissue removed during a prostatectomy, including a margin around the prostate, some lymph nodes and the seminal vesicles. Malignant cells in the margin or in other extraprostatic tissue indicate that a tumor presumed to be organ-confined is more extensive than was thought and has a good chance of having spawned undetected metastases.

Various studies in recent years have shown, for instance, that a disturbing 40 to 50 percent of patients clinically staged as having a prostate-confined tumor in fact have higher-stage disease that may not be eliminated by surgery or radiation. Of patients who seem initially to have been cured by surgery (according to pathological staging tests) or by radiation, roughly 10 to 30 percent will later have a recurrence stemming either from residual cancer cells in or near the prostate or from microscopic metastases that were unrecognized when therapy was first administered. Often the earliest sign of trouble is a rise in the PSA level; this elevation may occur as early as five or 10 years before metastatic tumors cause symptoms.

Tools able to provide more informative images of the primary tumor are beginning to improve the accuracy of clinical diagnosis. In most patients, neither CT scanning nor standard ultrasound procedures can provide a clear picture of a tumor or its spread beyond the prostate gland. An experimental ultrasound technique now showing promise applies a signal-processing technology known as spectrum analysis. Sound waves are bounced off the prostate as usual, but the machinery analyzes all the information in the sound echoes instead of the much smaller fraction used by more ordinary ultrasound devices. Then a sophisticated computer program translates the full set of data into a three-dimensional view of the gland, complete with color to highlight the tumor.

New approaches to magnetic resonance imaging (MRI) are under study in parallel. MRI devices emit magnetic fields around a patient to produce cross-sectional images of the body. Typical systems do not yield high-resolution maps of a prostate tumor. But when a patient also has a small emitter of electromagnetic waves inserted into his rectum (an "endorectal coil"), the resulting views can often show whether, and how far, the tumor has grown past the prostate gland. Magnetic resonance spectroscopy, which measures metabolic activity in a viewed area, may further help distinguish between normal and cancerous tissue. Neither ultrasound nor MRI can reveal microscopic extensions, however.

A more mathematical strategy for gauging a cancer's true stage has recently begun to serve as an aid for deciding on treatment. It relies on tabulations of the probability that a patient clinically determined to have organ-confined prostate cancer actually has a more extensive primary mass or metastatic disease.

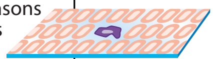
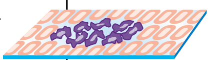
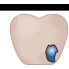
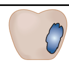
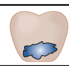
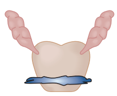
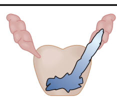
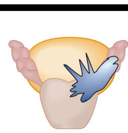
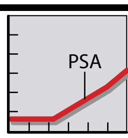
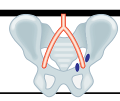
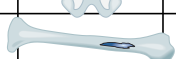
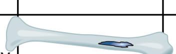
Various predictive models have been constructed, but one table frequently consulted by physicians and patients appeared in the May 14, 1997, issue of the *Journal of the American Medical Association*. It groups a large sampling of men according to the clinical stage of their tumor, their presurgical Gleason score and their presurgical PSA level, and it shows how men in each category fared when the tumors were restaged after surgery. The chart is complex but underscores that, in general, the odds of understaging and metastasis go up as tumor size, PSA level and Gleason score rise in concert. With the precise numbers in hand, a doctor can better predict a patient's true condition and can tailor therapy accordingly.

For example, the table suggests that about 80 percent of patients deemed clinically to have a small but palpable cancer (substage T2a), a low PSA (4 ng/mL or less) and the lowest possible Gleason score (2 to 4) do indeed have organ-confined disease. Moreover, none of those patients is likely to show signs of metastasis in the selected lymph nodes that were biopsied in the study group. Surgery, then, would be a viable option for men with that profile, and the odds of a cure would be high.

In contrast, probably only 5 percent of patients with a tumor of the same clinical stage but a PSA higher than 20 and a top Gleason score (8 to 10) truly have organ-confined disease, and more than 20 percent probably have metastases in the nodes. These results imply that for most patients in the same category, surgery alone probably would not be curative and that other treatments, such as a combination of local radiation and systemic hormonal therapy, merit consideration.

Other novel approaches to clarifying a

The Stages of Prostate Cancer

STAGE	SUBSTAGE		TYPICAL TREATMENTS
Stage T1 Microscopic tumor confined to prostate gland; palpated gland feels normal	T1a Tumor found in prostate tissue removed for reasons other than cancer; less than 5 percent of specimen is malignant		Observation, surgery to remove the prostate gland (prostatectomy) or local radiation
	T1b Same as T1 but more than 5 percent of specimen contains cancer		Surgery or radiation, possibly combined with hormonal therapy (to stop male hormones from stimulating tumor growth)
	T1c Tumor found through biopsy done in response to an elevated PSA test or to an abnormal ultrasound exam; may be less extensive than a T1b tumor		Same as for T1b
Stage T2 Palpable tumor confined to prostate gland	T2a Tumor confined to less than half of one lobe		Same as for T1b
	T2b Tumor affecting more than half of one lobe		
	T2c Tumor involving both lobes		
Stage T3 Tumor that has begun to expand beyond the prostate	T3a Tumor that protrudes beyond the prostate		Radiation with hormonal therapy; surgery for some patients
	T3b Tumor that has invaded the seminal vesicles		Radiation with hormonal therapy
Stage T4 Tumor that is fixed and has pushed well beyond the prostate into adjacent structures			Hormonal therapy, possibly with radiation to ease local obstructive symptoms; treatment usually is palliative (aimed at slowing disease progression and easing discomfort) rather than curative
Stage D1.5 (term borrowed from an earlier staging system) Locally recurring tumor or metastasis revealed by a rising PSA level after prostatectomy or radiation aimed at a cure			Observation, radiation to prostate area, hormonal therapy, investigational therapy or a combination of approaches; treatment may aim for a cure if a recurrence is near site of original tumor
Metastatic cancer	N+ Tumor that has spread to pelvic lymph nodes		Hormonal therapy, usually palliative
	M+ Tumor that has spread beyond pelvic lymph nodes		Same as for N+
	D3 Tumor that has become resistant to hormonal therapy		Palliative chemotherapy or investigational therapy

LAURIE GRACE

STAGE, or extent of spread, of a tumor is assessed as a guide to how the cancer should be treated. Many physicians have recently come to favor the TNM (tumor, node, metastasis) system, which classifies prostate malignancies according to features of the primary, or original, tumor (T) and according to whether the tumor has metastasized to pelvic lymph nodes (N) or to distant sites (M). This table is a refinement of the basic TNM system.

tumor's true stage concentrate specifically on assessing signs of aggressiveness—that is, they look for new clues to the growth rate and metastatic potential of the cancer. Before treatment, these tests can help determine which patients need prompt, and possibly systemic, therapy. They might also provide some guidance for deciding which technically curable tumors do not, in fact, need to be cured—because they are so slow-growing that they are unlikely to cause symptoms and turn lethal in a patient's lifetime. Assessments of tumor aggressiveness can also help indicate whether follow-up systemic treatment is advisable for patients who have already undergone surgery or radiation.

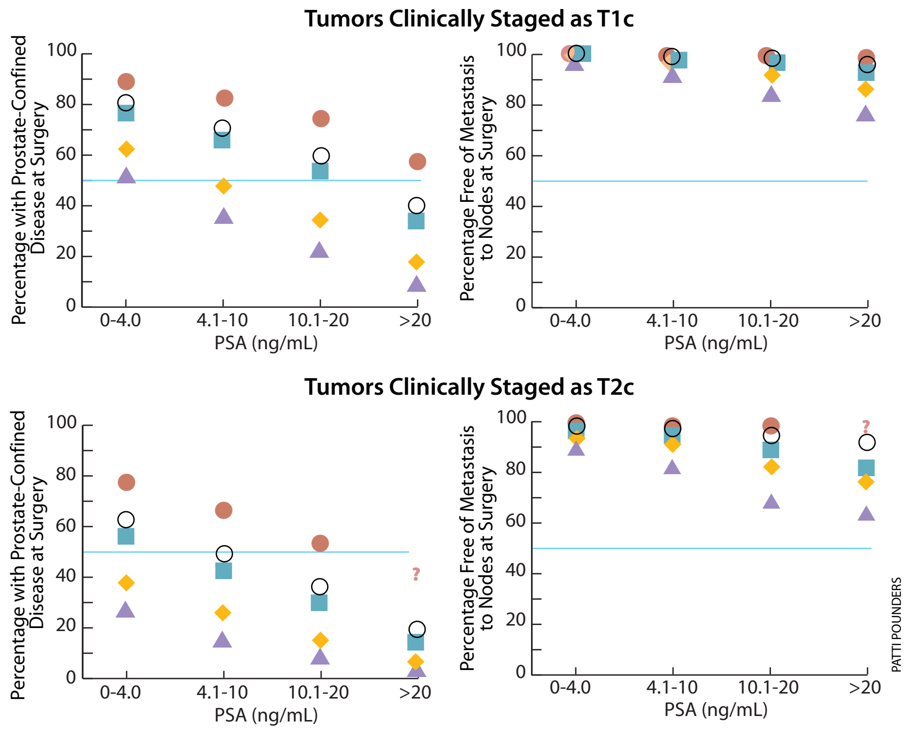
New Assessments of Aggressiveness

Turning again to mathematics, researchers have reviewed 15-year survival rates for more than 750 patients with seemingly prostate-confined cancer, stratified by their Gleason score at diagnosis. The findings—published by Peter C. Albertsen of the University of Connecticut Health Center and several colleagues in the September 16, 1998, issue of the *Journal of the American Medical Association*—show that men having tumors of Gleason grades 2 to 4 face minimal risk (4 to 7 percent) of dying from prostate cancer in 15 years, whereas men having tumors of grades 8 to 10 face a high risk (60 to 87 percent) even if they are diagnosed when they are as old as 74 years.

Such results tend to suggest that men with the lowest Gleason scores and apparently organ-confined tumors have a reasonable chance of doing well with close monitoring alone but that men at the other end of the scale, with the highest Gleason scores, are unlikely to do well without treatment. Men in the middle continue to pose more of a puzzle. Those with Gleason scores of 5, 6 and 7 have a 15-year risk of dying from prostate cancer of 6 to 11 percent, 18 to 30 percent and 42 to 70 percent, respectively, if they go untreated.

Several emerging or experimental approaches to predicting tumor behavior fall under the heading of "molecular" staging tools. They look at genetic alterations or at changes in protein structure or concentration that are more characteristic of metastatic prostate cancer than of localized tumors or normal prostate tissue. If those features appear in biopsied tissue, they suggest the cancer can be fast-growing and prone to metastasizing.

Predicting a Tumor's True Status



SOURCE: *Adapted from statistics from Alan W. Partin et al. in* Journal of the American Medical Association, *May 14, 1997*

Key
- Gleason 2-4
- Gleason 5
- Gleason 6
- Gleason 7
- Gleason 8-10
- ? No data available

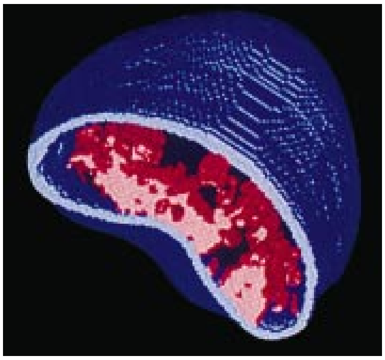
ODDS THAT TUMOR in a given patient has been accurately staged by clinical (pretreatment) assessments can be estimated by examining data on the fate of men who were evaluated before and after surgery. The graphs above, displaying some of those data, stratify patients according to their Gleason score (*colored shapes*), an indicator of tumor aggressiveness. They show that for a patient clinically deemed to have a prostate-confined tumor, the chances of having a truly organ-confined mass (*left graphs*) that has not yet metastasized to pelvic lymph nodes (*right graphs*) generally decline as the clinical stage, PSA level and Gleason score rise.

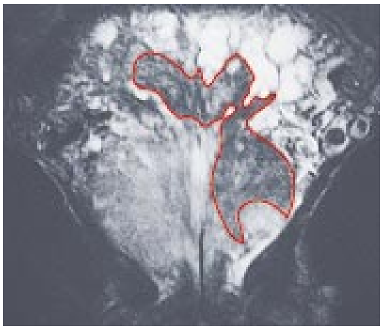
One experimental assay detects mutated copies of the *p53* gene, which in its healthy form functions as a tumor suppressor. Damaged versions of *p53* occur in many malignancies. They are rare in primary prostate tumors but do sometimes appear in metastatic deposits. Hence, discovery of aberrant *p53* genes in biopsy specimens from the primary tumor or in the excised gland after surgery signifies that the cancer is unlikely to be indolent even if it is still microscopic and fairly well differentiated. Other molecular changes under study as indicators of aggressiveness include increased levels of the Bcl-2 or Bcl-6 proteins and the appearance of an enzyme called telomerase; all three molecules seem to help cancer cells to survive long after they should have died.

The study of cancer-related molecules is also generating fresh ideas for pinpointing metastases. A promising avenue involves molecular "highlighters" (usually radioactively tagged antibodies) that circulate in the body, finding and marking prostate cells in nonprostatic tissues. Normal prostate cells cannot survive outside their original milieu. The presence of prostate cells far from the gland indicates, therefore, that the wayward cells are cancerous and may well have succeeded in establishing metastases in new sites. A test deploying an antibody able to recognize a protein called prostate-specific membrane antigen is already in use, and others are being investigated.

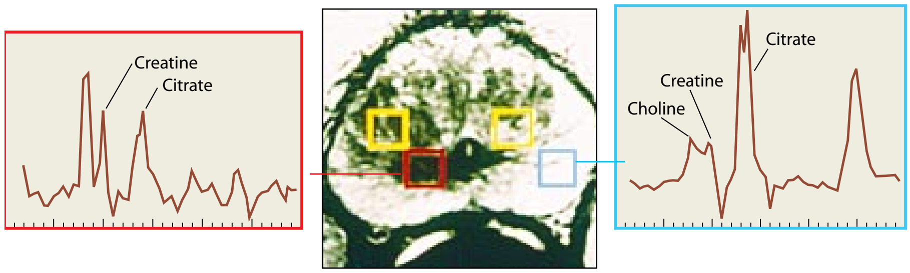
Making Therapy More Effective

Just as detection and staging methods are undergoing change, so too are treatments. In particular, enhanced approaches to radiation therapy and new applications of hormonal





NEW IMAGING APPROACHES may help reveal the full extent of a tumor before treatment is attempted. A technique that extracts extra information from ultrasound echoes can generate a three-dimensional picture (*top left*) that distinguishes normal tissue from a tumor (*red*). Combining an "endorectal coil" with standard magnetic resonance imaging (MRI) can also delineate a tumor (*bottom left, outline added*). And MR spectroscopy can add an extra dimension to such results (*below*). By assessing differences in metabolic activity across an imaged gland (*graphs*), it distinguishes cancerous tissue (*red box*) from normal tissue (*blue box*). (The yellow boxes highlight noncancerous abnormalities.)



Top left: ERNEST J. FELEPPA *Riverside Research Institute, New York City; bottom left:* CLARE TEMPANY *Brigham and Women's Hospital, Boston; right:* HEDVIG HRICAK *University of California, San Francisco*

therapy are improving the survival prospects for many patients.

Classical radiation therapy takes the form of external-beam radiation, in which a linear accelerator moves around a patient, shooting intense x-rays or gamma rays at the prostate from different angles. This rotation aims to limit the radiation hitting healthy tissue in the "line of fire" while still providing a high aggregate dose to the tumor (although normal tissue close to the prostate still receives potentially damaging doses).

In a recent study that followed patients for five years, this approach appeared to be as successful as prostatectomy in curing relatively small tumors confined to the prostate gland. When a mass in the prostate is large, however, standard doses of radiation may be too low to erase all cancer cells. Yet the higher doses that are needed may be too toxic to structures close to the prostate.

A relatively new technique, known as three-dimensional conformal radiation therapy (3-D CRT), makes it possible to deliver once unheard of doses to organ-confined tumors without increasing the risk of damage to nearby tissues. In this method, now available at most major medical centers, radiation physicists produce cross-sectional CT scans of the prostate. Then a computer combines the information into three-dimensional images of the gland as it will be "seen" by the rotating accelerator. The computer also directs the accelerator to shape and reshape the radiation beam so that at all times it matches the precise dimensions of the individual's prostate and thus minimizes the amount of radiation striking outside the gland's boundaries.

Although 3-D CRT has not yet been shown conclusively to produce higher cure rates, it looks promising and does seem to limit side effects. Proof of greater effectiveness might be needed before the technique, which is more expensive than standard radiation therapy, becomes accepted universally.

Many men choose a rather different form of radiation therapy: brachytherapy. A surgeon puts radioactive, rice-size pellets directly into the prostate, where they emit radiation from within the gland. The seed procedure often appeals to patients because implantation is relatively simple, requires minimal hospitalization (lasting perhaps a day or two) and leaves no surgical wound. If a tumor extends past the prostate, brachytherapy may be combined with external-beam radiation to attack the outer reaches of the mass.

When brachytherapy first became available decades ago, it seemed promising, but its long-term results were unsettling. The pellets had to be placed without the aid of imaging technology, and parts of the prostate often ended up with few or no radioactive seeds. These days many brachytherapists perform the procedure with the help of a template placed between the scrotum and rectum. They also watch their work on an ultrasound monitor to ensure that the implants are spaced evenly throughout the gland. The approach now appears to be about as effective as external-beam radiation or surgery for treating men who have low-stage (T1 or T2) tumors that seem relatively unaggressive (having Gleason scores of 6 or lower).

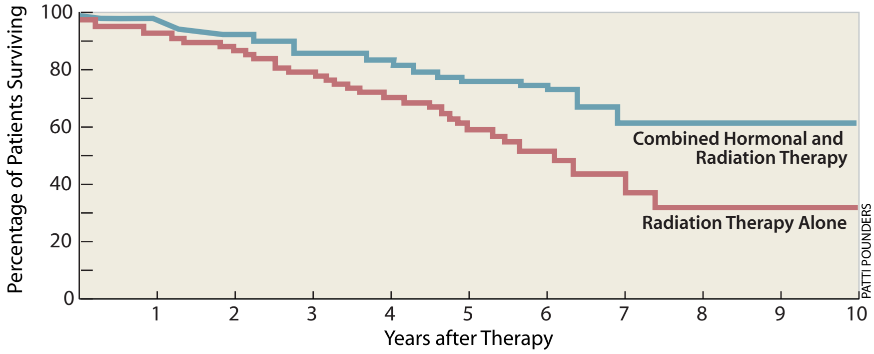
A number of medical centers offer another fairly simple way to attack tumors in the prostate: cryosurgery, or freezing the gland with probes containing liquid nitrogen or argon gas. Cryosurgery comes with a high risk of side effects, particularly incontinence, and its ability to eliminate tumors is not known. We cannot, therefore, recommend it as a first-line therapy for most men, but it may have merit when radiation therapy has failed to control a cancer.

Added Value from Hormonal Therapy

We are, however, impressed by recent findings supporting the value of hormonal therapy as a supplement to classical "definitive" therapies (those intended to achieve a cure). Preliminary reports suggest that such combination therapy often works better than the standard therapy alone. When hormonal therapy is delivered before radiation or surgery, it is known as neoadjuvant hormonal therapy. When it is given with or after those treatments, it is known as adjuvant hormonal therapy.

The idea behind combination treatment is simple. Neoadjuvant therapy aims to shrink bulky tumors so that radiation or surgery can eliminate them more readily. In the case of brachytherapy, for instance, physicians have a hard time inserting the radioactive seeds into glands containing large tumors. Reducing the tumor before insertion can ease the procedure and potentially increase the chance of success; it may also reduce side effects. Adjuvant therapy aims to mop up stray cells left behind at the tumor site after primary treatment

A Treatment Comparison



SOURCE: Michel Bolla et al. in New England Journal of Medicine, *July 31, 1997*

COMBINATION THERAPY, pairing hormonal treatment and radiation, was projected to yield longer survival than radiation alone in a study of 415 patients, most with locally advanced (T3 or T4) cancer. Hormonal therapy was delivered to kill residual cancer cells that had evaded radiation or had spread undetected to distant tissues. It works mainly by impeding the production or action of testosterone, a hormone that promotes tumor growth.

and also to destroy cells elsewhere that have broken free and could pose a metastatic threat. Animal studies suggest that hormonal therapy delivered before or with radiotherapy may, in addition, increase the sensitivity of prostate cancers to radiation.

Hormonal therapy usually consists of a combination of two drug classes. One such class includes so-called superagonists of gonadotropin-releasing hormone (GnRH), a substance that is released by the brain and that leads ultimately to testicular secretion of testosterone, the major male hormone that promotes the growth of prostate tumors. GnRH superagonists initially result in increased testosterone secretion, but after a few weeks, they inhibit testosterone manufacture and cause prostate tumors to shrink. The other drug class is made up of antiandrogens, which block testosterone from inducing the proliferation of cancerous prostate cells. A permanent means of halting testosterone production—surgical removal of the testes (bilateral orchiechtomy)—is also available.

The most impressive results have come from clinical trials of hormonal therapy combined with radiation. For example, in a study of 415 patients treated in Europe, those receiving three years of adjuvant therapy plus radiation survived longer than those who received radiation alone. Estimates projected that 79 percent of the first group but only 62 percent of the second group would still be alive five years after treatment. The study did not include a "hormonal-therapy-only" arm, however, so it cannot address whether combination therapy is superior to hormonal treatment alone.

Long-term investigations of neoadjuvant therapy have yet to be completed, but some studies strongly suggest a benefit from this approach as well. At the Memorial Sloan-Kettering Cancer Center in New York City, one of us (Fair) and his colleagues evaluated the ability of this treatment to ensure that tumors initially believed to be organ-confined were indeed fully within the prostate at the time patients underwent a prostatectomy. They found that three months of presurgical treatment increased the incidence of organ-confined disease at surgery and markedly lowered the frequency of worrisome tumor cells in the outer edges (margins) of the excised tissue. Yet to be determined is whether the tumor control achieved in the study will translate into a lower incidence of local recurrence or metastasis in the subjects and, hence, into enhanced survival rates.

Other studies that joined neoadjuvant hormonal therapy with surgery failed to show improved survival, but the patients were followed for only a short time. Trials testing more extended durations of neoadjuvant hormonal therapy and longer follow-up are under way.

Clearly, more research is needed. Scientists have to carry out extensive comparisons of combination therapies against surgery and radiation alone, and they need to determine optimal doses for and durations of neoadjuvant and adjuvant therapies. Nevertheless, the data to date have already convinced many physicians that combination therapy is worth trying in many patients having curative therapy for prostate cancer.

Hormonal therapy might find another role as well. Recall that the prostate abnormality known as high-grade PIN may be a precursor of cancer. Neoadjuvant hormonal therapy given to men before surgery eliminates or reduces PIN in many patients. This discovery raises the possibility that hormonal treatment might help prevent prostate cancer in some cases, although whether a reduction in PIN will in fact translate into a reduction in cancer is unknown.

Sadly, we have no dramatic news for men who already have metastatic can-

Risks of Localized Treatment

	Percent Who Die from Therapy	Percent Who Become Impotent	Percent Who Suffer Mild to Severe Incontinence
Radiation	<0.1	30–70	1–2
Brachytherapy (Seed Implantation)	<0.1	30–50	2
Prostatectomy	0.6	30–70	2–15
Cryosurgery	0.1	30–50	35

PATTI POUNDERS

RATES OF SOME SIDE EFFECTS have been calculated for men who undergo surgery or radiation aimed at directly eliminating tumors confined to the prostate gland. In general, the patients who fare best are those who are youngest, who have tumors of low stage and who are treated at facilities having the greatest expertise in performing the selected procedure. The drug-based hormonal therapy that may be administered as an adjunct to surgery or radiation in men with localized cancer usually causes adverse effects as well, but they often disappear after the patient stops taking the medicines.

cer. Hormone therapy usually extends life, but tumors eventually become resistant to the treatment. Investigators are attempting to uncover the molecular basis of this resistance, in hopes of designing drugs able to overcome it.

Scientists are, however, closing in on a way to eliminate a major drawback of hormonal therapy in those with metastatic prostate cancer. Recall that the GnRH superagonists usually prescribed as part of hormonal therapy initially stimulate testosterone production before shutting it down. In that early phase the drugs thereby promote tumor growth and so can exacerbate symptoms. An agent that blocks GnRH activity directly, an antagonist called Abarelix, is being developed by one of us (Garnick) and colleagues at Praecis Pharmaceuticals in Cambridge, Mass., in collaboration with other companies. It is now entering the final stages of human testing.

Promise of Dietary Intervention

As many researchers struggle to improve existing tools for detecting and managing prostate cancer, others are attempting to develop entirely new kinds of therapies. Most of these future treatments would work systemically, preventing cancer cells that escaped first-line attack from establishing metastases. If metastasis could be prevented, death rates from prostate cancer would surely plummet.

One idea being evaluated is decidedly low-tech: nutritional intervention, especially adoption of a low-fat diet. Conceivably, nutritional interventions might also prevent the development of symptomatic primary tumors.

Epidemiological studies comparing the eating habits of populations having high and low rates of prostate cancer indicate that a fatty diet, particularly one featuring a lot of red meat, favors the growth of prostate tumors. High consumption of fat is already infamous for promoting breast and colon cancer, but these studies indicate the effect is even stronger in prostate cancer.

An equally suggestive finding comes from placing countries on a grid according to death rate from prostate cancer and average fat consumption per person. The U.S. and western European nations, which ingest the most fat, also have the highest prostate cancer mortality rates. Conversely, men in the Pacific Rim nations, who consume the least fat, have much lower death rates from prostate cancer.

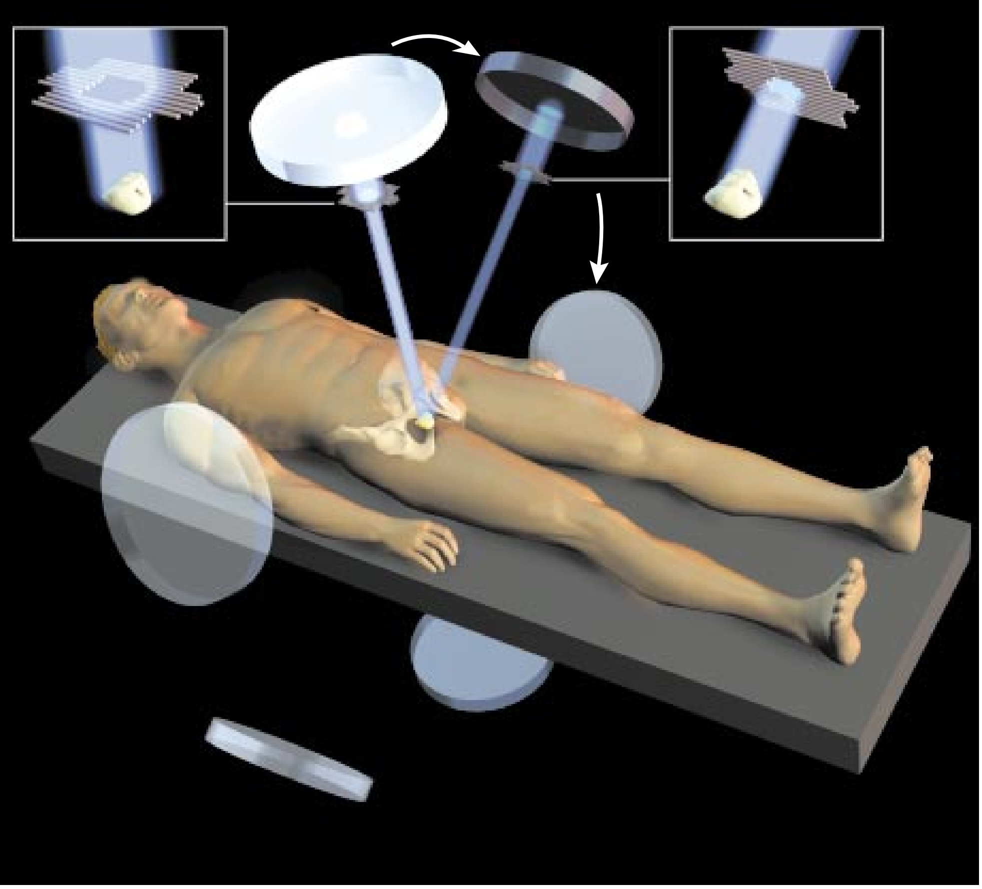
Laboratory experiments offer even more convincing evidence of a link between fat intake and prostate cancer. Fair and his co-workers at Sloan-Kettering have transplanted human tumors into mice and divided the animals into groups fed different amounts of fat. The tumors grew fastest in the groups having diets highest in fat.

Another dietary component that seems to influence prostate cancer—this time as an inhibitor of growth—is soy protein, a substance consumed in abundance in Japan. Soy reduces the amount of testosterone circulating in the blood and also inhibits an enzyme that converts testosterone to its more potent form in prostate cells. Some evidence implies that tomato products, vitamin E and the mineral selenium can inhibit tumor growth as well. Other components of food are also being explored as potential contributors to, or shields against, prostate cancer. Needed now are more human studies assessing the protective value of dietary manipulations

A Radiotherapy Advance

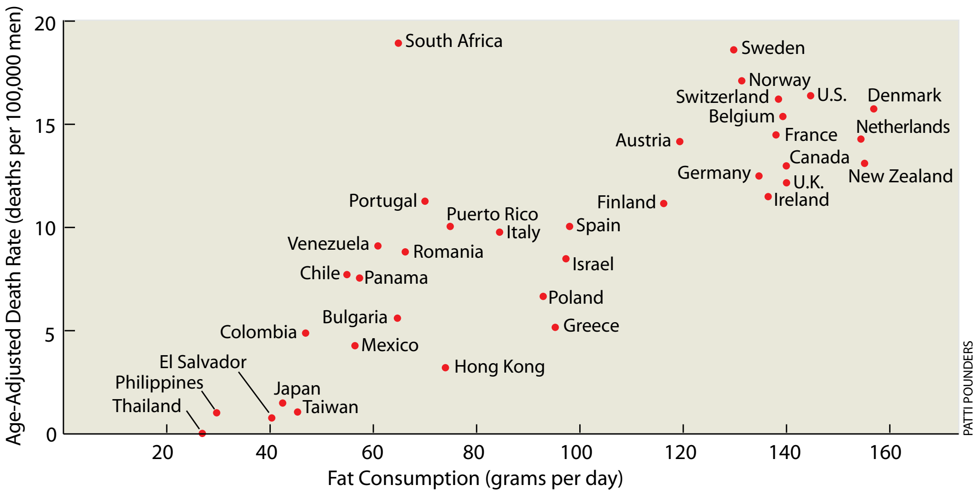
Three-dimensional conformal radiation therapy allows doctors to increase the doses of radiation delivered to the prostate gland without increasing damage to nearby tissues. As is true of standard radiation therapy, a linear accelerator rotates around a patient, pointing x-rays or gamma rays toward the prostate. But the conformal technique adds an important twist.

Before treatment is begun, digital images of the individual's prostate are prepared and compiled into virtual 3-D models of how the gland will "look" to the accelerator from all angles. Then the accelerator shapes the beam to match those "beam's-eye views" (*insets*), thus reducing the amount of radiation hitting the bladder, rectum or other unintended targets. —*M.B.G. and W.R.F.*



VISIBLE PRODUCTIONS, LLC

A Link between Diet and Prostate Cancer



SOURCE: K. K. Carroll and H. T. Khor in *Progress in Biochemical Pharmacology*, Vol. 10, 1975

MORTALITY from prostate cancer tends to be highest in countries that consume the most fat. This finding, from 1975, is now one of many indicating that fat consumption can promote prostate tumor growth and that a low-fat diet might limit such growth.

and nutritional supplements in men at risk for prostate cancer or its recurrence.

Interestingly, animal studies indicate that dietary components can increase or decrease the tendency of a microscopic cancer to grow into a dangerous mass but do not affect the processes that originally cause a normal cell to become malignant. This insight may help explain why the incidence of silent microscopic cancer (as measured by autopsies of men who die from causes unrelated to prostate cancer) is essentially the same worldwide, whereas that of palpable prostate cancers (ones that have managed to grow) varies with geography.

Tomorrow's Therapies

Several other intriguing ideas for systemic therapy derive from emerging understandings of how prostate cancer develops and becomes increasingly aggressive. These ideas are in very early stages of exploration.

A number of the genes and proteins being evaluated as markers of virulence seem to participate in tumor progression. Some of those substances, therefore, eventually may serve as useful targets of therapy. For instance, drugs able to block the action of the Bcl-2 protein are being tested in patients whose tumors display abnormally high levels of that substance. Similarly, workers are trying to identify agents that will stop fats from stimulating molecular pathways that facilitate tumor growth.

In recent years, scientists have shown that few if any cancers can reach large sizes unless they sprout new blood vessels [see "Fighting Cancer by Attacking Its Blood Supply," by Judah Folkman; Scientific American, September 1996]. Drugs that block such tumor blood vessels from arising are already being studied in many cancer patients, including those with prostate cancer.

Gene therapy is another possibility, although scientists will probably need many years to perfect this approach. A particularly intriguing idea would be to deliver genes coding for substances that are toxic to cells. If those genes were engineered to switch on only in prostate cells, they would give rise to the toxin in the prostate and in metastatic deposits but would have no effect on and do no damage to other kinds of cells.

Also in its infancy, but quite tantalizing, is research into vaccines: substances that would incite the immune system to attack cancerous prostate cells anywhere in the body without hurting nonprostatic cells. The immune system is capable of attacking malignant cells but often fails to recognize them on its own. Vaccines could potentially be administered both to prevent prostate cancer in men at high risk and to prevent recurrence in those who have already been treated for the disease.

Such targeted therapies will undoubtedly take many years to develop and evaluate. In the interim, research into improving detection, staging, treatment and prevention is intensifying. Certainly, much work remains to be done before the challenges of combating prostate cancer can be overcome, but we are heartened to see the pace of research quickening. SA

The Authors

MARC B. GARNICK and WILLIAM R. FAIR co-direct a yearly international conference on emerging treatments for prostate cancer. Garnick is clinical professor of medicine at Harvard Medical School and a physician at Beth Israel Deaconess Medical Center. He also serves as the chief medical officer of Praecis Pharmaceuticals in Cambridge, Mass., where he is developing a new hormonal therapy—a GnRH antagonist—for prostate cancer. Earlier in his career he developed GnRH analogues as well. Fair is Florence and Theodore Baumritter and Enid Ancell Chair of Urologic Oncology and director of the John and Robert Bendheim Prostate Cancer Research Center at Memorial Sloan-Kettering Cancer Center in New York City. He is also professor of urology at Cornell University Medical Center. He has devised many surgical procedures and has contributed insights into the role of nutritional factors in exacerbating and controlling prostate cancer.

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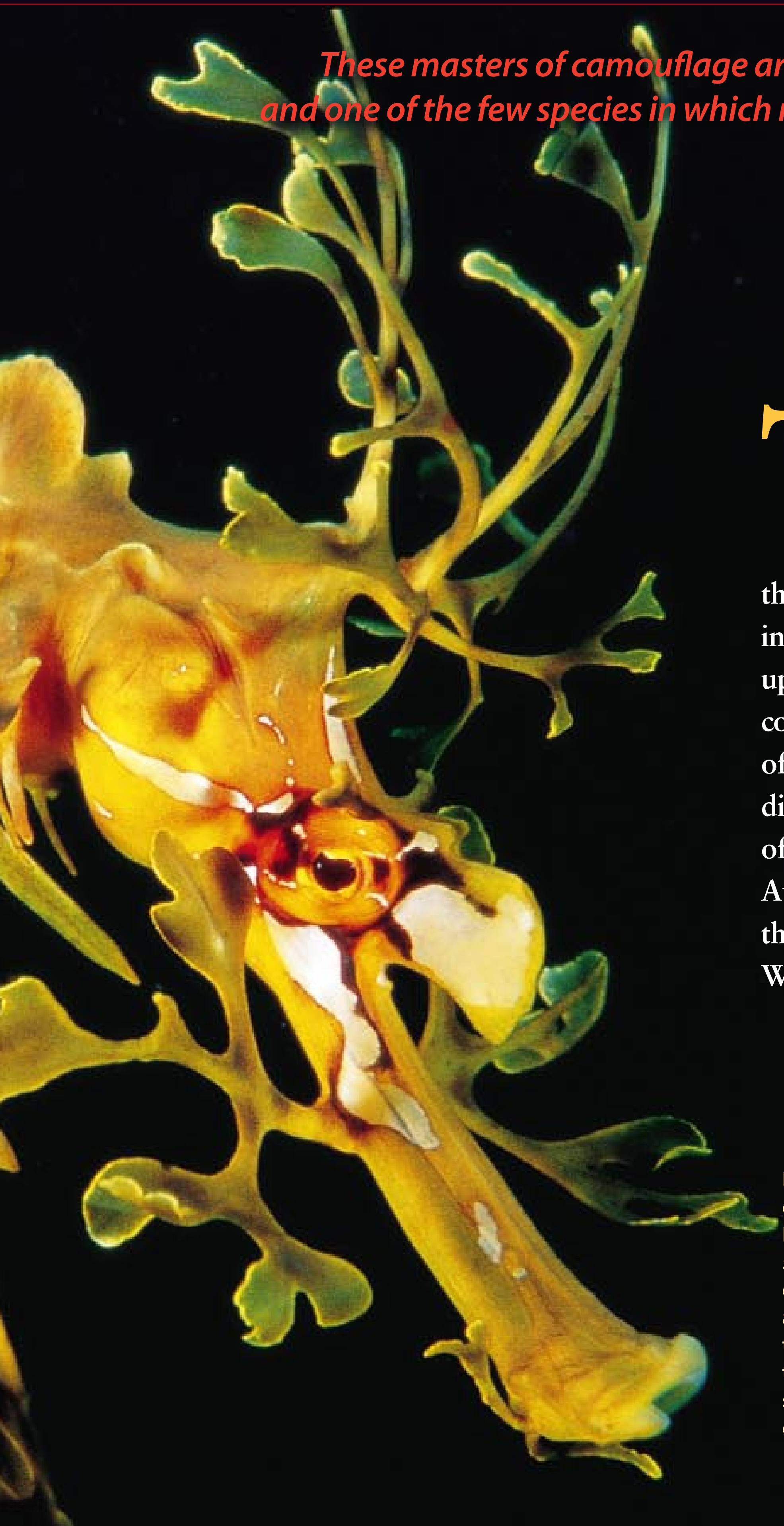
Leafy Sea Dragons

These masters of camouflage are fierce predators—
and one of the few species in which males become pregnant

by Paul Groves
Photographs by Paul Sutherland



LEAFY SEA DRAGONS inhabit the waters off the southwestern coast of Australia. Full-grown adults can reach a length of 50 centimeters (nearly 20 inches). The dragons are close relatives of sea horses and pipefish—a family of animals characterized by the bony plates surrounding their bodies and by snouts that are tube-shaped. In addition, males of these species are the ones that become pregnant.

The water is clear, calm and dark. As I drop off the rear of the boat with my fellow divers into the icy water, a chill runs up my spine—both from the cold and from my growing sense of anticipation. We are night diving in the Southern Ocean off the southwestern coast of Australia, in search of creatures that sound almost mythical. We are hunting for dragons—

more precisely, leafy sea dragons. And for our breeding program at Underwater World Perth, we want to catch a male—a pregnant male.

The leafy sea dragon (*Phycodurus eques*) and its more common cousin, the weedy sea dragon (*Phyllopteryx taeniolatus*), are the only sea dragons in the world. Along with sea horses and pipefish, they are members of the family Syngnathidae, fish characterized by a hard external skeleton arranged as a series of rings around the animal's body and by a long tubular snout with no teeth. Sea dragons are distinctive in that frondlike appendages branch out from their armor-plated bodies. As befits their names, the leafy sea dragons' appendages are broader and flatter than the more stringy ones of the weedy dragons. Both creatures are endemic to the southern Australian coastline. The waters off the islands of the Archipelago of the Recherche where we are diving are a favorite haunt for sea dragons. These huge, sparsely vegetated granite islands are a refuge for an amazing array of exotic animals, some of them found nowhere else in the world. Beneath the waves, the vertical granite faces plunge for hundreds of meters into the inky depths.

As I continue my descent, a shoal of prehistoric-looking boarfish, each about half a meter long, drift by as if in some sort of trance. At 15 meters down (about 50 feet), my torchlight picks up an algae-encrusted rock. Near the kelp and sargassum algae on the rock, I turn to shine my beam back into the open water. Nothing—all is still and quiet. I'm relieved: great white sharks make their home in these waters as well.

Once I point the light back onto the rocks, I quickly forget about the danger that may be lurking and concentrate on my search. It is much easier to locate sea dragons, masters of camouflage, at night in the narrow focus of a torchlight than during the day, when the abundance of marine life is distracting. After several minutes of searching, I spot a sea dragon. Once my heartbeat returns to normal, I realize with dismay that the creature is only a weedy sea dragon.

After being submerged for an hour in the dark at 15 degrees Celsius (59 degrees Fahrenheit), my extremities are starting to go numb, and I am all but ready to give up. I decide to take one last look over a boulder ahead of me before returning to the surface for a nice hot shower. As I glide over the boulder, I suddenly spy what I came for: an adult male leafy sea dragon, roughly the size of a dinner plate, with a brood of eggs.

Sea dragons and their relatives in the Syngnathidae family are unique in the fish world in that the male carries and hatches the eggs on the outside of its body. The eggs on the male I found were well developed, at least three weeks old, fixed firmly into cuplike indentations on the underside of its tail and covered in algae. Scientists believe that this type of breeding behavior evolved to hide the eggs from would-be predators.

Fortunately, this male dragon was in a relatively shallow five meters of water. If it had been any deeper, we would have had to bring it up to the surface slowly, giving the creature time to adjust to the decreasing pressure. This decompression process can put so much stress on a dragon that its eggs will be lost.

With the dragon safely on shore, we rushed home. After a two-hour, specially chartered flight, we arrived at the quarantine facility at Underwater World Perth, the only aquarium in Australia that exhibits these amazing animals. Here we took all the usual precautions to prevent the dragon from becoming stressed. Even sudden changes in light can be fatal to a leafy. After a day, we placed in the tank some mysid shrimp, each only a few millimeters in length, and the dragon started feeding almost straightaway. Sea dragons mimic drifting seaweed so that they can ambush their mysid prey. They strike at mysids by quickly expanding a joint on the lower part of their snout, causing a suction force that draws the shrimp in.

After a week at the aquarium, the algae-encrusted eggs on the tail of the captured male began to hatch. First a small tail protruded from an egg, wriggling and squirming. A few twitches more and our first baby sea dragon appeared—a miniature replica of its parent. At birth, leafy sea dragons are around 20 millimeters (0.8 inch) long; when they reach

SEA DRAGONS blend in with their environment, making them difficult for predators to spot. Humans often have trouble as well—so divers hoping to see a dragon often dive at night, when the animals stand out better in the beam of a flashlight.

CARL ROESSLER *Sea Images*

PREGNANT MALES carry the eggs for four to five weeks in cuplike indentations underneath their tails. Females initially produce the eggs but then transfer them to the male for fertilization, incubation and hatching. Little is known about the reproductive cycle of the leafy sea dragons. For instance, researchers are unsure how many times the sea dragons breed each year.

IKAN *Peter Arnold, Inc.*

YOUNG DRAGONS hatch from the eggs with a small yolk sac attached. The sac supplies food for the first few days of life. The newborns can swim and hunt for food almost immediately.

maturity, between 12 and 18 months old, they can attain a length of 50 centimeters (nearly 20 inches). It took 10 days for all of the 210 eggs to hatch; in the wild, this feature would serve to distribute the newborn dragons over a wider area, offering them a better chance of finding food without having to compete with their siblings.

Unfortunately, we lost 10 of the tiny newborns to a filter intake in the tank, but the rest survived and seemed to thrive in their new home. After several weeks, though, we found there was no way we could supply enough mysids to continue feeding all 200 dragons, so we arranged to return most to the spot where we found their father. Chances of survival in the wild for these dragons would be much greater than for most—the first few weeks of a sea dragon's life are particularly perilous, as young dragons are common prey for other fish. Our infant dragons were much larger and less fragile than when they were first born. Indeed, the biggest threat to them now would most likely be storms washing them ashore. Typically, leafy sea dragons live about five to seven years.

Mating Ritual

In 1997, two years after my frigid dive in the Archipelago of the Recherche, one of our juvenile leafy sea dragons, a female, became quite large in its abdominal area. In the preceding weeks, it had been spending a great deal of time side by side with one of our male leafys. The two had seldom been far apart from each other. The tail of the male also became swollen with fluid and wrinkled in appearance—a sure sign that mating was about to commence. In anticipation of what could be the first documented observation of sea dragons mating, I sat by with my video camera, watching intently.

Over the next several days, the two embraced in a delicate ballet, interlocking their leaflike appendages and ascending and descending in the water. They writhed left then right, up then down, in a sort of underwater wrestling match. Much to my delight, eggs soon began to appear from the abdomen of the female. But the moment was short-lived. The clusters of three to five bright orange eggs began dropping to the floor of the aquarium. Over about an hour, 150 of these eggs fell, without one hitting the tail of the male dragon.

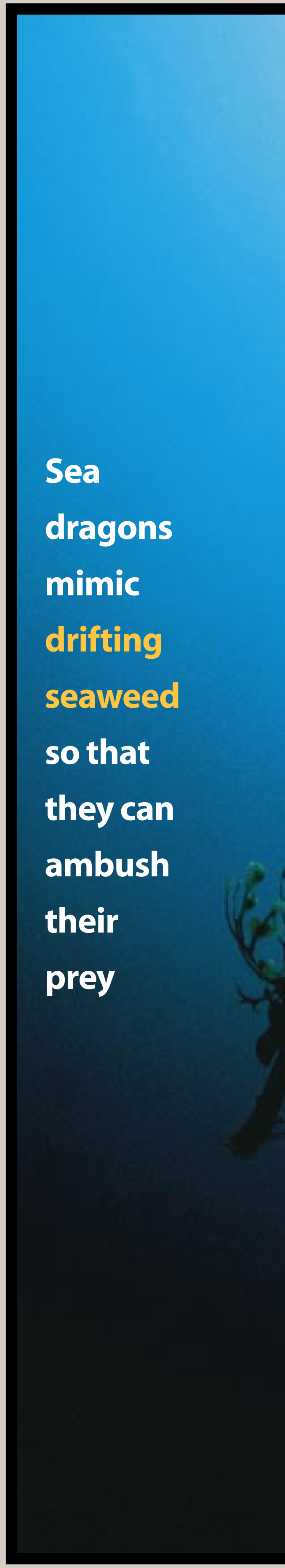
Because no one has observed and recorded the successful transfer of unfertilized eggs from a female to a male for fertilization and incubation, we are not exactly sure how this process is supposed to occur. But it is safe to say that something went wrong this time. Perhaps the presence of the other sea dragons in the aquarium distracted the couple. We were surprised to see that after depositing its eggs, the female dragon appeared totally exhausted, floating motionless on the surface. By the next day, however, she began swimming and feeding again.

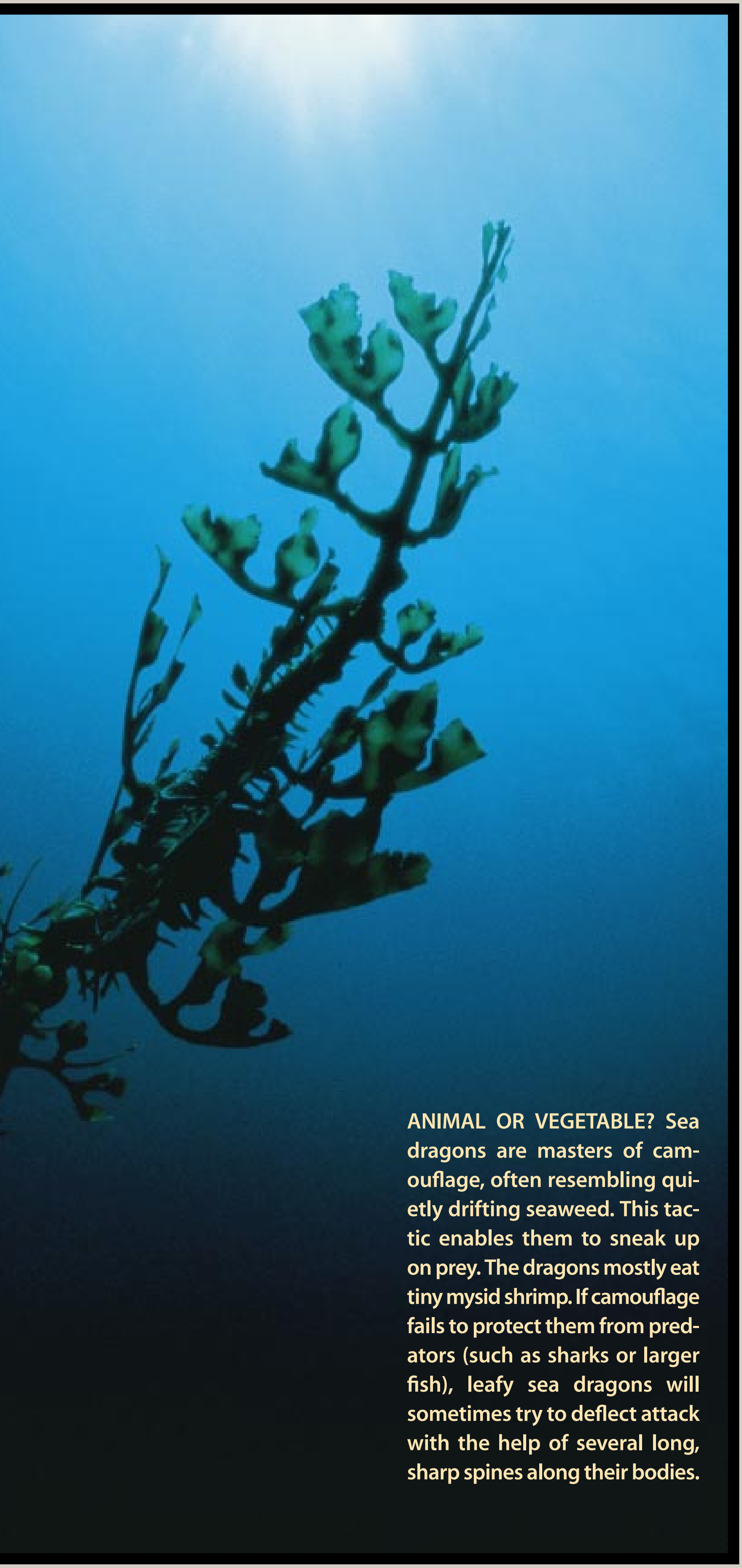
Happily, one pair in our aquarium now seems to be preparing to breed, so I will set up my video camera once more and hope for success. Our goal for the breeding program at Underwater World is to be able to maintain our own population of leafys without harvesting from the wild. When feasible, we plan to return young hatched in captivity to the wild (to date, we have been able to do this twice). And of course, we would like to learn more about these beautiful and unusual creatures—about their entire reproductive cycle, for instance, as well as about their biology in general. Should the numbers of wild sea dragons begin to fall, perhaps we will be able to help repopulate the area.

To stave off such a fall in numbers, however, several years ago Underwater World successfully campaigned to have the Australian government designate leafy sea dragons as a protected species. Now all Syngnathidae are being proposed for recognition by the Convention of International Trade in Endangered Species (CITES) Treaty. Under current Australian law (in effect only during this past year), Syngnathidae cannot be taken from the country without a special export permit from the government. And only specimens that have been bred in captivity or collected under an approved program will be considered for export.

Such laws should stop many Australian Syngnathidae from winding up as curios in novelty shops or as alleged aphrodisiacs in the herbal medicine trade in Asia. Improved tracking of the sea dragons sent to public and private aquariums should protect the creatures as well. Many aquariums would like to own leafy sea dragons—one reputedly sold for about U.S.$4,800 in Japan. Unfortunately, though, they are extremely difficult to care for in captivity, and many die once taken from the wild. Globally, sea dragons and other Syngnathidae are under threat not only from fishers but also from the effects of pollution and overfishing for other animals (Syngnathidae are often captured as bycatch in trawling nets).

In addition, Underwater World Perth helped to set up the Western Australian branch of Dragon Search, a joint program of various government departments and community groups throughout Australia. Initially the goal of Dragon Search was to monitor wild populations of leafy sea dragons, but now it monitors sea horses and pipefish as well. As part of an ongoing preservation effort, we hope to learn more about these animals—where they live and how large the populations are—by compiling reports from divers, fishers and beachcombers who find the creatures washed ashore. There is still much to learn about these magnificent animals, and we have only just begun. SA





ANIMAL OR VEGETABLE? Sea dragons are masters of camouflage, often resembling quietly drifting seaweed. This tactic enables them to sneak up on prey. The dragons mostly eat tiny mysid shrimp. If camouflage fails to protect them from predators (such as sharks or larger fish), leafy sea dragons will sometimes try to deflect attack with the help of several long, sharp spines along their bodies.

WEEDY SEA DRAGONS, a more common type of dragon, have fewer appendages than their herbaceous cousins but are roughly the same size as the leafy dragons. Males of the species carry the eggs for about four to five weeks during the summer months. Weedy sea dragons inhabit the waters of the southern coast of Australia.

KELVIN AITKEN *Peter Arnold, Inc.*

The Author

PAUL GROVES has been head aquarist at Underwater World Perth in Western Australia for three and a half years. He has worked with a full range of fishes, including sea dragons, sea horses, subantarctic fish, jellyfish and coral reef animals. With more than 10 years of diving experience, Groves hopes to re-create the oceans of Australia for nondivers and to contribute to the general conservation of ocean life.

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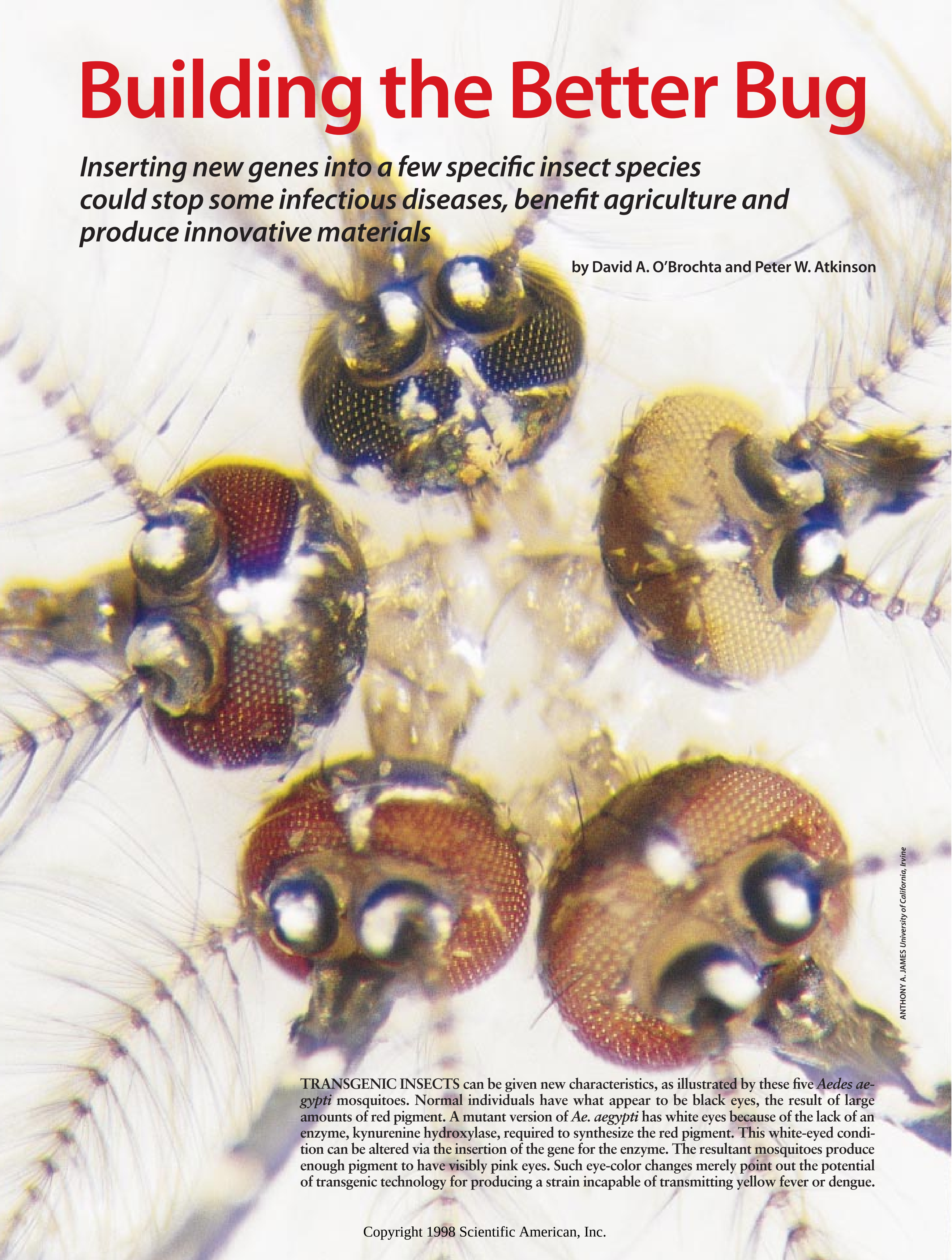
Building the Better Bug

Inserting new genes into a few specific insect species could stop some infectious diseases, benefit agriculture and produce innovative materials

by David A. O'Brochta and Peter W. Atkinson



ANTHONY A. JAMES *University of California, Irvine*

TRANSGENIC INSECTS can be given new characteristics, as illustrated by these five *Aedes aegypti* mosquitoes. Normal individuals have what appear to be black eyes, the result of large amounts of red pigment. A mutant version of *Ae. aegypti* has white eyes because of the lack of an enzyme, kynurenine hydroxylase, required to synthesize the red pigment. This white-eyed condition can be altered via the insertion of the gene for the enzyme. The resultant mosquitoes produce enough pigment to have visibly pink eyes. Such eye-color changes merely point out the potential of transgenic technology for producing a strain incapable of transmitting yellow fever or dengue.

An extraterrestrial visitor would surely acknowledge humanity to be the dominant species on the earth. Should that visitor move past individual species and up the levels of taxonomic classification, however, the alien's field report might well give the class Insecta top billing. More than one million insect species have been identified, accounting for five sixths of all species of animals. Each U.S. acre averages 400 pounds of insects, compared with only 14 pounds of people. Where humans and insects interact, vast economic interests hang in the balance. Even more profoundly, the clash of humans and insects that carry diseases is often a matter of life and death.

A few insect species, most notably those that feed on blood, are still responsible for spreading major human diseases, such as malaria, yellow fever, trypanosomiasis and dengue, as well as some conditions affecting livestock. Malaria alone accounts for between 300 million and 500 million clinical cases annually and some 1.5 million to 2.7 million deaths. About 200,000 people come down with yellow fever annually, and 30,000 die. Some 50 million people contract dengue every year; mortality can reach 15 percent without treatment. In many developing countries, nonfatal but debilitating conditions, such as dysentery, can be transmitted by insects, including the common housefly.

Public health efforts against insect-borne diseases have been limited to three basic strategies: rid the area entirely of the insect, use pesticides and physical barriers such as bed nets to keep at least some of the insects away, or develop a vaccine. The first undertaking has worked, in some areas [see "The Philadelphia Yellow Fever Epidemic of 1793," by Kenneth R. Foster, Mary F. Jenkins and Anna Coxe Toogood; Scientific American, August]. Lowering the exposure to insects has had limited success. Vaccine development remains spotty; for example, the world still awaits an effective and affordable malaria vaccine.

An additional approach could cut this Gordian knot: simply make the insect unable to transmit disease. Insect bites themselves have little health consequence for most people; the pathogenic viruses, protozoa and filarial worms they transmit are the culprits. In the 1960s Chris F. Curtis of the London School of Hygiene and Tropical Medicine proposed that malaria could be stopped in its tracks if a way could be found genetically to convert its carrier, the *Anopheles* mosquito, to a form incapable of transmitting the *Plasmodium* protozoan actually responsible for the disease. Some mosquitoes are in fact naturally "refractory," or unable to transmit *Plasmodium*.

Curtis's proposal was impossible to implement for decades. But it soon may be realistic, thanks to modern genetic technologies. Genetic material from one species can be permanently integrated into the DNA of individuals from another species, conferring new traits. The resultant plant or animal that carries the new DNA is called transgenic.

Finding ways to engineer refractoriness into disease-carrying mosquitoes and other insect vectors now drives an extremely active area of research. The benefits of developing transgenic insects are not limited to medicine, however. The insertion of genes for useful products into the genomes of cows and goats has already created animals that produce pharmaceuticals in their milk. Applied to insects, transgenics could fundamentally change agriculture and the synthesis of some materials.

Jumping Genes Open Doors

The first glimmers of transgenic insect research date back to the 1960s, with the motivation being improved gene analysis rather than any direct applications outside the lab. Most of the early efforts to alter a genome consisted of injecting an insect egg with, or even simply bathing it in, DNA. Neither technique ever developed into a reliable method for producing transgenic insects.

All genetic research leapt forward in the early 1980s with the insect work of Gerald M. Rubin and Alan C. Spradling, both then at the Carnegie Institute of Washington. Rubin and Spradling were investigating fascinating genetic entities known as transposable elements. These strange strings of DNA have the ability to cut and paste themselves repeatedly into different chromosomes. Formally called transposons, their acrobatics also earned them the nickname "jumping genes." Geneticist Barbara McClintock discovered transposons during research in the 1940s on corn. The importance of her findings finally won her the Nobel Prize in 1983.

The particular transposon that the Carnegie researchers investigated came

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MEDFLY ALIGHTS on coffee bean. Saving crops drives initial applications of transgenic insect technology. Genetic-control methods aimed at Medflies, the perpetrators of much agricultural damage, already save billions of dollars annually worldwide.

from the genome of that workhorse of the laboratory, the fruit fly *Drosophila melanogaster.* This species has little importance as an agricultural pest but has been fundamental in genetics research for the past 70 years. Acknowledging the propensity of the transposon to integrate itself into chromosomes, Rubin and Spradling had a simple and clever notion: Why not attach to it the gene they wanted the fly to have? They introduced an altered transposon into a cell, where it indeed pasted itself into the chromosome, creating transgenic *D. melanogaster.* The success and simplicity of their technique revolutionized the way researchers study the genetics and biology of that species.

The *Drosophila* transposon is known as the P element. It was discovered in the 1970s when geneticists noted a puzzling phenomenon. When males from certain populations mated with females of other populations, their progeny had numerous genetic aberrations, such as mutations, broken chromosomes and developmental abnormalities. Because the genetic entities responsible were discovered to come from only the paternal lineage, they were dubbed P factors. Eventually shown to be a transposon, the P factor of most interest to geneticists was renamed the P element and has proved priceless to *Drosophila* geneticists, allowing analysis of isolated genes and their effects.

Unfortunately, in 1986 a set of experiments by one of us (O'Brochta) and Alfred M. Handler of the U.S. Department of Agriculture in Gainesville, Fla., came to a frustrating conclusion: the P element is of little practical value beyond basic genetics research involving *D. melanogaster.* It will not readily insert itself into the chromosomes of other species. Ultimately, however, these experiments led to a new path, by shifting experimenters' attention to other transposable elements and strategies. Recent work has begun to uncover methods for creating transgenic insect species of greater importance.

The realization that the P element would not prove useful outside of *D. melanogaster* sent biologists in search of more generally functional transposons. An obvious question became one of choice: Which transposable elements showed the most promise? Most researchers believed we should stick with a proved commodity and seek transposons that generally resembled the P element (called short inverted repeat-type transposable elements). Our lab developed techniques to determine quickly whether a particular transposon would successfully incorporate itself into the DNA of an insect species, which has helped speed the entire process of vector evaluation and development. Early efforts with transposons having structures similar to the P element have rewarded the choice to sail within sight of charted land.

In 1995 Charalambos Savakis and his colleagues at the Institute of Molecular Biology and Biotechnology on the Greek island of Crete succeeded in using a transposon called *Minos,* isolated from *D. hydei*. Using *Minos* to insert a novel gene into a Medfly, they created the first transgenic version of that animal. The transformation changed a fly with colorless eyes to one that expressed a gene for red-colored eyes (in a sense, effecting gene therapy). Subsequently, Handler and his co-workers successfully transformed Medflies with pigment-free eyes to ones having color, using a transposon called *piggyBac* that comes from the cabbage looper moth. Obviously, changing an insect's eye color is of little inherent interest; the importance of these groundbreaking successes is their illustration of the potential for creating transgenic insects that express truly valuable genes.

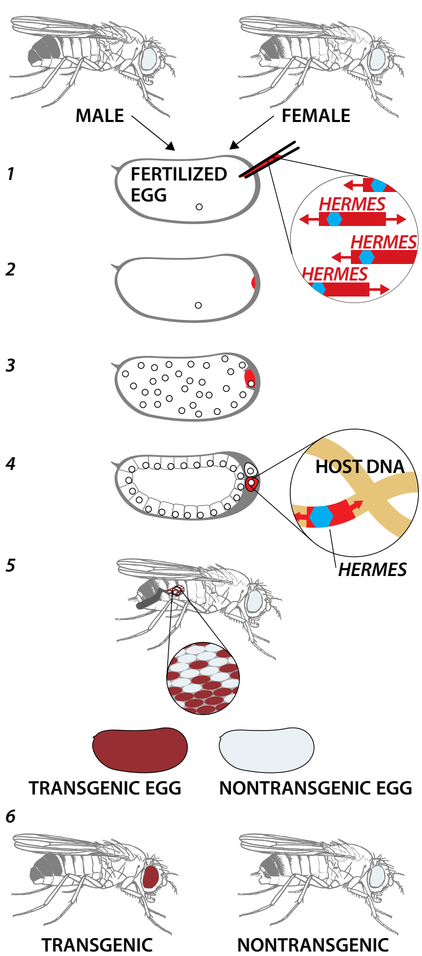
SUSAN McCOMBS *University of Hawaii*

TRANSGENIC MEDFLY has its natural eye color restored. White-eyed mutants produce red pigment but cannot transport the pigment to the eyes. The red-eyed Medfly on the left is a transgenic that has been given the transposable element *piggyBac,* which is carrying a normal copy of the gene enabling pigment transport to the eye.

Earlier this year investigators reported two discrete transformations of the *Aedes aegypti* mosquito, which transmits yellow fever and dengue. The successful manipulations of this inadvertently malevolent creature have led to greater optimism that geneticists will soon be able to convert it into a noncombatant in the disease wars. First, Anthony A. James and his colleagues at the University of California at Irvine altered *Ae. aegypti* via a housefly transposon called *Hermes,* which was originally isolated in our laboratory. (In contrast to the P element, *Hermes* appears to be an efficient vehicle for the creation of transgenic insects ranging from moths to mosquitoes. Work with it is helping to further the understanding of the biochemistry of transposon movement and regulation.) James and his research group then succeeded in incorporating into *Ae. aegypti* a transposon called *mariner,* isolated from the fruit fly species *D. mauritiana*. Again, the effect was simply to change eye color.

In research that dovetails with these two transgenic developments, Barry J. Beaty and his co-workers at Colorado State University demonstrated the feasibility of engineering refractoriness into *Ae. aegypti.* One way to get a host to express a gene it does not ordinarily have is to infect it with a virus carrying that novel DNA sequence. Beaty's team infected the mosquitoes with a nonpathogenic virus that included a gene that prevented the dengue virus from replicating in its host's salivary glands. The infection stops subsequent transmission.

Beaty's research shows that it is possible to create a refractory insect, and therefore no theoretical barriers exist to impede creation of such a creature via genetic insertion. An overarching problem remains, however. Merely waiting for a transgenic insect to pass on its new gene to huge numbers of descendants in



DMITRY KRASNY; SOURCE: PETER LAWRENCE

MAKING TRANSGENIC INSECTS requires the insertion of a gene (*blue*), carried by a transposable element such as *Hermes* (*red*), into a fertilized egg (*1*). The new genetic material is strategically placed at the polar plasm (*2*), that section of the egg destined to become the still nascent insect's own egg cells when it reaches maturity. After numerous divisions of the egg's nuclear material (*3*), most of it segregates to the periphery, where it will become the nuclei of the cells of the insect's body; two nuclei, however, will migrate to the pole to become the insect's egg cells (*4*) when it reaches maturity (*5*). Should those cells have incorporated the transgene, progeny will be transgenic (*6*).

a strictly Mendelian fashion—in which a parent possessing one copy of the gene contributes it to only half of his or her descendants—can be a lengthy process.

A more practical plan would spread the genetic change through large numbers of insects much more quickly. Fortunately, the basic components for quickly creating an entire insect population all carrying the key gene appear to be available. Once again, the transposon makes things possible.

Because of their propensity for jumping to new chromosomes, as well as making multiple copies of themselves, transposons burst free of the constraints of strict Mendelian heredity. A transformation event achieved by a scientist may have placed a single transposon, carrying a single key gene, into the genome of the target animal. But that transposon then may act as a free agent and spread itself throughout the genome. When that happens, more than half the offspring inherit the transgene. Within the relatively short time of a very few insect generations, most of the population expresses the trait.

This type of gene dispersal has been seen in nature. In fact, the P element itself appears to be a recent addition to *D. melanogaster*'s genome, most likely jumping over from *D. willistoni* no more than a century ago.

Other techniques may be effective at creating transgenic species. Human gene therapy is based in part on unique systems (derived from retroviruses but no longer infectious themselves) that are able to integrate genes into a new host's genome. (This is a true transgenic transformation, as opposed to Beaty's use of viruses to simply infect an individual organism that will henceforth produce the viral gene product.) These stripped-down viral vectors, known as pantropic pseudotyped retroviruses, can interact with virtually any cell from any organism. They have recently been used to create transgenic fish and clams and have successfully integrated genetic material into cultured mosquito cells. These viral vectors may yet prove their worth in efforts with whole insects.

Because the objective is to alter an insect's phenotype—the outward expression of its genetic makeup, or genotype—most workers have logically concentrated on ways to integrate foreign genetic material into the chromosomes of the host insect itself. But Frank F. Richards and his colleagues at Yale University are developing a clever approach that sabotages the cargo rather than the ship. Because virtually all insects harbor microbes, either as passive hitchhikers or active colonists, Richards is counting on transforming them rather than their hosts. Insects that carry engineered microbes are called paratransgenic, as the insect genome itself is untouched.

Richards and Charles B. Beard of the Centers for Disease Control and Prevention have produced paratransgenic, blood-sucking kissing bugs that can no longer transmit the trypanosome microbe responsible for Chagas' disease, which afflicts some 18 million South Americans with cardiovascular, gastrointestinal and neurological problems. The researchers isolated a bacterial symbiont from the kissing bugs and genetically modified it to secrete a protein that killed its trypanosome fellow travelers. The researchers placed the bacteria back in the insects, which then no longer served as hosts for the disease-causing protozoa. The genetically engineered symbionts successfully spread through a caged population of insects, converting them from vectors of a horrific disease to mere pests.

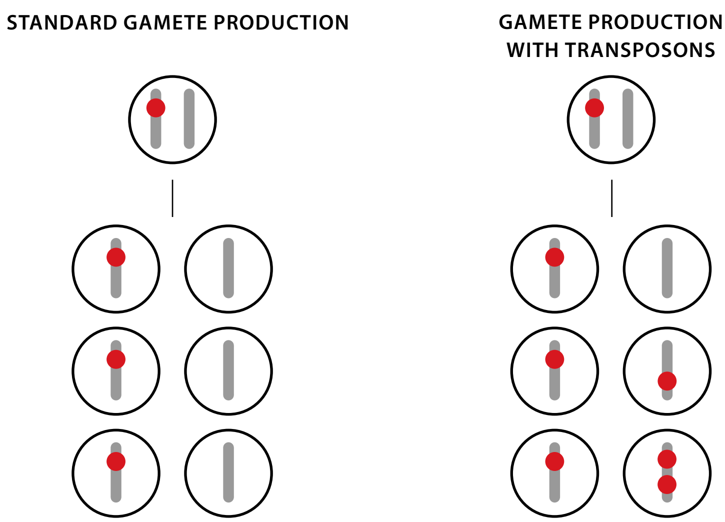
Agricultural Applications

Obviously, insects play crucial roles, both positive and negative, in agriculture. Most species are, in fact, beneficial or even essential. For example, honeybees are responsible for the pollination of $10 billion worth of produce in the U.S. Countless other species take part in nutrient recycling and help to maintain high soil quality. A small minority, however, compete with us for food. Since the development of agriculture, these pests have continually threatened our capacity to grow, harvest and store crops.

The concept of employing a genetic approach to deal with insect pests was first proposed in the 1940s by an American and a Russian. Edward F. Knipling of the USDA and Aleksandr S. Serebrovsky proposed similar schemes: inundate a pest population with sterile members of the same species. The majority of matings then become ineffectual. Serebrovsky's contribution was unknown in the West until 1968, when scientists, in particular Curtis, rediscovered it. Today this strategy is known as the sterile insect technique (SIT). Large numbers of insects can be sterilized, usually by ionizing radiation, and repeated infusions of such sterile organisms can wipe out a pest population [*see illustration at bottom on next page*]. The altered insect itself is, in effect, the weapon.

SIT is currently protecting parts of the agricultural economies of the U.S., Mexico, Guatemala, Chile, Argentina, Japan and Zanzibar, among other places. The strategy is ideal in locations as divergent as urban Los Angeles and tropical Zanzibar, where the aim is to eradicate a specific insect pest without harming the surrounding environment with chemical insecticides.

One of SIT's crowning achievements



DMITRY KRASNY; SOURCE: MARGARET KIDWELL AND JOSÉ RIBEIRO

NON-MENDELIAN HEREDITY is one of the added benefits of working with transposable elements. In ordinary gamete production (*left*), a gene of interest will appear in one half of gametes and will be transmitted, on average, to one half of progeny. Transposable elements, however, reproduce themselves and jump to other chromosomes. They can therefore wind up on more than one half of gametes and far more than one half of the members of the next generation.

MEDFLY MAGGOTS, one of which is being plucked from this papaya, can destroy valuable crops. The edible pulp of the neck of the papaya, to the right of the black seeds, has been visibly damaged by the feeding of the insect larvae. Genetic controls can prevent such agricultural losses.

PHOTOGRAPHS BY USDA/AGRICULTURAL RESEARCH SERVICE

ENORMOUS CAGES hold the hundreds of thousands of Mediterranean fruit flies that are needed to implement genetic-control strategies.

was the eradication of the New World screwworm, first from the southeastern U.S. and eventually from Mexico, by the 1970s. (The screwworm will receive little sympathy from most onlookers. It lays eggs in open wounds in livestock, which then hatch into larvae that consume the animals' flesh. In effect, the screwworm eats its victims alive.) The technique has recently been used successfully against the dreaded Medfly in the Los Angeles area, with greater economic benefit: a permanent Medfly infestation would cost California approximately $1.5 billion annually.

SIT depends on genetics, in the form of traditional breeding programs. For example, a strain of Medfly has been created that allows scientists to kill all the female embryos with a pulse of high temperature. This strain permits entomologists to mass-produce, sterilize and release only males. By eliminating the females, the entire SIT program becomes more effective. Producing such strains, however, is difficult and time-consuming.

With transgenic technology, it should be possible to create insect strains in which only the females carry lethal genes. These deadly DNA segments would get expressed under specific conditions, such as the high-temperature pulse used in the traditional approach.

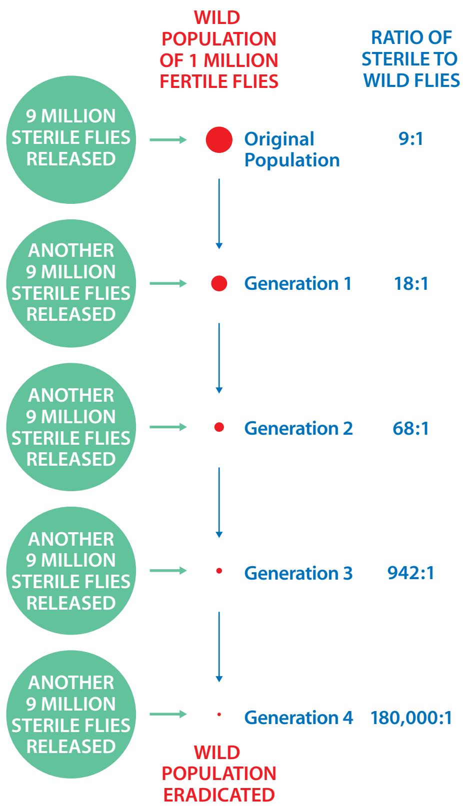
Transgenic technology also has the potential to reduce dependence on chemical pesticides. More than 900,000 American farms currently use insecticides, a reliance that can be counterproductive. Literally bathing insects in pesticides has actually driven the development of resistance to those killing agents. At least 183 species of insect and arachnid pests have developed resistance to one or more insecticides in the U.S. Furthermore, accumulation of chemical insecticides and their toxic breakdown products in our food, water, soil and textiles present a serious health issue. Biologists are therefore looking toward transgenics for the next wave of insect-control weapons.

One major problem with insecticides is that they kill many nontarget, beneficial species. They may wipe out useful predators and parasites, giving secondary pest species a chance to emerge. Transgenic technology may allow farmers to curtail pesticide use dramatically.

Currently a field can be sprayed with a wide array of different chemicals, each able to kill one or more harmful species. Unfortunately, the chemical controls against negative species often harm positive species as well. For example, mites attack California almond trees. One solution is to use an insecticide against those mites. Another is to release a species of predatory mite that kills the harmful mites. The trees, however, also fall victim to beetles and moths, so they are sprayed with other insecticides against those pests. And one of these insecticides kills the predatory mite that would free the tree from attack by the other mite species. A transgenic beneficial mite that could withstand the insecticides aimed at beetles and moths would allow farmers to spray fewer chemicals overall on their crops.

Of course, artificial selection for pesticide-resistant natural enemies is routine in labs, through conventional breeding practices. Brian A. Croft and his colleagues at the University of California at Riverside introduced insecticide-resistant predatory mites obtained from Washington State into orchards in southern California with good effect. Marjorie A. Hoy, now at the University of Florida, subsequently developed techniques that enabled the artificial selection of chemical resistance in natural predatory arthropods. Hoy and her coworkers developed an insecticide-resistant predatory mite that took part in the almond tree scenario just described.

This kind of effort, however, usually takes many insect generations and can



DMITRY KRASNY; SOURCE: GERALD FRANZ

STERILE INSECT TECHNIQUE (SIT) can be an effective weapon against pests. Wave after wave of sterile insects, mostly males when possible, far outnumber the fertile members of the same species, and cause most matings to be fruitless. Within a few generations, the pest population is decimated. Traditional breeding programs have made for successful SIT interventions, but transgenic technology has the potential to streamline these procedures.

BIOLOGICAL CONTROL, in the form of predatory mites, saved the almond trees on the left side of the road. The unprotected trees on the right were decimated by spider mites. Transgenic technology has the potential to increase the availability of biocontrols.

result in a decrease in genetic diversity in these laboratory colonies when resistant progeny are bred with one another. The loss in genetic diversity can then be responsible for a lower general level of fitness outside the lab, in the field. This problem has limited the application of artificial selection for resistance in agricultural efforts to improve biological control. In contrast, transgenic insect technology can permit the rapid creation of resistant species. Natural enemies would become more practical and less expensive, making it more attractive to switch from chemical control.

Insecticide resistance is only the most obvious useful phenotype that could enhance the effectiveness of some beneficial arthropods. Other desirable qualities that could be engineered into insects with transgenic technology include pathogen resistance, general environmental hardiness, increased fecundity and improved host-seeking ability. One especially interesting application of transgenic engineering is the improvement of materials that insects supply to humans. Silk is a prime example. Breeding programs have created strains of silkworms that churn out more and better silk. Such programs, however, have limits: they cannot turn a silk purse into a steel one. But transgenic technology may. Some spider silks, for example, are stronger than Kevlar, a constituent of bulletproof vests and high-performance aircraft parts. Unfortunately, spider silk cannot be mass-produced as Kevlar is by humans or silk is by the larvae of silkworms. Transgenics offers the interesting possibility of introducing other species' silk genes into the genomes of silkworms. The creation of silkworms that spin bulletproof cocoons sounds fanciful, but such notions may be within the grasp of transgenic technology.

Ecological Considerations

The ability to engineer insects genetically confronts scientists and policymakers with questions about proper deployment, both in the laboratory and in the field. Guidelines already in place to govern the transfer of existing genetic expertise from the lab to the field can provide part of a regulatory framework. All technologies have risks associated with their use, and we need to develop an understanding of the specific risks inherent to insect transgenics and how to minimize them. For example, unintentional movement of transgenes between insect species is of some concern and is being investigated. In some cases, the risk should be minimal: when only sterile members of the transgenic species are released, the inserted genetic sequences should remain sequestered from the overall gene pool.

As the term "risk-benefit" implies, the good that could come from transgenics should be taken into account in decisions about development and deployment. Government agencies, such as the USDA's Animal and Plant Health Inspection Service, have established mechanisms to ensure that field releases of transgenic insects are done strictly with regard to genetic and ecological consequences. (Readers can review this implementation process, as well as the present application for field trials of transgenic arthropods, by visiting the USDA Web site at www.aphis.usda.gov/bbep.)

The genetic transformation of a given organism has, in every case, revolutionized the study of its biology. Furthermore, research in one species may inform work in others. Mendel's humble pea plants broke the ground, and studies of *Drosophila* laid the foundation for most of modern genetic research. Investigations with *Escherichia coli* led to pioneering research into regulatory mechanisms that hastened the development of genetic engineering technology in bacteria, plants and animals. Transgenic mammals already produce a variety of medical products. Applied to insects, transgenic technology can offer biologists new ways to investigate, control and exploit these creatures that hold sway over such a substantial proportion of human affairs. SA

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Physicists in Wartime Japan

During the most trying years of Japan's history, two brilliant schools of theoretical physics flourished

by Laurie M. Brown and Yoichiro Nambu

"The last seminar, given at a gorgeous house left unburned near Riken, was dedicated to [electron] shower theories.... It was difficult to continue the seminars, because Minakawa's house was burnt in April and the laboratory was badly destroyed in May. The laboratory moved to a village near Komoro in July; four physics students including myself lived there. Tatuoki Miyazima also moved to the same village, and we continued our studies there towards the end of 1945."

—Satio Hayakawa, astrophysicist

Between 1935 and 1955 a handful of Japanese men turned their minds to the unsolved problems of theoretical physics. They taught themselves quantum mechanics, constructed the quantum theory of electromagnetism and postulated the existence of new particles. Much of the time their lives were in turmoil, their homes demolished and their bellies empty. But the worst of times for the scientists was the best of times for the science. After the war, as a numbed Japan surveyed the devastation, its physicists brought home two Nobel Prizes.

Their achievements were all the more remarkable in a society that had encountered the methods of science only decades earlier. In 1854 Commodore Matthew Perry's warships forced the country open to international trade, ending two centuries of isolation. Japan realized that without modern technology it was militarily weak. A group of educated samurai forced the ruling shogun to step down in 1868 and reinstated the emperor, who had until then been only a figurehead. The new regime sent young men to Germany, France, England and America to study languages, science, engineering and medicine and founded Western-style universities in Tokyo, Kyoto and elsewhere.

Hantaro Nagaoka was one of Japan's first physicists. His father, a former samurai, initially taught his son calligraphy and Chinese. But after a trip abroad, he returned with loads of English textbooks and apologized for having taught him all the wrong subjects. At university, Nagaoka hesitated to take up science; he was uncertain if Asians could master the craft. But after a year of perusing the history of Chinese science, he decided the Japanese, too, might have a chance.

In 1903 Nagaoka proposed a model of the atom that contained a small nucleus surrounded by a ring of electrons. This "Saturnian" model was the first to contain a nucleus, discovered in 1911 by Ernest Rutherford at the Cavendish Laboratory in Cambridge, England.

As measured by victories against China (1895), Russia (1905) and in World War I, Japan's pursuit of technology was a success. Its larger companies established research laboratories, and in 1917 a quasigovernmental institute called Riken (the Institute of Physical and Chemical Research) came into being in Tokyo. Though designed to provide technical support to industry, Riken also conducted basic research.

A young scientist at Riken, Yoshio Nishina, was sent abroad in 1919, traveling in England and Germany and spending six years at Niels Bohr's institute in Copenhagen. Together with Oskar Klein, Nishina calculated the probability of a photon, a quantum of light, bouncing off an electron. This interaction was fundamental to the emerging quantum theory of electromagnetism, now known as quantum electrodynamics.

When he returned to Japan in 1928, Nishina brought with him the "spirit of Copenhagen"—a democratic style of research in which anyone could speak his mind, contrasting with the authoritarian norm at Japanese universities—as well as knowledge of modern problems and methods. Luminaries from the West, such as Werner K. Heisenberg and Paul A. M. Dirac, came to visit, lecturing to awed ranks of students and faculty.

Hiding near the back of the hall, Shinichiro Tomonaga was one of the few to understand Heisenberg's lectures. He had just spent a year and a half as an undergraduate teaching himself quantum mechanics from all the original papers. On the last day of lectures, Nagaoka scolded that Heisenberg and Dirac had discovered a new theory in their 20s, whereas Japanese students were still pathetically copying lecture notes. "Nagaoka's pep talk really did not get me anywhere," Tomonaga later confessed.

Sons of Samurai

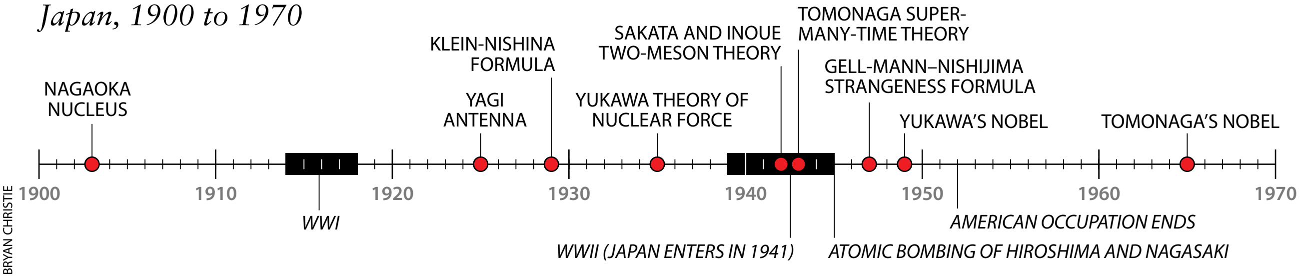
He was, however, destined to go places, along with his high school and college classmate Hideki Yukawa. Both men's fathers had traveled abroad and were academics: Tomonaga's a professor of Western philosophy, Yukawa's a professor of geology. Both were of samurai lineage. Even before going to school, the younger Yukawa had learned the Confucian classics from his maternal grandfather, a former samurai. Later he encountered the works of Taoist

IN JANUARY 1942 author Yoichiro Nambu reads in laboratory room 305 of the physics department at the University of Tokyo. Soon after, he was drafted. When the war ended, Nambu lived in this room for three years; neighboring laboratories were similarly occupied by homeless and hungry scientists.

COURTESY OF YOICHIRO NAMBU

Discoveries in Physics

Japan, 1900 to 1970



sages, whose questioning attitude he would liken to the scientific pursuit. Tomonaga was inspired to study physics by hearing Albert Einstein lecture in Kyoto in 1922, as well as by reading popular science books written in Japanese.

The two men obtained their bachelor's degrees in 1929 from Kyoto University, at the start of the worldwide depression. Lacking jobs, they stayed on as unpaid assistants at the university. They taught each other the new physics and went on to tackle research projects independently. "The depression made scholars of us," Yukawa later joked.

In 1932 Tomonaga joined Nishina's lively group at Riken. Yukawa moved to Osaka University and, to Tomonaga's annoyance, confidently focused on the deepest questions of the day. (Yukawa's first-grade teacher had written of him: "Has a strong ego and is firm of mind.") One was a severe pathology of quantum electrodynamics, known as the problem of infinite self-energy. The results of many calculations were turning out to be infinity: the electron, for instance, would interact with the photons of its own electromagnetic field so that its mass—or energy—increased indefinitely. Yukawa made little progress on this question, which was to occupy some of the world's brilliant minds for two more decades. "Each day I would destroy the ideas that I had created that day. By the time I crossed the Kamo River on my way home in the evening, I was in a state of desperation," he later recalled.

Eventually, he resolved to tackle a seemingly easier problem: the nature of the force between a proton and a neutron. Heisenberg had proposed that this force was transmitted by the exchange of an electron. Because the electron has an intrinsic angular momentum, or spin, of one half, his idea violated the conservation of angular momentum, a basic principle of quantum mechanics. But having just replaced classical rules with quantum ones for the behavior of electrons and photons, Heisenberg, Bohr and others were all too willing to throw out quantum physics and assume that protons and neutrons obeyed radical new rules of their own. Unfortunately, Heisenberg's model also predicted the range of the nuclear force to be 200 times too long.

Yukawa discovered that the range of a force depends inversely on the mass of the particle that transmits it. The electromagnetic force, for instance, has infinite range because it is carried by the massless photon. The nuclear force, on the other hand, is confined within the nucleus and should be communicated by a particle of mass 200 times that of the electron. He also found that the nuclear particle required a spin of zero or one to conserve angular momentum.

Yukawa published these observations in his first original paper in 1935 in *Proceedings of the PMSJ* (Physico-Mathematical Society of Japan). Although it was written in English, the paper was ignored for two years. Yukawa had been bold in predicting a new particle—thereby defying Occam's razor, the principle that explanatory entities should not proliferate unnecessarily. In 1937 Carl D. Anderson and Seth H. Neddermeyer of the California Institute of Technology discovered, in traces left by cosmic rays, charged particles that had about the right mass to meet the requirements of Yukawa's theory. But the cosmic-ray particle appeared at sea level instead of being absorbed high up in the atmosphere, so it lived 100 times longer than Yukawa had predicted.

Tomonaga, meanwhile, was working with Nishina on quantum electrodynamics. In 1937 he visited Heisenberg at Leipzig University, collaborating with him for two years on theories of nuclear forces. Yukawa also arrived, en route to the prestigious Solvay Congress in Brussels. But the conference was canceled, and the two men had to leave Europe hurriedly.

War brought the golden age of quantum physics to an abrupt end. The founders of the new physics, until then concentrated in European centers such as Göttingen in Germany, scattered, ending up mainly in the U.S. Heisenberg, left virtually alone in Germany, continued at least initially to work on field theory—a generalization of quantum electrodynamics—and to correspond with Tomonaga.

A War Like No Other

By 1941, when Japan entered the world war, Yukawa had become a professor at Kyoto. His students and collaborators included two radicals, Shoichi Sakata and Mitsuo Taketani. At the time, Marxist philosophy was influential among intellectuals, who saw it as an antidote to the militarism of the imperial government. Unfortunately, Taketani's writings for the Marxist journal *Sekai Bunka* (*World Culture*) had drawn the attention of the thought police. He had been jailed for six months in 1938, then released into Yukawa's custody thanks to the intervention of Nishina. Although Yukawa remained totally wrapped up in physics and expressed no political views at all, he continued to shelter the radicals in his lab.

Sakata and Taketani developed a Marxist philosophy of science called the three-stages theory. Suppose a researcher discovers a new, inexplicable phenomenon. First he or she learns the details and tries to discern regularities. Next the scientist comes up with a qualitative model to explain the patterns and finally develops a precise mathematical theory that subsumes the model. But another discovery soon forces the process to repeat. As a result, the history of science resembles a spiral, going around in circles yet always advancing. This philosophy came to influence many of the younger physicists, including one of us (Nambu).

Meanwhile, as war raged in the Pacific, the researchers continued to work on physics. In 1942 Sakata and Takeshi Inoue suggested that Anderson and Neddermeyer had not seen Yukawa's parti-

HIDEKI OGAWA (*second from left*) and his brothers gather at home in Kyoto, around 1912. As an adult, Hideki took the surname Yukawa, by which he is known, from his wife. While Hideki became a Nobel laureate in physics, Shigeki (*left*) became a historian of China, Tamaki (*third from left*) a professor of Chinese literature and Yoshiki a professor of metallurgy.

cle but instead had seen a lighter object, now called a muon, which came from the decay of the true Yukawa particle, the pion. They described their theory to the Meson Club, an informal group that met regularly to discuss physics, and published it in a Japanese journal.

Yukawa was doing war work one day a week; he never said what this entailed. (He did say that he would read the *Tale of Genji* while commuting to the military lab.) Tomonaga, who had become a professor at the Tokyo Bunrika University (now called the University of Tsukuba), was more involved in the war effort. Together with Masao Kotani of the University of Tokyo, he developed a theory of magnetrons—devices used in radar systems for generating electromagnetic waves—for the navy. Through the hands of a submarine captain he knew, Heisenberg sent Tomonaga a paper on a technique he had invented for describing the interactions of quantum particles. It was in essence a theory of waves, which Tomonaga soon applied to designing radar waveguides.

At the same time, Tomonaga was tackling the problem of infinite self-energy that Yukawa had given up. To this end, he developed a means of describing the behavior of several interacting quantum particles, such as electrons, moving at near the speed of light. Generalizing an idea due to Dirac, he assigned to each particle not just space coordinates but also its own time coordinate and called the formulation "super-many-time theory." This work, which became a powerful framework for quantum electrodynamics, was published in 1943 in Riken's science journal.

By this time most students had been mobilized for war. Nambu was among those assigned to radar research for the army. (Intense rivalry between the army and the navy led each to duplicate the other's efforts). Resources were short and the technology often very primitive: the army could not develop mobile radar systems to pinpoint enemy targets. Nambu was once handed a piece of Permalloy magnet, about three by three inches, and told to do what he could with it for aerial submarine detection. He was also told to steal from the navy Tomonaga's paper on waveguides, labeled "Secret," which he accomplished by visiting an unsuspecting professor [see "Strings and Gluons—The Seer Saw Them All," by Madhusree Mukerjee, News and Analysis; Scientific American, February 1995].

(Curiously, Japan's past technical contributions included excellent magnetrons designed by Kinjiro Okabe and an antenna; the latter, invented by Hidetsugu Yagi and Shintaro Uda in 1925, still projects from many rooftops. The Japanese armed forces learned about the importance of the "Yagi array" from a captured British manual.)

Younger physicists around the Tokyo area continued their studies when they could; professors from the University of Tokyo, as well as Tomonaga, held special courses for them on Sundays. In 1944 a few students (including Satio Hayakawa, whose quote begins this article) were freed from war research and returned to the university campus. Even so, times were difficult. One student's house was burned down, another was drafted, and a third had his house burned down just before he was drafted. The venue for the seminars shifted several times. Tomonaga, who had always been physically weak, would sometimes instruct his students while lying sick in bed.

Meanwhile Nishina had been instructed by the army to investigate the possibility of making an atomic bomb. In 1943 he concluded that it was feasible, given enough time and money. He assigned a young cosmic-ray physicist, Masa Takeuchi, to build a device for isolating the lighter form of uranium required for a bomb. Apparently Nishina thought the project would help keep physics research alive for when the war ended. Taketani, back in prison, was also forced to work on the problem. He did not mind, knowing it had no chance of success.

Across the Pacific, the Manhattan Project was employing some 150,000 men and women, not to mention a constellation of geniuses and $2 billion. In contrast, when the Japanese students realized they would need sugar to make uranium hexafluoride (from which they could extract the uranium) they had to bring in their own meager rations. A separate effort, started by the navy in 1943, was also far too little, too late. By the end of the war, all that the projects had produced was a piece of uranium metal the size of a postage stamp, still unenriched with its light form.

And two atom bombs had exploded in Japan. Luis W. Alvarez of the University of California at Berkeley was in the aircraft that dropped the second bomb over Nagasaki, deploying three microphones to measure the intensity of the blast. Around these instruments he wrapped a letter (with two photocopies) drafted by himself and two Berkeley colleagues, Philip Morrison and Robert Serber. They were addressed to Riokichi Sagane, Nagaoka's son and a physicist in Tomonaga's group. An experimenter, Sagane had spent two years at Berkeley learning about cyclotrons, enormous machines for conducting studies in particle physics. He had become acquainted with the three Americans who now sought to inform him of the nature of the bomb. Although the letter was recovered by the military police, Sagane learned of it only after the war.

A Hungry Peace

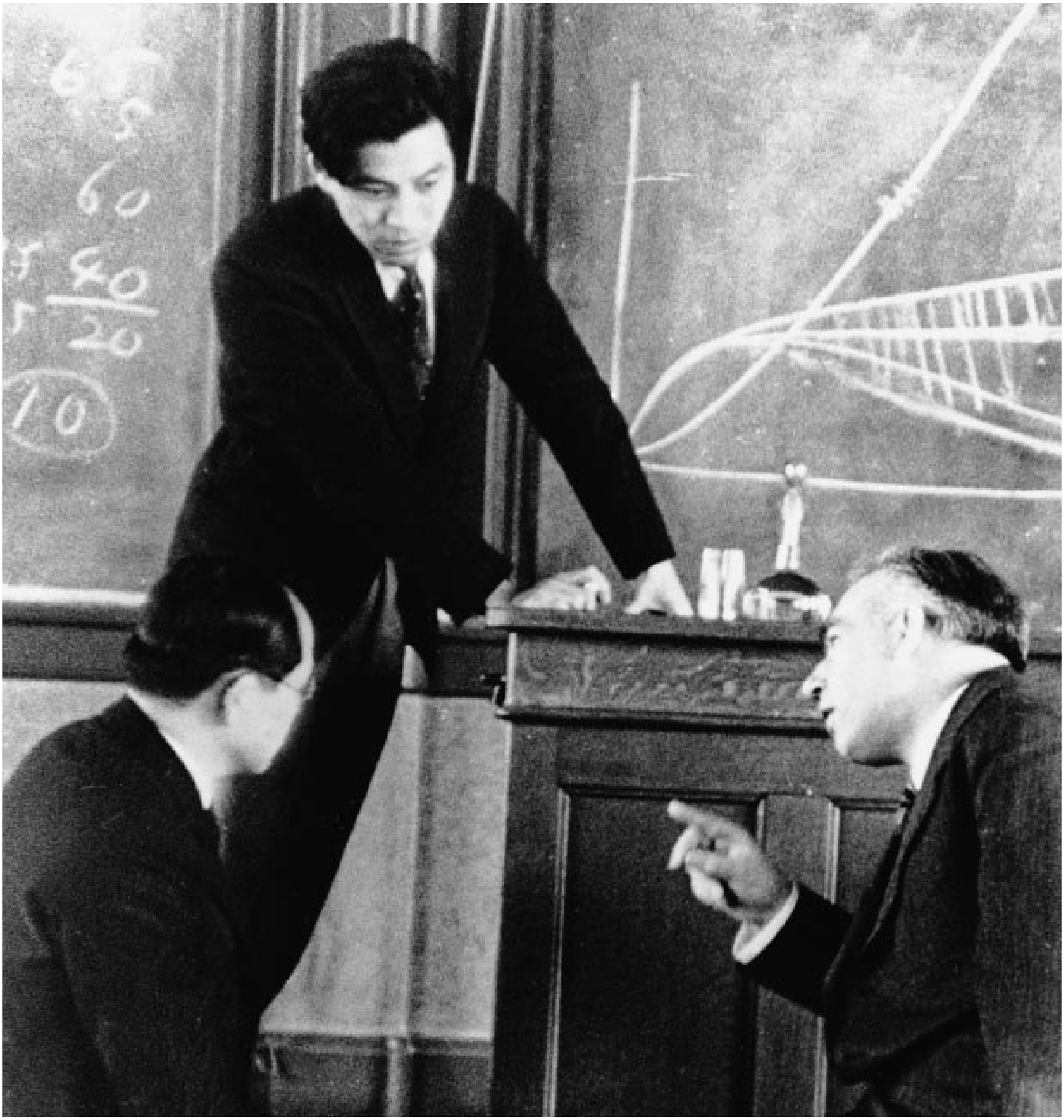
After the Japanese surrender in August 1945, the country was effectively under American occupation for seven years. General Douglas MacArthur's administration reformed, liberalized and expanded the university system. But experimental research in nuclear and related fields was essentially prohibited. All cyclotrons in Japan were dismantled and thrown into the sea, for fear that they might be used to research an atomic bomb.

In any case, the miserable economy did not allow the luxury of experimental research. Tomonaga was living with his family in a laboratory, half of which had been bombed to bits. Nambu arrived at the University of Tokyo as a research assistant and lived for three years in a laboratory, sleeping on a straw mattress spread over his desk (and always dressed in military uniform for lack of other clothes). Neighboring offices were similarly occupied, one by a professor and his family.

Getting food was everyone's preoccupation. Nambu would sometimes find sardines at Tokyo's fish market, which rapidly produced a stench because he had no refrigerator. On weekends he would venture to the countryside, ask-

NISHINA MEMORIAL FOUNDATION, COURTESY OF HIROSHI EZAWA

OUTING AT MOUNT FUJI in 1936 drew physicists from laboratories at Riken. Shinichiro Tomonaga is in the front row (*third from left*). Yoshio Nishina, "the boss," who ran a large and prolific group at Riken, is third from the right (*front row*).



NISHINA MEMORIAL FOUNDATION, COURTESY OF HIROSHI EZAWA

DISTINGUISHED VISITOR Niels Bohr (*right*) discusses physics with Nishina and Seishi Kikuchi (*standing*) during a trip to Japan in April 1937. Nishina had visited Bohr's institute in Copenhagen in the early 1920s and maintained connections with several European scientists. Kikuchi was an experimenter who performed some of the earliest studies with electron waves.

ing farmers for whatever they could offer.

Several other physicists also used the room. One, Ziro Koba, was working with Tomonaga's group at Bunrika on the self-energy problem. Some of the officemates specialized in the study of solids and liquids (now called condensed-matter physics) under the guidance of Kotani and his assistant Ryogo Kubo, who was later to attain fame for his theorems in statistical mechanics. The young men taught each other what they knew of physics and regularly visited a library set up by MacArthur, perusing whatever journals had arrived.

At a meeting in 1946 Sakata, then at Nagoya University—whose physics department had moved to a suburban primary school—proposed a means of dealing with the infinite self-energy of the electron by balancing the electromagnetic force against an unknown force. At the end of the calculation, the latter could be induced to vanish. (At about the same time, Abraham Pais of the Institute for Advanced Study in Princeton, N.J., proposed a similar solution.) Although the method had its flaws, it eventually led Tomonaga's group to figure out how to dispose of the infinities, by a method now known as renormalization.

This time the results were published in *Progress of Theoretical Physics,* an

English-language journal founded by Yukawa in 1946. In September 1947 Tomonaga read in *Newsweek* about a striking experimental result obtained by Willis E. Lamb and Robert C. Retherford of Columbia University. The electron in a hydrogen atom can occupy one of several quantum states; two of these states, previously thought to have identical energies, actually turned out to have slightly different energies.

Right after the finding was reported, Hans Bethe of Cornell University had offered a quick, nonrelativistic calculation of the "Lamb shift," as the energy difference came to be known. The effect is a finite change in the infinite self-energy of the electron as it moves inside an atom. With his students, Tomonaga soon obtained a relativistic result by correctly accounting for the infinities.

Their work strongly resembled that being done, almost at the same time, by Julian S. Schwinger of Harvard University. Years later Tomonaga and Schwinger were to note astonishing parallels in their careers: both had worked on radar, wave propagation and magnetrons as part of their respective war efforts, and both used Heisenberg's theory to solve the same problem. The two shared a Nobel Prize with Richard Feynman in 1965 for the development of quantum electrodynamics. (Feynman had his own idiosyncratic take—involving electrons that moved backward in time—which Freeman Dyson of the Institute for Advanced Study later showed was equivalent to the approach of Tomonaga and Schwinger.) And both Tomonaga's and Schwinger's names mean "oscillator," a system fundamental to much of physics.

At about the time the Lamb shift was reported, a group in England discovered the decay of the pion to the muon in photographic plates exposed to cosmic rays at high altitude. The finding proved Inoue, Sakata and Yukawa to have been spectacularly correct. After the dust settled, it became clear that Yukawa had discovered a deep rule about forces: they are transmitted by particles whose spin is always an integer and whose mass determines their range. Moreover, his tactic of postulating a new particle turned out to be astoundingly successful. The 20th century saw the discovery of an abundance of subatomic particles, many of which were predicted years before.

In 1947 new particles began to show up that were so puzzling that they were dubbed "strange." Although they appeared rarely, they often did so in pairs and, moreover, lived anomalously long. Eventually Murray Gell-Mann of the California Institute of Technology and, independently, Kazuhiko Nishijima of Osaka City University and other Japanese researchers discovered a regularity behind their properties, described by a quantum characteristic called "strangeness." (Discerning this pattern was the first step in the three-stages theory.)

In subsequent years Sakata and his associates became active in sorting through the abundance of particles that were turning up and postulated a mathematical framework, or triad, that became the forerunner of the quark model. (This framework formed the second stage. At present, high-energy physics, with its precise theory of particles and forces known as the Standard Model, is in the third and final stage.)

Meanwhile physicists in Japan were renewing ties with those in the U.S. who had made the atomic bomb. Their feelings toward the Americans were ambiguous. The carpet bombings of Tokyo and the holocausts in Hiroshima and Nagasaki had been shocking even for those Japanese who had opposed the war. On the other hand, the occupation, with its program of liberalization, was relatively benevolent. Perhaps the deciding factor was their shared fascination for science.

YOICHIRO NAMBU

GROUP SNAPSHOT taken in Rochester, N.Y., around 1953 features Japanese researchers with physicist Richard Feynman. Masatoshi Koshiba (*back row, left*) went on to design the Kamiokande facility; the others became prominent theorists. The picture was taken by Nambu (*front row, center*), whose skills lay in areas other than photography.

Reconciliation

Dyson has described how, in 1948, Bethe received the first two issues of *Progress of Theoretical Physics*, printed on rough, brownish paper. An article in the second issue by Tomonaga contained the central idea of Schwinger's theory. "Somehow or other, amid the ruin and turmoil of the war, Tomonaga had maintained in Japan a school of research in theoretical physics that was in some respects ahead of anything existing elsewhere at that time," Dyson wrote. "He had pushed on alone and laid the foundations of the new quantum electrodynamics, five years before Schwinger and without any help from the Columbia experiments. It came to us as a voice out of the deep."

J. Robert Oppenheimer, then director of the Institute for Advanced Study, invited Yukawa to visit. He spent a year there, another at Columbia, and received the Nobel Prize in 1949. Tomonaga also visited the institute and found it extremely stimulating. But he was homesick. "I feel as if I am exiled in paradise," he wrote to his former students. He returned after a year to Japan, having worked on a theory of particles moving in one dimension that is currently proving useful to string theorists.

From the early 1950s, younger physicists also began to visit the U.S. Some, such as Nambu, stayed on. To an extent mitigating this brain drain, the expatriates retained ties with their colleagues in Japan. One means was to send letters to an informal newsletter, *Soryushiron Kenkyu,* which was often read aloud during meetings of a research group that succeeded the Meson Club.

In 1953 Yukawa became the director of a new research institute at Kyoto, now known as the Yukawa Institute for Theoretical Physics. In the same year he and

TOMONAGA strikes a pose at home. This somber picture was taken in 1960, five years before Tomonaga shared a Nobel Prize for his solution of the infinity problems of quantum electrodynamics, discovered during World War II.

Tomonaga hosted an international conference on theoretical physics in Tokyo and Kyoto. Fifty-five foreign physicists attended, including Oppenheimer. It is said that Oppenheimer wished to visit the beautiful Inland Sea but that Yukawa discouraged him, feeling that Oppenheimer would find it too upsetting to see Hiroshima, which was nearby. Despite their lifelong immersion in abstractions, Yukawa and Tomonaga became active in the antinuclear movement and signed several petitions calling for the destruction of nuclear weapons.

In 1959 Leo Esaki, a doctoral student at the University of Tokyo, submitted a thesis on the quantum behavior of semiconductors, work that eventually led to the development of transistors. He would bring home a third Japanese Nobel in physics, shared with Ivar Giaever and Brian D. Josephson, in 1973.

One wonders why the worst decades of the century for Japan were the most creative ones for its theoretical physicists. Perhaps the troubled mind sought escape from the horrors of war in the pure contemplation of theory. Perhaps the war enhanced an isolation that served to prod originality. Certainly the traditional style of feudal allegiance to professors and administrators broke down for a while. Perhaps for once the physicists were free to follow their ideas.

Or perhaps the period is just too extraordinary to allow explanation. SA

The Authors

LAURIE M. BROWN and YOICHIRO NAMBU often collaborate on projects involving the history of Japanese physics. Brown is professor emeritus of physics at Northwestern University and has turned his interests in the past two decades to the history of physics. He is the author or co-author of eight books on the subject. Nambu is professor emeritus at the University of Chicago. He is responsible for several key ideas in particle theory and has received the Wolf Prize, the Dirac Medal, the National Medal of Science, the Order of Culture (from the Japanese government) and numerous other awards. Nambu last wrote for *Scientific American* in November 1976, on the confinement of quarks.

Further Reading

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Sizing Up Software

Unlike oil, steel or paper, software is an intangible commodity. This elusive quality makes computer programs difficult to quantify

by Capers Jones

Modern society has become increasingly reliant on software—and thankfully so. Computer programs routinely execute operations that would be extraordinarily laborious for an unaided person—handling payrolls, recording bank transactions, shuffling airline reservations. They can also complete tasks that are beyond human abilities—for example, searching through massive amounts of information on the Internet.

Yet for all its importance, software is an intangible quantity that has been devilishly tricky to measure. Exactly how should people determine the size of software?

The question is not just an academic exercise. Without a good gauge of software, the industry has had trouble improving the quality of computer applications and increasing the efficiency of their development. In fact, most companies and government agencies have only a hazy idea of the caliber of their software and the productivity of their programmers. Consequently, predicting the investment of money and time needed to create programs becomes such a difficult task that overruns and delays are the norm rather than the exception.

Indeed, software has proved to be a troublesome technology, as evidenced by the well-publicized computer debacle in Denver International Airport's baggage-handling system that set back the facility's opening by more than a year. In fact, until the so-called Year 2000 computer problem became pressing, most organizations did not know how much software they owned, even though it is a critical and costly asset. In my opinion, this basic problem of measurement is one of the biggest obstacles now facing the software industry.

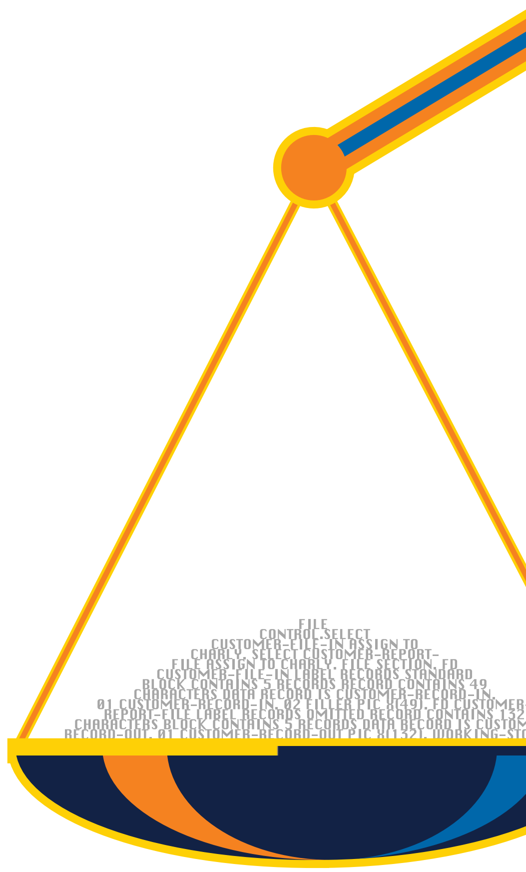
Of course, one way to size up software would simply be to tally all the bytes that a particular program occupies in computer disk storage. Another approach would be to count the number of lines of "code," the lengthy list of instructions required for each computer application. Such measurements, however, do not always reflect how capable the software truly is. Sometimes a program with three million lines will in fact be richer in functionality and features than an application containing five million.

A better approach, then, is to assess the operations that a particular program performs. One formal method for doing so counts "function points," which are quantitative indicators of what a program can do. Computer scientists pioneered this formalism more than two decades ago, and their efforts may soon result in an international standard. Still, it is far from certain whether function points will eventually provide a universal system for measuring software.

What Exactly Is Software?

By themselves, digital computers are merely containers for the software that operates them. A player for compact discs acts similarly. With a disc containing a Mozart symphony in the player, the listener hears classical music. With one for Billie Holiday, jazz is heard. Likewise, with different software a computer can serve as a word processor, manipulate spreadsheets or read documents from the World Wide Web.

The software itself is a series of thousands or sometimes millions of individual commands that instruct a computer to take various actions, such as displaying information, performing calculations or storing data. To continue the music analogy, a programmer is like a composer. Just as the latter conceives music and then describes it note by note, the for-



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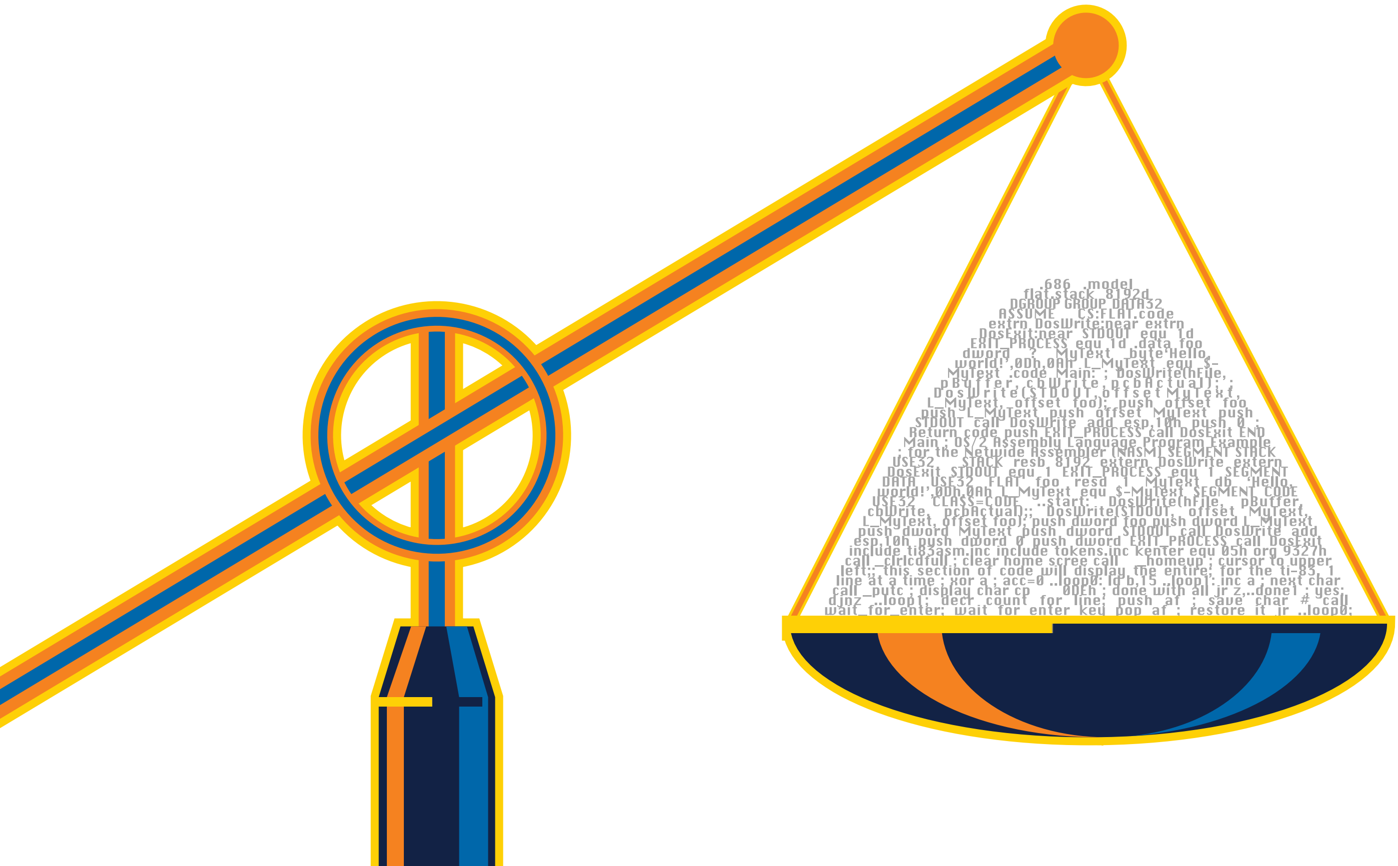


mer envisions and then writes software instruction by instruction.

Here, though, the parallelism with music begins to fail. For one, composers use the same symbols and notation regardless of whether the music they are creating is a pop song or an operatic aria. Programmers, on the other hand, have at least 500 different languages at their disposal. Some computer languages, such as COBOL, are aimed at business problems. Others, such as FORTRAN, are geared for the mathematical and scientific fields. In addition, languages such as PL/I can be used for a wide range of applications.

The availability of so many diverse languages, each with its own structure and syntax, is one of several reasons why counting lines of code has proved to be difficult and unreliable. Specifically, there are no general rules or standards for determining exactly what constitutes a line of code in all programming languages. For a newer language, such as Visual Basic, the very concept has little meaning, because programmers typically use so-called graphical controls as well as code to establish how the application being developed will function. Furthermore, sometimes several languages are used within the same software.

And even if code could be counted with absolute precision, it would still not be a perfect solution. The similar approach of assessing software by simply measuring the amount of computer disk storage it occupies is even more flawed. Among various other reasons, the identical application written in different languages will take up very unequal amounts of storage space, even after the programs have been converted into the computer's binary world of 0s and 1s. Thus, the careless use of such bulk measurements—especially when applied to large programs—can produce deceptive results.

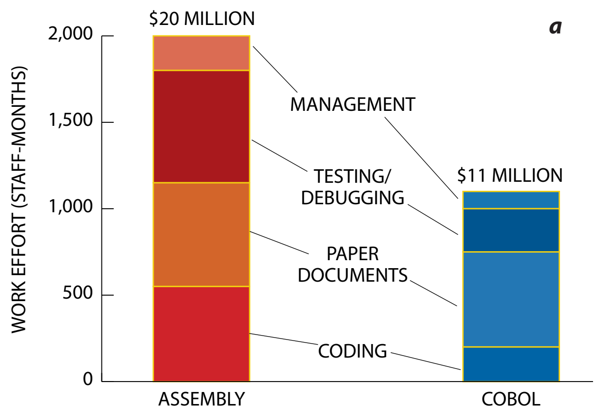
A Perplexing Paradox

Many applications used today consist of more than one million discrete statements. Some applications have more than 10 million. The expense of writing such large software is determined by considerably more than just the cost of the actual coding process. In practice, companies spend a greater amount of money to produce paper documents (specifications and user manuals) and to test the program and correct the errors that invariably turn up. Furthermore, the cost of managing a large software project can itself be quite steep.

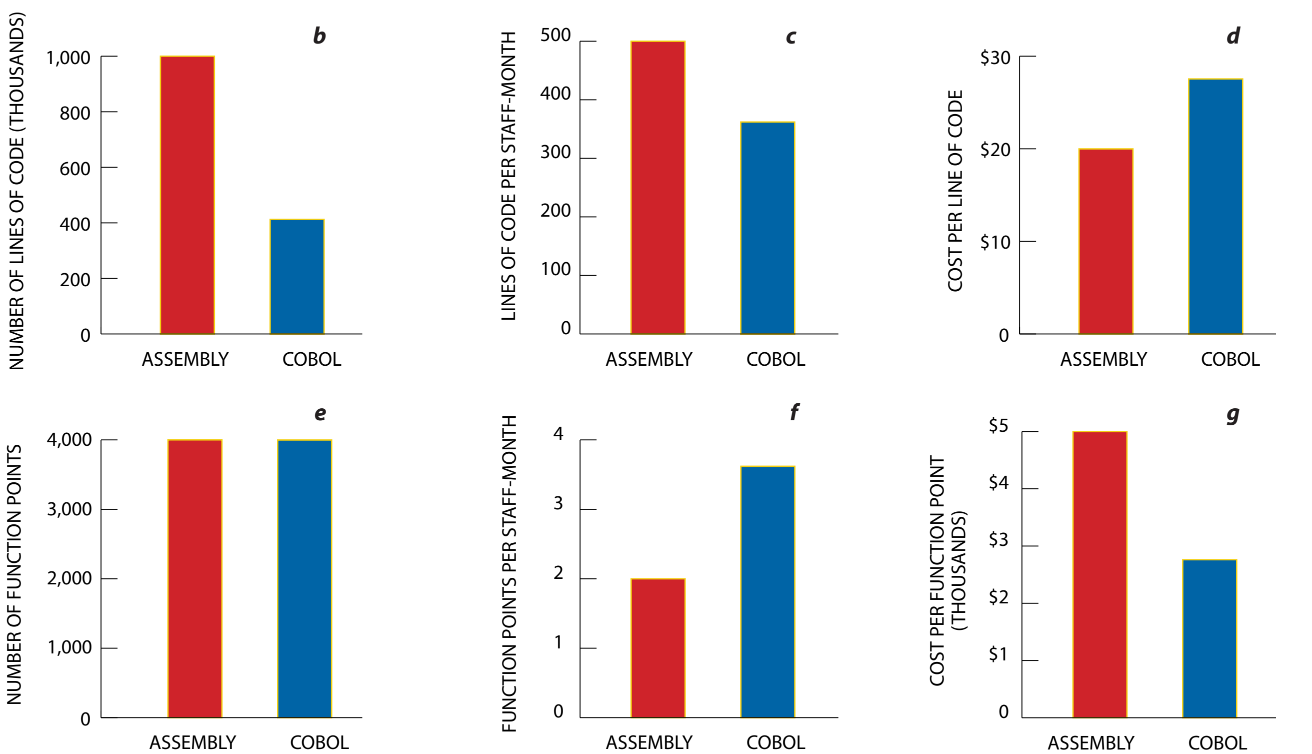
The fact that much of the work of building large applications is not directly related to coding leads to a surprising paradox [*see illustration below*]. Suppose that two companies decide to create programs that do exactly the same things. One firm uses assembly language, which requires many instructions to handle basic tasks, such as adding one number to another. With such a low-level language, the application requires, say, one million lines of code. The second company uses COBOL, a business-oriented language that takes fewer statements to perform the same functions. With this high-level language, the program contains perhaps just 400,000 statements. These line counts would superficially indicate that the former software is more than twice as "large" as the latter even though both programs are, in effect, identical.

The comparison is complicated further if the programmers at the two hypothetical companies write code at different rates (as would be expected even if they have the same fundamental abilities). Because of the different languages used, each staff member at the first firm may be able to deliver 500 lines of code each month, whereas the comparable number for the second company might be 360. Even so, the second company would be able to develop the application faster—1,100 staff-months versus 2,000—because fewer lines need to be written and because programs in high-level languages typically require less debugging, among other reasons. As a result, the total cost of the program for the first company would be $20 million, and the corresponding expense for the second firm would be $11 million. Yet each line of code at the first company costs $20, as opposed to $27.50 for the second firm. So it might at first glance appear that the programmers in the first company are more productive even though the second company is able to develop the same application faster and more cheaply. Thus, a low cost per line of code does not necessarily indicate economic efficiency.

Clearly, blindly counting lines of code can be misleading. Computer scientists realized as much years ago, and consequently several research teams at IBM, one of the largest software development organizations in the world, began to



SOFTWARE ECONOMIC ANALYSIS requires a suitable method for measuring the size of computer programs; otherwise the results can be misleading. Consider the same application that is developed in two different computer languages, assembly and COBOL, with the former requiring more work, resulting in a higher cost (*a*). If the software is measured by counting the number of lines of programming code, the assembly version will appear to be more than twice as large as its COBOL counterpart (*b*), even though both do identical things. This distortion will make it seem that the assembly project has higher productivity (*c*) and is more cost-effective (*d*). But if the software is measured in function points, which indicate a program's capability [*see top illustration on opposite page*], the two programs will be equal in size (*e*), leading to a truer picture of productivity (*f*) and cost (*g*).



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explore other approaches to measuring software. One group, which included me, noted the productivity paradox in 1973, when we compared software written in assembly language with programs developed in PL/I. On average, the former required about four times as many statements as the latter. But both languages could be coded at roughly the same rate.

So our immediate solution to the problem of comparing apples with oranges was simply to multiply the PL/I line count by 4 to convert it into an equivalent number of assembly statements. Although this method provided a rough equivalency, it was far from ideal. Essentially we were doing nothing more than performing a monetary currency exchange, as if converting dollars into yen.

The Point of Function Points

Other investigators at IBM in White Plains, N.Y., and elsewhere began a more fundamental research program. Allan Albrecht and his colleagues decided to formulate units of software complexity, which they dubbed function points. They designed this novel accounting method to be independent of programming languages.

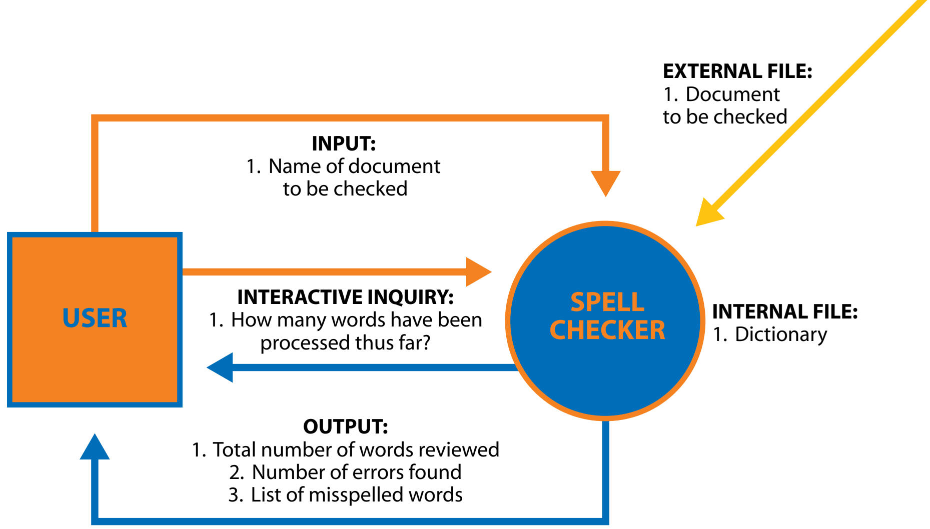
To calculate function points, people examine five attributes of a program: its inputs, outputs, interactive inquiries (when the user issues a query and the computer returns a response), external logical files (interfaces) and internal logical files. Consider a simple spell checker that has one input (the name of the file that needs to be examined), three outputs (the total number of words reviewed, the number of errors found and a listing of the misspelled words), one inquiry (a user can interactively obtain the number of words processed thus far), one external file (the document that needs to be inspected) and one internal file (the dictionary). For this simple program, the number of elements is 1 + 3 + 1 + 1 + 1 = 7.

In practice, function-point analysis proves much more complicated than the mere counting of the five types of attributes. Practitioners of this method use various weights to account for the complexity (low, average or high) of each element, according to detailed guidelines maintained by the International Function Point Users' Group (IFPUG), an organization based in Westerville, Ohio. The actual calculations are quite involved, but the weighted sum of function points for the example of a simple spell checker would be 40 if each of the seven elements were of average complexity.

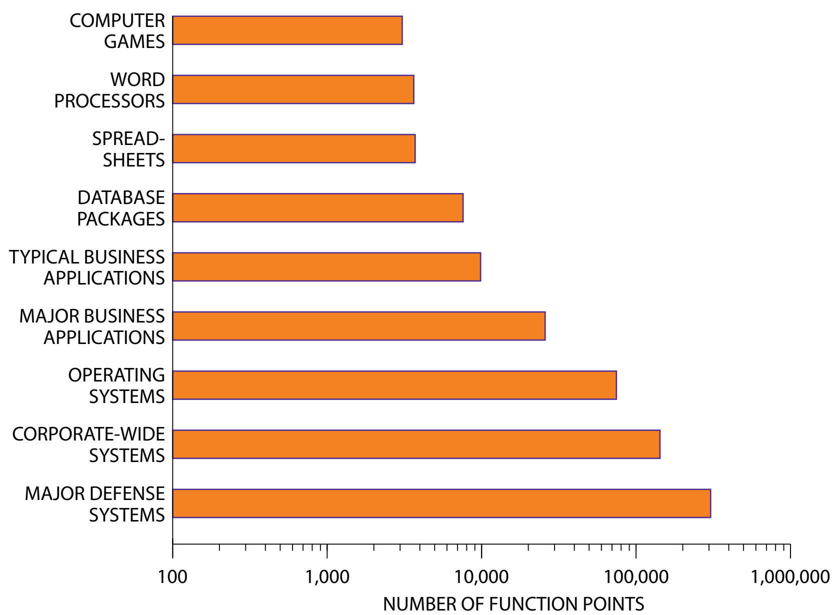
Last, the function-point total is either increased or decreased with a multiplier to match the perceived intricacy of the overall system. This adjustment is based on 14 factors, including, for instance, whether the processing of the application will be split across different computers and whether parts of the software need to be designed for reusability by future programs [*see box on next page*].

The calculation of function points for complex software is fairly complicated; it typically requires specialists who have passed a certification examination. Few software managers need to know the actual mechanics of function-point counting, but all of them should understand the assessments of productivity and quality now being expressed with such measurements.

Because they are independent of the programming language used, function



FUNCTION POINTS provide a means to assess the size of a program in terms of its capability. The measurement requires the examination of five attributes of an application: its inputs, outputs, interactive inquiries, external files and internal files. For a simple spell checker, the number of such elements is seven, and each item needs to be weighted according to its individual complexity. The weighted sum of function points is then either increased or decreased to match the perceived intricacy of the overall program, as judged with 14 criteria [*see box on next page*]. The final total will thus indicate the functionality and complexity of the application.



SOFTWARE SIZE of typical programs, such as word processors and operating systems, can be compared with function points. Major defense systems are the largest kind of application, containing about 300,000 function points (roughly 27 million lines of code).

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Filling in the Scorecard

The function-point methodology allows analysts to judge the complexity of a computer program using 14 criteria. The actual assessment, which requires people with special training who have passed a certification exam, is a detailed process with guidelines specified by the International Function Point Users' Group, based in Westerville, Ohio. The 14 factors, with corresponding examples of high-scoring programs for each, are listed below.

1. Complex data communications: A program for a multinational bank that must handle electronic monetary transfers from financial institutions around the world.

2. Distributed processing: A Web search engine in which the processing is performed by more than a dozen server computers working in tandem.

3. Stringent performance objectives: An air-traffic-control system that must continuously provide accurate, timely positions of aircraft from radar data.

4. Heavily used configuration: A university system in which hundreds of students register for classes simultaneously.

5. Fast transaction rates: A banking program that must perform millions of transactions overnight to balance all books before the next business day.

6. On-line data entry: Mortgage approval program for which clerical workers enter data interactively into a computer system from paper applications filled out by prospective home owners.

7. User-friendly design: Software for computer kiosks with touch screens in which consumers at a subway station can purchase tickets using their credit cards.

8. On-line updating of data: Airline system in which travel agents can book flights and obtain seat assignments. The software must be able to lock and then modify certain records in the database to ensure that the same seat is not sold twice.

9. Complex processing: Medical software that takes a patient's various symptoms and performs extensive logical decisions to arrive at a preliminary diagnosis.

10. Reusability: A word processor that must be designed so that its menu tool bars can be incorporated into other applications, such as a spreadsheet or report generator.

11. Installation ease: An equipment-control application that nonspecialists will install on an offshore oil rig.

12. Operational ease: A program for analyzing huge numbers of historical financial records that must process the information in a way that would minimize the number of times computer operators have to unload and reload different tapes containing the data.

13. Multiple sites: Payroll software for a multinational corporation that must take into account the distinct characteristics of various countries, including different currencies and income tax rules.

14. Flexibility: A financial forecasting program that can issue monthly, quarterly or yearly projections tailored to a particular business manager, who might require that the information be broken down by specific geographic regions and product lines.

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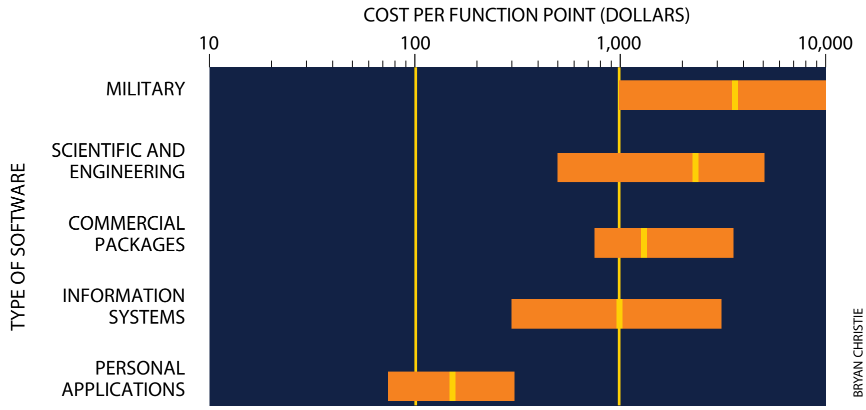
points provide the most accurate way to compare different software. For the earlier paradoxical example, if both the assembly language and COBOL applications contain 4,000 function points (the two programs, having the same functionality, will score an equal number of points), then the total cost for the first company is $5,000 per function point, compared with $2,750 for the second [*see illustration on page 106*]. This result gives a truer picture of the actual economies of the two projects.

Using function points, corporate managers can now conduct more reliable analyses of productivity and quality. Currently this methodology is the most widely used approach for such studies in the U.S. and in much of Europe. The total number of software projects worldwide measured using function points surpasses 100,000. My colleagues and I, among others, have used information from these studies to examine variations in productivity and quality by country, industry and programming language.

Such investigations have spawned many useful rules of thumb that can aid companies developing software, particularly before they undertake large projects. (If the software is completely specified at the outset, the total number of function points of a project can be calculated before even a single line of code has been written.) For instance, raising the function-point total of a system to the 1.25 power gives a ballpark estimate of the number of errors that will have to be removed. Dividing the number of function points by 150 approximates the number of programmers, software analysts and technicians who will be needed to develop that application, and raising the function-point total to the 0.4 power gives a rough estimate of the time in months that staff will need to complete the project. Obviously, these rules of thumb are no substitute for formal, detailed estimates, but they do provide preliminary numbers that can temper unrealistic and excessively optimistic schedules, which are a common problem in software development.

Despite such helpful information, the regrettable fact is that most organizations do not perform any kind of useful software measurements at all. Although more than 100,000 projects have been sized with function points to date, that number is below 1 percent of the total number of software applications in use. Among smaller firms, especially those with fewer than 100 software professionals, neither function points nor any other measurement techniques are yet widespread. But function-point usage has become quite common among large companies with more than 10,000 people involved in developing, testing and maintaining computer programs. For such corporations, software is a major cost, one that demands accurate measurement and estimation.

It is also interesting to look at the size of personal software applications. The word processor with which I wrote this article contains about 435,000 lines of code and has roughly 3,500 function points. In the course of daily business, an office worker might use more than 25,000 function points' worth of software in the form of spreadsheets, word processors, database applications, statistical tools and custom programs. All these applications run under the control of operating systems, which can top 100,000 function points in size.



COST OF SOFTWARE can be investigated using function points. This chart compares the expense of building different types of software: military applications; scientific and engineering programs; commercial packages, such as Microsoft Word; information systems used by companies to run their business operations; and personal applications developed by nonspecialists. Cost ranges are given with average values indicated.

Not a Perfect Metric

The use of function points has expanded throughout the world, but not without some debate. A number of researchers have faulted the approach as too prone to human misinterpretation, for example, in assigning the various weights according to software complexity. Such subjectivity does exist, but the use of certification programs and exams has narrowed the range of counting variance to within about 10 percent. This margin of error is roughly in the same range as that associated with the counting of lines of code for widely used languages such as COBOL. (In fact, companies that lack standards for counting lines of code have experienced huge variances of more than 100 percent when different managers or programmers measured the same program.)

Many researchers have complained that the calculation of function points is too labor-intensive. This criticism is valid, but automated counting tools might soon ease the burden. Others have stated that because function points were developed for business information systems, they are not adequate for assessing other types of software. But function points have helped measure systems software, applications permanently programmed into various consumer devices and high-tech weapons. And computer professionals continually revise the rules for function points to include newer types of software, such as applications for the World Wide Web.

Standardization may be the greatest challenge. Many people in the software field have questioned some of the counting procedures in the original IBM approach as well as in the current method established by IFPUG. As a result, there are now about 20 variations of the technique.

In the early 1980s Charles R. Symons, a researcher with Nolan, Norton & Company in London, developed a scheme for counting function points called Mark II. Among other modifications, Mark II expands the number of adjustment factors from 14 to 19. Another adaptation, called feature points, is aimed at engineering and scientific applications. Because such software can be quite complex but sparse in the number of inputs and outputs, the use of traditional function points can sometimes lead to underestimation. Thus, the feature-point approach considers the number of algorithms in a program and reduces the number of adjustment factors from 14 to only three. Other offshoots include so-called 3-D function points, engineering function points, object points and full function points.

The International Standards Organization and the major associations of function-point users around the world are now working to draft a consolidated set of rules. Because representatives from various countries are involved, it appears likely that the final standards may embody concepts from IFPUG and from the major variations, if indeed standardization is possible.

In spite of the shortcomings, function points currently provide the best way to measure software. And the growing use of this formalism is indeed welcome, for without some kind of objective criteria, software development will have great difficulty in taking its place as a true engineering discipline rather than an artistic activity, as it has been for much of its history. SA

The Author

CAPERS JONES is chief scientist and an executive vice president of Artemis Management Systems in Boulder, Colo., which recently acquired Software Productivity Research in Burlington, Mass., a consultancy that he founded. He is the designer of several tools for estimating the cost and quality of software and the author of 11 books on programmer productivity and software quality. Jones was formerly an assistant director at the ITT Programming Technology Center in Stratford, Conn. Before joining ITT, he was with IBM for 12 years, where he received an outstanding contribution award for his work in software quality and programmer productivity. He is a member of the IEEE Computer Society, IFPUG and ISPA.

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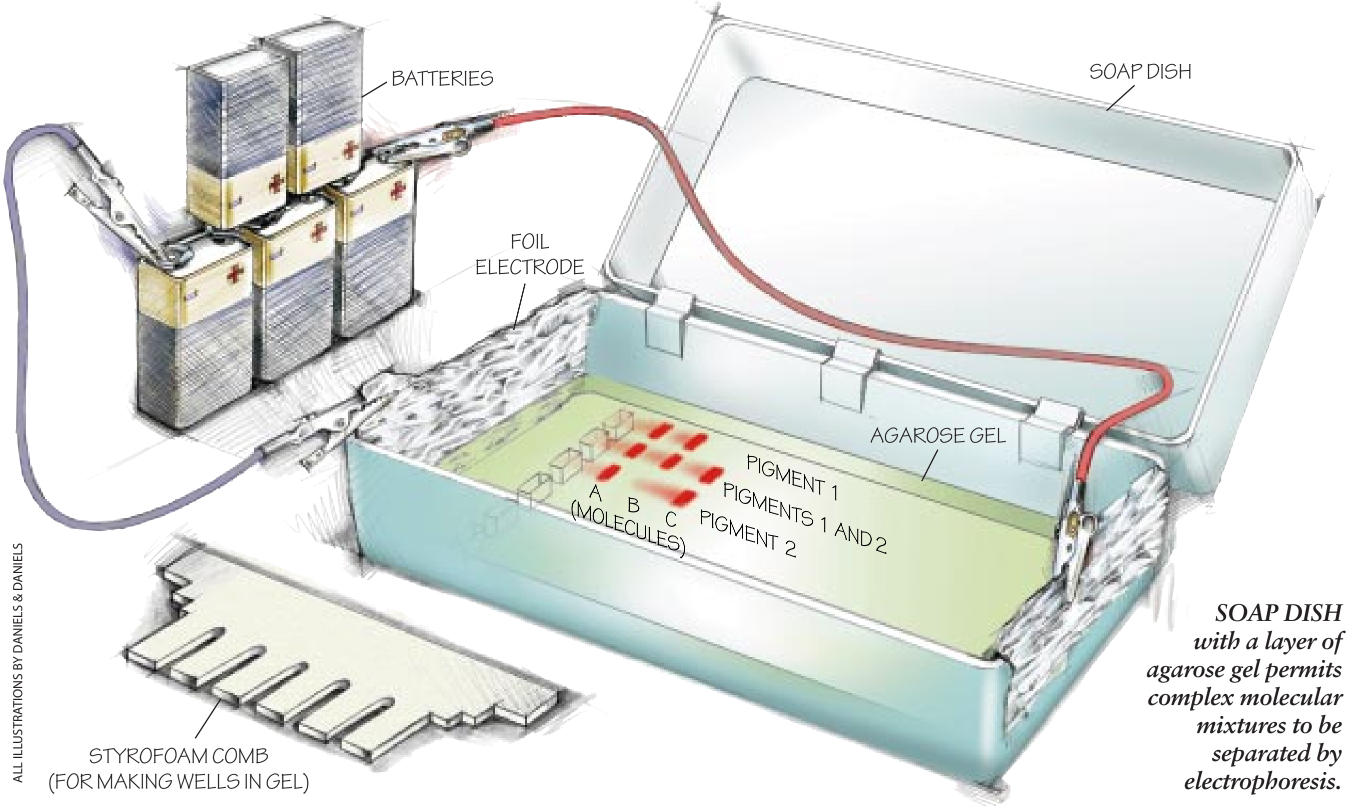
by Shawn Carlson



ALL ILLUSTRATIONS BY DANIELS & DANIELS

***SOAP DISH** with a layer of agarose gel permits complex molecular mixtures to be separated by electrophoresis.*

Sorting Molecules with Electricity

The most wonderful private garden I have ever seen is tucked away behind a modest house in La Jolla, Calif., not far from where I live. The gardener is a British-born psychology professor and dear friend who sends me home with fruit and flowers each time I visit. Recently I noticed that two of his plants, though very different in shape, produced flowers of the exact same shade of purple. This observation made me wonder whether the two species might be related.

One normally traces evolutionary connections by identifying physical similarities between species. So I decided to extract and isolate the pigments in the two flowers so that I could compare them in detail. That process is actually much easier than it sounds. In fact, using a simple technique called electrophoresis, I could carry out the experiment in about an hour for very little money.

Most molecules are electrically neutral, but some important biological molecules, including proteins, DNA fragments and many natural dyes, carry a net negative charge when they are in solution. Electrophoresis cleverly uses a weak electric field to force such charged molecules to drift through a medium that separates them by offering differing amounts of resistance to motion.

You can easily see this phenomenon in action when you place a droplet of dye on a strip of blotting paper that has been wet by a conductive fluid, such as salt water. When the ends of the paper are connected across a battery, a voltage is set up, which drives the charged dye molecules through the paper. Positively charged particles move toward the negative terminal, whereas negative ones move toward the positive terminal. Usually, larger molecules have a more difficult time than smaller ones in passing through paper fibers, so the smaller molecules drift faster. Thus, over time, the different molecules in a mixture will tend to sort themselves by size.

It takes only a few minutes to set up a basic apparatus. From a large coffee filter cut a rectangular strip of paper that is about one centimeter (about half an inch) wide and about 15 centimeters (six inches) long. Place this paper band inside a flat glass pan or cooking dish. Roll each end of the paper strip around a nail, and use an alligator clip to secure it. Wire the clips to five nine-volt batteries connected in series.

To make the conductive solution, mix about 100 milliliters (four ounces) of distilled or bottled water with 1.5 grams (about a quarter teaspoon) of table salt. Then thoroughly wet the paper, including the nails, with the salt so-

***TEMPLATE** allows the "comb" to be cut from a Styrofoam meat tray.*

lution, but don't add so much that the paper is submerged in a puddle.

To begin, use a toothpick to place droplets from several different hues of food coloring in a line, then connect the electrodes. The colors will rapidly spread into streaks as the pigment molecules migrate toward the positive electrode. Next, mix two of the dyes, say, red and green, and run a tiny splotch of the combination. After about 20 minutes, the colors should begin to separate. The same technique can be used to separate other molecular mixtures.

So here's how to find out if two plant species use the same molecules as pigments. First, crush the flowers and immerse them in clear isopropyl alcohol, letting the solids settle. Pour off each of the resulting color-tinged liquids into separate containers and then concentrate them by letting the alcohol evaporate. Once the alcohol is nearly gone, dissolve the pigments in a few drops of the salt solution you made earlier.

Next, line up three tiny dots of pigment on a strip of soaked filter paper by placing a pure sample from each plant on the outside and an equal mixture from both in the center. Then connect the batteries. If the outside dots separate into different sets of colored swaths and the center streak appears to be a combination of the outer ones, then you know that different pigments are involved. But if all three dots form the same pattern, then both plants probably rely on the same molecules for color.

Note that the salt ions will also drift toward the electrodes, where they will quickly create a layer of tarnish that impedes the flow of electricity. So after each run, you will have to scrub the electrodes. As all this cleaning rapidly becomes tiresome, you might try to replace the steel nails with another conductive material that does not tarnish as quickly—stainless-steel wire or aluminum foil, for example. Small pieces of gold or platinum wire or chain work especially well.

Although many great discoveries have been made using paper-based electrophoresis, this simple method does have a big drawback: the molecules tend to get caught up in the fibers of the paper. This complication explains why even pure dyes form streaks instead of remaining well-defined dots as they move along. So these days biologists often replace the paper with a more uniform material called agarose—a clear substance with the consistency of stiff gelatin. The DNA "fingerprint" patterns you may have seen are produced by electrophoresis on such a gel. Each of the individual lines in the fingerprint indicates strands of DNA of a certain length. Compared with results with paper, the degree of separation possible with a gel electrophoresis is amazing.

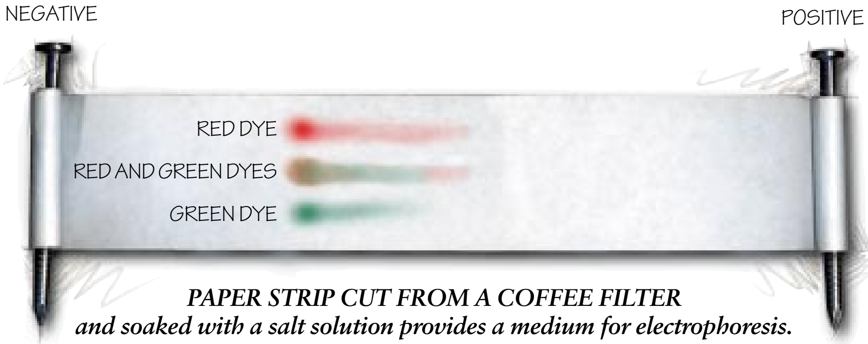
September's Amateur Scientist column explained how to extract DNA from living tissues. Unfortunately, the extracted material must be subjected to sophisticated laboratory manipulations using expensive reagents before a fingerprint can be created. But similarly diagnostic patterns can be made using plant pigments. Indeed, complex pigments often separate so cleanly that the results are just as stunning. After about 20 minutes, you can often isolate virtually every molecule involved in such a mixture.

Although ordinary gelatin does not work well, I'm told that a food additive called agar-agar may and that it can be found in Chinese food markets. But I suggest that you spend $25 and purchase enough agarose gel for about 40 experiments from Edvotek, an educational biotechnology company in West Bethesda, Md. (301-251-5990; www.edvotek.com).

You can quickly fashion a gel-based electrophoresis unit from any small, rectangular container that is waterproof. I used the bottom of a plastic soap dish. Bend some aluminum foil over the two shorter sides to serve as electrodes and then pour enough of the hot, liquid agarose into the dish to cover it with a half-centimeter layer. Because your gel must contain reservoirs to hold the concoctions you wish to separate, cut out a comb shape [*see bottom illustration on opposite page*] from a Styrofoam tray—the kind used to pack meat at the grocery store—and suspend it so that the tines penetrate the liquid agarose but don't poke through the bottom. Let the gel set before carefully removing the comb. This maneuver should produce a series of nicely spaced wells for your samples. Now add enough of the salt solution to cover the gel and keep it from drying.

With an eyedropper, place your test substances into the wells, rinsing the dropper thoroughly between samples. To start your experiment, just connect the aluminum foil to your batteries with alligator clips, with the positive terminal attached to the side opposite the wells so that the negatively charged molecules have some room to move. Don't worry if you notice some bubbling along the foil as water molecules are split apart by electrolysis. And don't be concerned if the color of the pigments changes (a common effect of altered pH). Because of its tendency to tarnish, you will have to replace the aluminum foil when you renew the agarose after each run.

Electrophoresis is a cornerstone of molecular biology. Armed with this technique you can isolate the basic stuff of biology for further exploration. There are far too many living systems for professionals to study them all, and so there are many discoveries waiting for the ambitious amateur armed with this technique, a textbook and some perseverance. So why not get to work! SA



***PAPER STRIP CUT FROM A COFFEE FILTER** and soaked with a salt solution provides a medium for electrophoresis.*

The Society for Amateur Scientists has joined forces with Edvotek to create a complete gel-based electrophoresis unit for kitchens and classroom labs. Send $55 to SAS, 4735 Clairemont Square, Suite 179, San Diego, CA 92117, or call the society at 619-239-8807. You will find more information about this and other articles from the Amateur Scientist at web2.thesphere.com/SAS/WebX.cgi on the World Wide Web.

MATHEMATICAL RECREATIONS

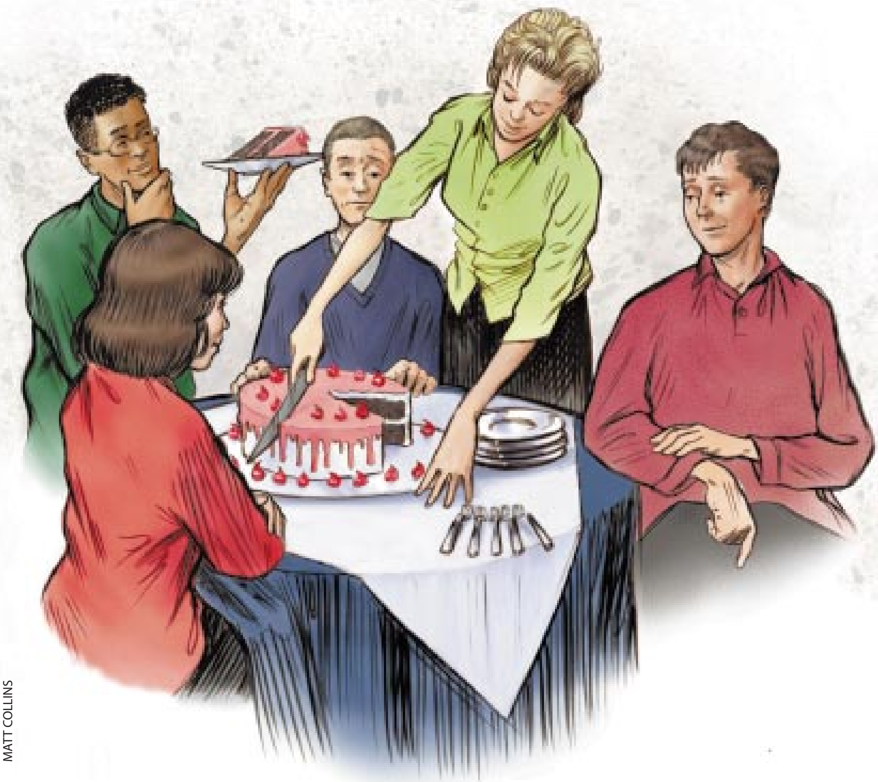
by Ian Stewart

Your Half's Bigger Than My Half!

A big man and a small man were sitting in the restaurant car of a train, and both ordered fish. When the waiter brought dinner, the big man promptly took the bigger fish; the small man complained that this was extremely impolite.

"What would you have done if you'd been offered first choice, then?" asked the big man, annoyed.

"I would have been polite and picked up the small fish," the small man said smugly.



MATT COLLINS

SHARING A CAKE
among several people so that each one is satisfied requires a complex algorithm.

"Well, that's what you've got!"

As this ancient joke illustrates, some folk are hard to please.

For the past 50 years, mathematicians have grappled with problems of fair division, usually formulated in terms of a cake rather than fish. Jack Robertson and William Webb have recently published a fascinating book, *Cake Cutting Algorithms* (A. K. Peters, Natick, Mass., 1998), which surveys the field.

In this and next month's column, we'll take a look at some ideas that have emerged from the deceptively simple question of dividing a cake so that everybody is happy.

The simplest case involves just two people who wish to share a cake so that each is satisfied that they have a fair share. "Fair" here means "half or more by my valuation," and the recipients may disagree on the value of any given bit of cake. For example, Alice may like cherries, whereas Bob prefers icing. Curiously, it is easier to divide the cake when the recipients disagree on what its parts are worth.

You can see this makes sense here, because we can give Bob the icing and Alice the cherries, and we're well on the way to satisfying both of them. If they both wanted icing, the problem would be harder.

Not that it's terribly hard when there are only two players. The solution "Alice cuts, Bob chooses" has been traced back 2,800 years! It is fair in the sense that neither Alice nor Bob has a right to complain about the result. If Alice dislikes the piece that Bob leaves, it's her own fault for not being more careful to make equal cuts (according to her valuation). If Bob doesn't like his piece, he made the wrong choice.

The problem begins to get interesting with three players. To begin with, Robertson and Webb analyze a plausible but incorrect answer. Tom, Dick and Harry want to divide a cake so that each is satisfied he's got at least one third. The cake, by the way, is always assumed to be infinitely divisible (although much of the theory works if it has valuable "atoms"—single points to which at least one recipient attaches a nonzero value). The algorithm goes like this:

STEP 1: Tom cuts the cake into two pieces x and w, where he thinks x is worth $1/3$ and w is worth $2/3$.

STEP 2: Dick cuts w into two pieces y and z, which he thinks are each worth $1/2$ of w.

STEP 3: Harry chooses whichever of x, y and z he prefers. Then Tom chooses from the two pieces left. Dick gets the last piece.

It's clear that Harry will be satisfied, because he has first pick. Tom is also satisfied, for slightly more complex reasons. If Harry picks x, then Tom can pick whichever of y and z he considers more valuable. Because he thinks they are worth $2/3$ in total, he must think at least one of them is worth $1/3$. On the other hand, if Harry chooses y or z, then Tom can choose x.

Dick, however, may not be so happy. If he disagrees with Tom about the first cut, then he might think w is worth less than $2/3$, meaning that the only piece that will satisfy him is x. But Harry could choose y, say, and Tom x, so Dick has to take z—which he doesn't want.

The first fair division was found in

1944 by Hugo Steinhaus, one of a group of Polish mathematicians who met regularly in a café in Lvov. His method involves a technique called trimming.

STEP 1: Tom cuts the cake into two pieces x and w, where he thinks that x is worth 1/3 and w is worth 2/3.

STEP 2: He passes x to Dick and asks him to trim it so that Dick values it at 1/3, if he thinks it's worth more than that, and to leave it alone if not. Call the resulting piece x': this is either x or smaller.

STEP 3: Dick passes x' to Harry, who can either agree to take it or not.

STEP 4: (*a*) If Harry accepts x', then Tom and Dick pile the rest of the cake—w plus any trimmings from x—in a heap and treat this as a single (messy) cake. They play "I cut, you choose" on that.

(*b*) If Harry does not accept x', and Dick has trimmed x, then Dick takes x', and Tom and Harry play "I cut, you choose" on the rest.

(*c*) If Harry does not accept x', and Dick has not trimmed x, then Tom takes x, and Dick and Harry play "I cut, you choose" on the rest.

That's one answer—I'll leave it to you to verify the logic. Basically, anyone who isn't satisfied with what he gets must have made a bad choice or cut at an earlier stage, in which case he has only himself to blame.

In 1961 Lester E. Dubins and Edwin H. Spanier proposed a solution involving a moving knife. Arrange for a knife to float smoothly and gradually over the cake, starting from the left. At any instant, l is the part to the left of the knife. Tom, Dick and Harry are all told to shout "Stop!" as soon as the value of l, in their opinion, becomes 1/3. The first to shout gets l, and the other two divide the rest either by "I cut, you choose" or by moving the knife again and shouting as soon as the perceived value reaches 1/2. (What should they do if two players shout simultaneously? Think about it.)

This method extends readily to n recipients. Move the knife across and tell everyone to shout as soon as l reaches $1/n$ in their estimation. The first person to shout gets l, and the remaining $n - 1$ players repeat the process on the remaining cake, only of course they now shout when the perceived value reaches $1/(n-1)$ and so on.

I must say that I'm never terribly happy with moving-knife algorithms because of the time lag involved in the players' reactions. The best way to get round this quibble is to move the knife slowly. Very slowly.

Let's call the first kind of answer a fixed-knife algorithm, the second a moving-knife algorithm. There is a fixed-knife algorithm for three-person division that also extends readily to n people. Tom is sitting on his own, staring at "his" cake, when Dick shows up and asks for a share. So Tom cuts what he thinks are halves, and Dick chooses a piece. Before they can eat anything, Harry arrives and demands a fair share, too. Tom and Dick independently cut their pieces into three parts, each of which they consider to be of equal value. Harry chooses one of Tom's pieces and one of Dick's.

It's not hard to see why this successive-pairs algorithm works, and the extension to any number of people is relatively straightforward. The trimming method can also be extended to n people by offering everyone around the table a chance to trim a piece if they are willing to accept the result.

Which method requires the fewest cuts? The moving-knife method uses $n - 1$ cuts to get its n pieces, and that's as small as you can get. The fixed-knife methods are more cumbersome. With n people, a generalization of the trimming algorithm uses $(n^2 - n)/2$ cuts, and the successive-pairs algorithm uses $n! - 1$, where $n! = n(n-1)(n-2)\ldots 3 \times 2 \times 1$ is the factorial. This is bigger than the number of cuts used in the trimming algorithm, except when $n = 2$.

A more efficient fixed-knife method is the divide-and-conquer algorithm, which works roughly like this: try to divide the cake using one cut so that roughly half the people would be happy to have a fair share of one piece, whereas the rest would be happy to have a fair share of the other piece.

Then repeat the same idea on the two separate subcakes. The number of cuts needed here is about n log2n. The exact formula is $nk - 2k + 1$, where k is the unique integer such that $2k - 1 < n \le 2k$. This may be as good as you can get for a fixed knife.

In principle the cake-cutting methods can be applied to some real-life situations as well. When Germany was divided among the Allies and Russia for administrative purposes, the first attempt created leftovers—Berlin—that had to be divided as a separate step. So negotiators intuitively applied cake-cutting technology. Something rather similar is straining Israeli-Palestinian relations right now, with Jerusalem as the main "leftovers" and the West Bank as another bone of contention.

Might not the mathematics of fair allocation assist the negotiations? It would be nice to think we lived in a world that was sufficiently rational for such an approach. SA

FEEDBACK

Robert L. Henrickson of Billings, Mont., wrote about the column "Glass Klein Bottles" [March], providing some fascinating information about similar bottles in pottery. *The Life, the Times, and the Art of Branson Graves Stevenson,* by Herbert C. Anderson, Jr. (Janher Publishing, 1979), reports that "in response to a challenge from his mathematician son, Maynard, Branson made his first Klein bottle using the topology suggestion [sic] of the German mathematician, Klein. He failed in his first try, until the famous English potter, Wedgwood, came to Branson in a dream and showed him how to make the Klein bottle." This was around 50 years ago. Branson's study of claywork and pottery eventually led to the formation of the Archie Bray Foundation in Helena, Mont.

People have made Klein bottles from all kinds of materials. There is a knitting pattern for a woolly Klein bottle and even a paper Klein bottle with a hole (*left*), sent in by Phillip A. M. Hawley of Paonia, Colo. —*I.S.*

Paper-strip Klein bottle

IAN WORPOLE

The Scientific American Young Readers Book Awards

by Philip and Phylis Morrison

This year we examined more than 800 books from more than 120 publishers. Making the first cut was not too hard, but selecting the fine books we had room to present leaves us certain there are at least as many other books as good as these.

Fire Truck

Written and illustrated by Peter Sís. (Uses lots of red.) Greenwillow Books, New York, 1998 ($14.95)

Matej, going on four, lives not too far from Ladder Company 20, NYCFD. He has shelves of rolling firefighting toys and likes anything red. His first words on arising may be "fire truck." Peter Sís ought to know, for Matej is his son. Running out of new fire truck books to read from, talented Peter wrote one of his own, Matt approving. Make way for a fiery fantasy.

One day young Matej awoke, a red FIRE TRUCK himself! He was part of it, resembling his little red bed, but much larger, here painted across two full pages. It had *one* driver, two ladders and everything else you might count, up to 10 big boots. He raced around on six wheels, eight sirens blaring, rescued a cat and a teddy bear and put out a fire, all in the living room. Then Matt smelled something special, parked in red cap and suit at the kitchen table, and the little boy ate his pancakes.

The Best Paper Airplanes You'll Ever Fly

Design by Kevin Plottner. Aerodynamics by Paul Doherty. Laminated sheet, text and drawings in color. Klutz Press, Palo Alto, Calif., 1998 ($4.95)

Three simple designs are here, guaranteed to be "the best paper airplanes on the planet." We cannot certify that, but the ones we made flew splendidly. The authors are proud of record indoor flights of between 60 and 80 feet, hand-launched. This small guide is as close to physics as to technology, for it suggests the principles of good results—although it also includes precise instructions for the folding.

You have to trim a paper airplane; if not, it will fly like a rock. "This is not an opinion. It is a guarantee," and grade-school builders are not excepted. Symmetry is the aim, carefully secured. "The left side MUST look just like the right." Here is how to check on that and how to adjust, with five troubleshooting hints, plus launch instructions for indoors and out. Take care. (Outdoors you might hit a thermal, and your plane can really go out of sight.)

Mud Matters: Stories from a Mud Lover

Written and illustrated by Jennifer Owings Dewey. Photographs by Stephen Trimble. Marshall Cavendish, New York, 1998 ($14.95)

Well-known Santa Fe author Jennifer Owings Dewey lives not far from her childhood ranch home; she was then a little "desert rat," waiting to dance in the brief, pounding storms of summer, amid dramatic thunder, winds, fresh wetness and damaging floods. But as the clouds departed, theirs was a glorious gift, squishy mud that "smelled like death or something just born."

Quicksand was part of that mud—holes rain-filled with bubbling layered mud, sinister, maybe bottomless? You could see how quickly the test stones you threw in would vanish. In her 11th summer, this adventurer imprudently entered such a hole alone. The experience of steady, slow sinking was frightening. She had no idea of how to get out. A residual caution had led her to bring a sturdy stick; embedded into the edge, it saved her a long, scary wait for help.

PETER SÍS

The first mud technology the Mud Lover practiced was that of adobe brick-making. Most houses of the region were built that way—hard and heavy work. But her schoolgirl version used tiny adobes to form clusters of Lilliputian houses, which would be flooded away when the waters came down.

She saw Ritual Mud, too, the coating that reddened and disguised the Mudhead dancers of Zuni, half-clowns, half-beings of mystery. Magic Mud left a weighty lesson. She and her sisters heard tales of Utah healing mud; their parents remarked on it at length as the family drove to far Utah on holiday. The eager girls were sure that the silky, red stuff they found one long day was just that. In spite of utter parental skepticism, they took it home. Two pale girl cousins visited from the East, "afraid of spiders" even. They were offered the spiritual cure of Magic Mud; once freely drenched, the cousins became "as brave as any kids we knew," undaunted by spiders. So the text ends, suggesting a wider conclusion: such cures often owe more to happy believers than to the mud. Reminiscences of learning as personal and well told as these make irresistible reading.

Painters of the Caves

By Patricia Lauber. Map and photographs in color. National Geographic Society, Washington, D.C., 1998 ($17.95)

The bounty of this art is a celebration. The brief text by a long-admired writer is clear, informed and measured, just right for readers in the middle grades and upward. It is knit into a lustrous set of large color photographs of European cave art, well supported by modern paintings (in particular, reconstructions by Jack Unruh) and by apt photographs of ancient carvings and implements. The vigorous beauty of murals painted by the light of lamps fueled by animal fat is stunning. Here are full masterpieces—bison and reindeer, cave lions and spotted horses—done hundreds of centuries back, when woolly rhinos roamed the south of France. The carbon dating that fixes those times long before history is made credible in a simple page or two.

One editorial slip labels a famous Lascaux painting by a caption that ascribes it to the cave of Chauvet. When the old painters were at work in Lascaux, the paintings in Chauvet were already about as old as Lascaux is now. Today the two appear to be of remarkably similar merit.

Anatomy of a Doll: A Fabric Sculptor's Handbook

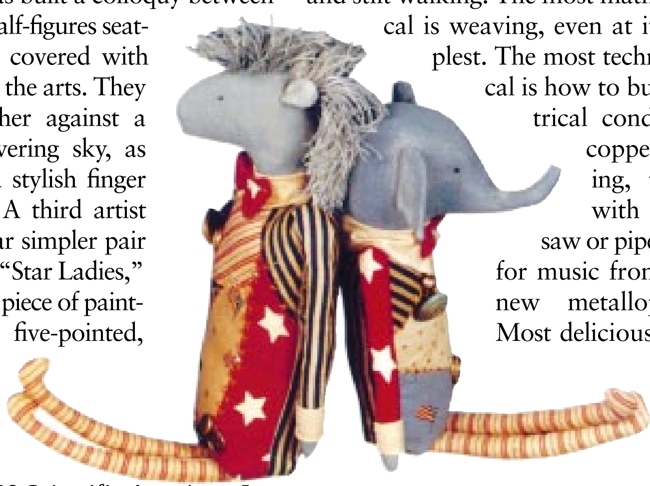
By Susanna Oroyan. Illustrated with color photographs and line drawings. C&T Publishing, P.O. Box 1456, Lafayette, CA 94549, 1997 (paperbound, $25.95)

Making Things: The Handbook of Creative Discovery

By Ann Sayre Wiseman. Little, Brown and Company, Boston, 1997 (paperbound, $12.95)

Dollmaker Susanna Oroyan has made some 500 original dolls. Her book shows in color the diverse work of 100 and more contemporary artist-dollmakers. Like any sensible philosopher, she delays defining a doll for quite a few pages. "I am sure ... I don't know what a doll is. It seems to be a representation of the human figure."

One of the author's own dolls, "Angel," is an 18-inch tangle of airily gleaming wire around a copper chest plate and a solid white head, hands and feet. Another artist has built a colloquy between two life-size half-figures seated at a table covered with real books on the arts. They face each other against a painted, glowering sky, as each points a stylish finger at the other. A third artist has made a far simpler pair of seven-inch "Star Ladies," each a stuffed piece of painted cloth, in five-pointed, hair-flying star shape, all points so artfully extended and curved that the illusion of comic flight is intense.



CHRISTINE GARCEW

How would you write an anatomy textbook for so complex an art? This is one. It begins with graded study of the fundamentals—scale, materials, colors, joints, faces. Line drawings show how legs, for instance, can be made to suggest the true complex form. Molding of plastic media; needle sculpture by multiple piercing and tautening a stuffed cloth head; body joints by stitching, tying, hinging, ball-and-socket; wire armatures; draped clothing—all strive to approximate the living body. This is not the place for mere patterns but for a choice of resources presented to the reader, open to the needs of both beginners and experts. Using ordinary cloth, threads, buttons, yarn, one of us has been caught in this net, finding her way to small portraits of character. Your male reviewer has made no dolls yet but has enjoyed this book as a peerless museum guide, as a user's manual of the inventive hand and mind, and as a parable of science. High school needleworkers, artists and their teachers who use Oroyan will soon concur.

Ann Sayre Wiseman has made a book that is untied to any single task. A teacher of teachers, she has developed the material over 25 years of working among schoolchildren and adults of many ages. For more than 100 activities, the drawings and clear, hand-lettered text take a reader into her cheerful presence. A list will suggest what is here: papermaking in variety; papery products such as simple masks, beads and mobiles; printing from fingertips, from whole scaly fish, from carved potatoes and many variants. The most athletic demand is a nifty page on stilts and stilt walking. The most mathematical is weaving, even at its simplest. The most technological is how to buy electrical conduit or copper tubing, to cut with hacksaw or pipe cutter for music from your new metallophone. Most delicious is the bread sculpture. The author has extended it to produce bread mermaids, crocodiles, and a lion peaceably enfolding a lamb.

In sum, the best learning is doing; feedback from failure is often the path to success; take time and path to suit yourself—but the act of creation is often messy! Success is not won simply by whim. Wiseman's book is aimed at guiding the work of hours or days. The exacting doll arts need years, even careers. That the two authors so converge in spirit is a prize, a prize too little evident in our schools.

Invisible Enemies: Stories of Infectious Disease

By Jeanette Farrell. Farrar, Straus & Giroux, New York, 1998 ($17)

Seven major killers are discussed here in up-to-date, straightforward essays, about 30 pages for each, with four or five images of worthies, posters, cartoons and the like. The emphasis is historical and clinical: what happened, what still happens and what is done for it. Not much of the laboratory is here, little talk of viral strains or physiology; the scene is implicitly hospital, office or sickbed, a familiar level well suited to readers 12 years old and up.

"Leprosy," long misnamed and misunderstood, is a fascinating chapter. Hansen's disease—it was he who found the germ in the 1870s—is in fact the *least* contagious of all the scourges discussed in the book. It was false fear that has doomed leprosy sufferers: a Greek term for a blotchy skin disease was used to translate the Old Testament Hebrew term for "unholy." The patients had varied facial disfigurements, sometimes specific numbness in hands, feet, even eyelids, all very rarely fatal. On so slight a curse they were exiled and rejected for 2,000 years. The World Health Organization thinks it may effectively end the public health problem—that is, reduce the prevalence of leprosy to one person in 10,000 worldwide in a few years. The U.S. caseload is below that now, at about 7,000 cases.

Smallpox is extinct, barring biological warfare. Plague is carried in the U.S. mainly by prairie dogs; antibiotics and rat catchers may soon end it in cities. Cholera was all but ended by understanding that its fatalities were brought on by dehydration; copious drinks of water cure patients in a day or two (with a little salt and sugar to help it down). But malaria rages on; maybe a Chinese botanical drug of high promise will eventually succeed. And tuberculosis might be met with enough money, but the battle against HIV/AIDS is still at crisis.

Silent Thunder: In the Presence of Elephants
By Katy Payne. Maps by Laura Payne. Simon & Schuster, New York, 1998 ($25)

The living presence of elephants is both the root and the ripest fruit of this wonderful book for any good reader. The volume opens on an amazing insight. The author, an acoustic biologist preparing to shift from years of field study among whales, recognized the flutter she felt standing before a contented elephant group at a zoo. It was similar to what she first knew as a choirgirl, when the organist pulled the great stop to begin the second half of Bach's *St. Matthew Passion.* She could feel sounds from the elephants too deep to hear, just as she felt them three decades earlier in Sage Chapel at Cornell University.

It goes without saying that one who dwells among African elephants will encounter lions. Katy Payne recalls one striking night when she remained alone to record lion roars: "At sunset I threw down my bag" two or three yards within the link fence, recorder ready. That fence had a large hole patched with chicken wire. By the time she saw the patch, Yellow Mane, a lion, had arrived to sit down outside, pressed against the weakened wire. She knew to lie there still as death while the moon rose, as they both watched unblinkingly. Her eyes smarted; her arms were all pins and needles. The moon shone first on her face, then later on his, marking every detail, his eyes an exquisite brown and gold. Yellow Mane slowly drooled. But he never lifted a paw to that feeble fencing. After 12 hours, he stretched, yawned and walked a little ways off along the fence, there to kill a kudu.

A small, talented subculture of wildlife biologists is always present in these pages. Payne and others hold that killing for ivory can and must be ended but that ivory can still offer needed income to local people. Stop all elephant kills: no culling, no sports killing, no poachers. Instead organize and aid the communities to find, remove and sell the ivory tusks of naturally dead animals. Competition for land will remain.

First Woman and the Strawberry: A Cherokee Legend
Retold by Gloria Dominic. Illustrated in color by Charles Reasoner and with photographs. Troll Communications, Mahwah, N.J., 1998 (paperbound, $4.95)


CHARLES REASONER

Long ago First Man and First Woman of the Cherokees lived happily in the green forest, among colorful birds and fish-filled ponds. One spring day they disagreed about which path to take, and First Woman grew very angry. She went her own way. "What do I care?" First Man asked himself. Soon he saw it was a silly fight; he ran after her but could not catch up.

The Great Spirit intervened and first put out grapes, then wild cherries, then huckleberry bushes to tempt First Woman to slow down. She ignored them all. So he created a new berry, red, irresistibly delicious and growing close to the ground. It worked! After First Woman had stopped to eat her fill, she soon ran to seek First Man. "Are you still angry?" Great Spirit asked her. "No, the sweetness of these berries has reminded me of the sweetness of our love." When she found her husband, they shared the wonderful berry, anger forgotten. Since that time strawberries have always been there to remind them and their children of their mutual love.

The book offers a dozen more illustrated pages of actual Cherokee history, including the Cherokee syllabary published by Sequoyah in 1821. The courage of the Cherokee against enduring mistreatment, their present unity and high hopes suggest that maybe—against much evidence—it really was that wise people who first found strawberries!

Optical Tricks
Written and photographed in color by Walter Wick. Construction assistance by Dan Helt. Scholastic, New York, 1998 ($13.95)

Abracadabra! Secret Methods Magicians and Others Use to Deceive Their Audience
By Nathaniel Schiffman. Prometheus Books, Amherst, N.Y., 1997 ($27.95)

A dozen triumphs of optical deception fill Walter Wick's book of large-page color photographs, almost all of them showing puzzling scenes exquisitely built and lucidly explained. Few are novel in idea, but they are so well presented that they are compelling. Thoughtful kids eight and up will delight in them, just as will anyone who likes to think clearly about images. They include a forklike object, impossibly made with three tines and two tines all at once; surfaces with hollows as abundant as moon craters (or maybe they are bumps); and a cubical "box" that casts no shadows. Mirrors, shadows and cunning cabinetry act both to induce illusions and to reveal them. The details of that strange open framework of wood that looks as though it passes through itself are viewed here in a mirror placed *just right,* although the false fit is so elegant that even as you see it you can hardly accept what you know.

Abracadabra! is another unusually captivating book of the strange. A well-documented argument at book length, it is open to interested readers from their teens on up. Most books on magic are mainly broad historical accounts or detailed explanations of how to carry out some specific deception as entertainment. This is, instead, a wide-ranging analysis of the principles of illusion, and it is a hard book to lay down.

To sample minimally: the key words are two—misdirection and professionalism. Misdirection in space is familiar, waving a left hand while putting the right one into a pocket. Misdirection in time can be examined through a version of an escape illusion of Houdini's, often brilliantly done these days by a husband-wife team in Las Vegas. The man is tied into a bag and placed within a locked trunk. Much is made of lacing a large canvas around the trunk. The woman stands on the trunk holding a silk curtain. She lifts the curtain once before her face and form; it is lowered in seconds, but now only the man is there. He proceeds to unlace the trunk, open the bag and recover his magical wife. The exchange seems to have taken place in a blink of the eye as the silk fell. Not at all: the man's escape can begin as soon as the trunk is closed. He is soon out—if he ever was within. The second exchange really lasted a minute; its abruptness was an illusory emphasis, a powerful misdirection in time. The performer's guiding patter, the side view, the sounds, even the smell—any information channel can be used to mislead.

Yet how can anyone enter and leave those trunks and bags in a minute? Her entry was sudden, dropping down into the trunk via an unseen open trapdoor into the bag. The bag may have no bottom or one held by Velcro. Here the entire development of an illusionary technology is drawn on, a culture of ingenious professionals who design and make such devices and of the skills and theatricality of the performers. How can a spectator outwit them? That needs a viewer cleverer than they—by no means a likely assumption. A close-up video recording is a minimum of what is needed: one such study is narrated here.

The lesson of these two fine books runs deep. Studied illusion, old as the shamans, lies near physical science, for both analyze false perceptions, the older art to induce them, the newer to avoid them. Albert Einstein once explained what he saw in this difference: "The Lord God is subtle, but malicious he is not." Humankind cannot claim that same innocence, and illusion is a much more serious matter offstage than on.

BARNABAS KINDERSLEY

Celebrations! Festivals, Carnivals, and Feast Days from around the World
By Anabel Kindersley. Photographed in color by Barnabas Kindersley. In cooperation with UNICEF, DK Publishing, New York, 1997 ($17.95)

Anabel is a young teacher, Barnabas a photographer of children. They spent more than a year flying to 18 countries around the world, lugging camera gear that weighed the same as the two of them together. They certainly enjoyed it, along with the local kids who became their friends on festive days. Here we will meet only a few kids.

Twelve-year-old Janaina dances in pink-feathered boots and green sequins as Queen of the Drummers, at the Carnival in Rio de Janeiro for the oldest Samba School in the city; she rehearses every Monday for that one grand day. People eat pink popcorn and drink coconut milk as the huge flamboyant parade dances past to the music's beat.

In Sri Lanka the Buddhist processions go on for 10 nights in the old city of Kandy. There are 100 elephants in that parade, with dancers, acrobats, flame throwers and drummers. We see 15-year-old Nishantha, a tambourine dancer, beside a costumed elephant that wears a gold-dotted suit of red velvet. Celebrants feast on the tropical fruits that are in full season.

M'sangombe is a dancer at 10; he dresses for the part with a zebra-mane headdress, a leopard-skin costume, a cowhide shield and a long hardwood stick. A dozen villages send teams of young and old each year at harvest time to perform the fierce warrior dance before the Paramount Chief of the Ngoni people of Zambia. The women surround their favorites and sing their praises. Plenty of people enjoy the fresh corn on the cob.

There are two dozen more kids. Some as familiar as Halloween trick-or-treaters in western Canada, others as novel as young Dalia in Amman who has a first good breakfast—and a day of gifts to come—after the fast of Ramadan, when no food or drink is taken between sunrise and sunset for a month. Around the world we are very much alike—and different, too.

Tibaldo and the Hole in the Calendar
By Abner Shimony. Illustrated by Jonathan Shimony. Springer-Verlag, New York, 1998 ($21)

This delightful tale of a lucky boy is an introduction to the time and place that gave rise to modern science: the 16th-century city-states of Italy. The hero Tibaldo was born into a large and happy family in Bologna on October 10, 1570, a lively, good-hearted kid, bright, adventuresome, even a little quirky.

Tibaldo was going on 12 when the hole appeared in the calendar. Pope Gregory had grasped a few years earlier that the old Julian calendar of Rome adopted by the Church in the fourth century was now badly in error. It had used the leap year to manage the approximation of the year at 365.25 days on average, by skipping the correction in three out of four years and taking the full slippage all in one day. But the year is in fact longer than that by almost 12 minutes. That bothers no one, less than one day in a long lifetime. But in the 12 centuries since the early Church had adopted the rules for calculating the date of Easter by the position of the sun among the stars, the day count had run slow by 11 full days compared with the sun's way around its yearly circle. The spring equinox was early: Easter would in time be celebrated in midwinter cold, and no one wanted so full a break with the ancient harmony between spring and the Resurrection. The calendar change was proclaimed in late February 1582 by the learned Pope Gregory: the year 1582 would have the day following October 4 designated as October 15.

For Tibaldo, it meant his birthday would be missing that year, fallen into an unprecedented hole in the calendar! Surely Tibaldo knew this was but a change in name; no days were lost, only their names. But the people rioted more than once asking for a return of their 10 days, and Tibaldo, too, was obsessed by his sense of personal loss. He managed to be made one of the students who would display their Latin fluency to the pope on his forthcoming visit to Tibaldo's school and found the chance to describe his loss, adding wisely that many people would lose anniversaries and name days, and the saints' days, too, would go unremarked. Pope Gregory was moved and amused; he at once added a paragraph saying all festivals, personal or public, should be observed according to both the new and the old dates. Each of the 10 days would do double duty just this once; no one would lose, and many would gain from the double celebration. Tibaldo was a hero!

Verily, this book is a delicious, instructive fiction. The pope and the calendar change are quite real, however, although Pope Gregory did not revise his reform message. The pope had power over all Catholic lands, but other countries kept the Julian form for some time. Britain and its American colonies changed over in 1752, Russia only in 1919, when the hole had grown to 13 days. History is less reasonable and less sweet than ingenious physicist-philosopher Abner Shimony. His artist son (really) provided dozens of enlivening drawings done in sepia in a persuasive period style.

Hidden under the Ground: The World beneath Your Feet

Written and illustrated in color by Peter Kent. Dutton Children's Books, New York, 1998 ($16.99)

Across a dozen big double-spread pages Peter Kent has drawn sections of the underground world of life, chosen to span a wide range of what some animals and many peoples have done there—or at least imagined. These works are not like any home basement, but large and complex. He draws with an informal style; human figures are small, but details are savored, and some of the scenes are humorous.

Moles, badgers and rabbits dig impressive branching tunnel apartments for such small animals. The representation of medieval views of afterlife underground has plenty of pitchfork-wielding red devils but uses serious ideas of old artists to show us more imaginative and dreadful tormentors, one a lobster with a flame-throwing tail. There are mines, caves, a subterranean village, a royal tomb and a dungeon, too. You don't even want to see the rock-lined oubliettes, the prisoner bottled up alone underground, thrown bread and water daily down through the bottleneck, and otherwise forgotten.

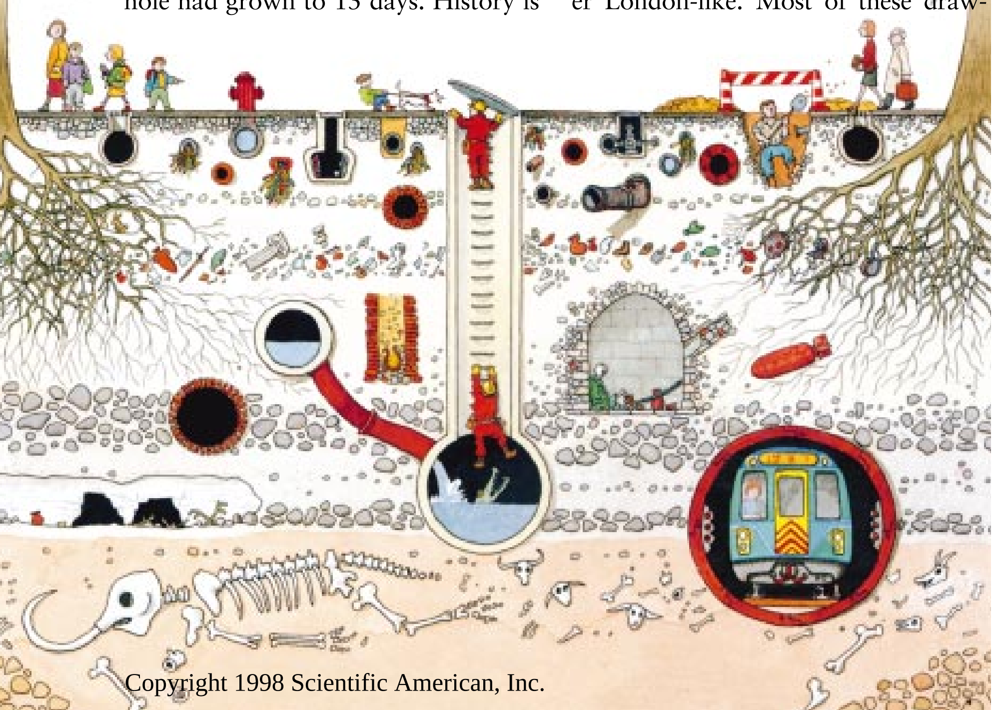
The subway station is lively and rather London-like. Most of these drawings, however, are not of specific places but are meant to reflect the typical. The city street underground is most interesting: it has water mains and sewers old and new, large and small, and a plethora of cables, tubes and pipes, with more on the way. Note the roots of big trees, spread almost as wide as their limbs extend aboveground. Deep-buried, unexploded bombs below streets are not rare where air war has raged, though unknown in the lucky U.S.A. On the other hand, a well-manned missile silo is on view, not a souvenir of an old war but a harbinger of attack that will not, we hope, come. A specific modern hydroelectric power plant is shown beside a Swiss lake. Extra pages offer digging tools, from wheelbarrows to tunnel borers, celebrities of the underground, and other extensions to complete an attractive book for mid-grade readers.

Slime Molds and Fungi

By Elaine Pascoe. Photographs in color by Dwight Kuhn. Blackbirch Press, Woodbridge, Conn., 1999 ($16.95)

It is hard to think of a more apt topic for a middle-grades book on nature seen close-up than this! The color photographs show a mold-stricken peach, fruiting bodies, spore prints of mushrooms, and lichens both dry and moist. This is a fair representation at modest magnification of a whole living kingdom to which too little attention is paid. Even yeasts are treated, more by their gas production from sugar water than by unfamiliar high-power microscopic images.

A general chapter on the distinctions between these life-forms and either animals or plants opens the 48-page book. The approach is hands-on: you are shown how to grow a dark-gray mold on white bread and green-gray penicillium on a lemon section. Emphasis is on keeping the mold cultures sealed and safely destroyed. A few more difficult tasks are set: growing slime molds on bark from the woods and looking for and watching them grow out there, too. A list of sources for fungal supplies opens the purchase of kits for growing edible mushrooms and slime molds and also names some books at a higher level. This book is a cheerful, handsome beginning; some boys or girls who enjoy these early steps are at risk of becoming microbiologists or biotechnicians.



PETER KENT


ASHLEY WOLFF

A String of Beads

By Margarette S. Reid. Color paintings by Ashley Wolff. Dutton Children's Books, New York, 1997 ($14.99)

We're beaders, Grandma and I," a little girl remarks happily on page one, followed by a spread whereon overflowing heaps and bowls of close to 200 distinct beads are carefully painted. That scene has been played, we expect, in all the languages of the species for 40,000 years and more. Beads are stringable disks and spheres and seeds and bugles and even carvings, big and little, from materials of all kinds—pasta, polymer clays, acorn caps, amber, quills, intricate millefiori. Beads are many, strings of them are many, many more; strings may break or decay, but beads are more or less everywhere, and all but forever. (Check with your local archaeologist.) Who wears them? Everyone. These 32 colorful pages open a path to mathematics and to human cultures for the read-to and for start-up readers. What better metaphor do we have for the integers, certainly discrete, but unlike the world's atoms, also widely diverse?

Calculus Made Easy

By Silvanus P. Thompson and Martin Gardner. Revised edition. St. Martin's Press, New York, 1998 ($17.95)

Equal-opportunity reviewers, we welcome a book on behalf of the continuum! It is for the mathematically eager who know some algebra. The first edition appeared anonymously in 1910 in England, and overall a million copies have been sold. In fact, most talk of continuum and its infinities is suppressed; the eye is nicely fixed on little bits of *x*, called *dx*, their differences and sums among all kinds of functions, their geometric meaning, and what they can do for you—a lot. Martin Gardner, himself an American mathematical landmark, says, "This is the leanest and liveliest introduction to calculus ever written," and, taken with his own present augmentation, three whole chapters and more, including infinite series and some neat problems, he is quite right.

The times they are a-changing, and we admit we are not current in computer resources. Maybe "little bits of *x*" ought to—or have been—placed on the screen in a serious pedagogic structure that students can manipulate. Graphics programs that share the scope and spirit of Thompson/Gardner would make a valued complement to their paper-and-pencil book.

Isaac Newton and the Scientific Revolution

By Gale E. Christianson. Oxford University Press, New York, 1996 (paperbound, $11.95)

Born early on Christmas morning of 1642, his illiterate father recently dead, Isaac Newton was raised by his grandmother. His life was fed by his vigorous mind and hands; the lonely boy read widely and filled his days with sky-watching, kites, sundials, carving and model making. He attended boarding school near his home, ranking second to last among 80 students, but he graduated at 18 the star of the school and went on to the University of Cambridge.

A new college graduate, his genius yet unrecognized, he returned home at age 22, after the university was closed by the coming of plague. For almost two years, he worked alone, establishing the modern methods and much of the matter of theoretical physics for two centuries: the ideas of the calculus, its application to motion for apple and moon alike, gravitation made semiquantitative and perhaps universal, and the nature of white light and color. The resemblance to the young Einstein at the Patent Office in Bern is evident; the human differences between Newton, without wife or nearby friends, and Einstein's happier world are manifest.

Less a scientific biography than a personal one, it does not try to popularize Newton's physics. Of course, it includes his entire career, his litigious rivalries, his work style, so secretive and shy, and his voluminous accomplishments, until a complex emotional breakdown took him away to official London at age 52. Newton died wealthy and celebrated, even rather less lonely through his niece, a famous beauty, and her slightly scandalous high-society circle.

Earthquake Games: Earthquakes and Volcanoes Explained by 32 Games and Experiments

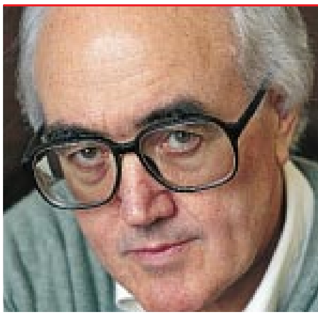
By Matthys Levy and Mario Salvatori. Illustrated by Christina C. Blatt. Simon & Schuster Children's Publishing, New York, 1997 ($16)

This rich, little book merits its long title, for it carries a brief and understandable text for readers in the upper primary grades, with a set of experiments, some gamelike, along with helpful drawings for each one, and a lively list of Qs and As. It began some time back when the children of P.S. 45 in the Bronx asked, "Mario, how do earthquakes work?"

The two authors tell how. They are partners, expert structural engineers whose words build an unusually good base for the varied experiments, not always easy but always fun. Their text begins with an account of the earth's drifting continents and urges a reader to use his or her hands to model the forces that, on a huge scale over a long time, raise mountain ranges, suddenly set the earth a-shake, or start awesome ocean-crossing rollers that dwarf any hurricane surge.

An early experiment uses a lightly boiled egg, whose shell is no bad image for the dozen big moving pieces of the earth's broken-crust tectonic plates. The ocean waves are modeled dramatically in the bathtub: simply with your hand or, more elaborately, using a few bricks and a piece of plywood. Add a few rice grains to a pot of boiling water to simulate the enormous slow currents of hot rock that power plate motions from below. These experiments are workable for one person, better still among a few young friends with some aid from teacher or parent.

Myths surrounding earthquakes are recounted from around the world, blame put on giant but unseen bulls, dragons, turtles, even catfish. Birds, fish, horses and other animals of ordinary size can perhaps sense a quake soon to come; that issue is not yet closed. SA



CONNECTIONS
by James Burke

Tea, Anyone?

The king's horticulturist thought nature needed a haircut.

The other day I was reading for this column while abstractedly stirring some sugar (too much, as it turned out) into my cuppa, thinking how the English tea-drinking thing is all a myth. It was the Dutch who really started the craze. In 1610 the first shipment of *chai* from China arrived in Amsterdam and turned Holland into a nation of addicts. Within a few years the eminent Dutch physician Cornelius Bontekoe was prescribing 200 cups a day for the general health. By 1650 the Dutch East India Company was importing tons of tea, reexporting it as far as New York, making a million and going back east for more. Tea (and the porcelain cups it went into) made Holland very rich. And paid for all those instrument makers working on things like barometers and telescopes (and such) that would make it easier for company navigators to find China every time, pick up the magic leaves, then head home. And find Amsterdam every time.

DUSAN PETRICIC

As usual, this was another case of the bottom line driving science and technology. Precision at sea required instruments that soon made possible precision in measurement of all kinds. Which is what (as I described in a recent column) drove German Daniel G. Fahrenheit to do what he did around 1713. And here I owe you an apology for a sin of omission in that previous column. What I left out of the account was that in 1708 Fahrenheit snitched the idea for which he is famous from the ex-mayor of Copenhagen. This guy, Ole Rømer, had come up with the idea of the thermometer scale way ahead of Fahrenheit. All the latter did was to fiddle with the numbers. Shortly thereafter, all Rømer's research notes were destroyed in a fire, and Fahrenheit was happily home free.

Still, Rømer had already made his name for other, more cosmic reasons. Earlier, in 1671, he had been picked up by a passing French astronomer, Jean Picard, who was on his way to identify the exact position of Tycho Brahe's astronomy center at Uraniborg (on the island of Hven, where he had taken certain crucial stellar fixes), so as to get some geodetic matter sorted out. Picard persuaded Rømer to move back to Paris with him to work in the posh new observatory there. Rømer's subsequent discovery of the differing times of the eclipses of Jupiter's moon Io convinced him that these related to the differing Earth-Jupiter distances, and he concluded from this that the speed of light was finite and not instantaneous as had been thought since Aristotle.

Picard himself was an astronomical biggie and general whiz, who did science things for Louis XIV. Louis, being a divine-right monarch and vested with power of thumbscrew, tended to get what he wanted. At this point (1674), what he wanted was water. Problem being the fountains and pools and water-powered amusements at his new palace of Versailles. Which weren't doing what they were supposed to because for some reason the water supply wouldn't supply. To Picard, who had recently worked out the degree of meridian to within a few feet, this little difficulty was a mere bagatelle, and in no time at all his telescope level helped to identify the discrepancy causing all the problems. The palace at Versailles was very slightly higher than the surrounding terrain. Adjustments to cisterns, reservoirs and channels were made, and water soon flowed freely.

Just as well, since the other little thing the king had in mind for Versailles was the biggest garden this side of Babylon. Visit the place. You'll see why Le Nôtre, the king's horticulturist, must have thought nature needed a haircut. His Disneyfication of a large bit of the French countryside took him and his 36,000 laborers more than 20 years, became the salon topic of choice for the chattering classes and made it fashionable for French aristos to get dirt under their fingernails. Among the new genteel grubbers was Henri Duhamel du Monceau, who set up one of the first arboretums on his estate at Chateau Denainvilliers and wrote about manure and muck and such. And because this led him to intimate knowledge of everything that happened between sapling and great oak, naturally enough Duhamel moved on to become inspector general of Marine. This was the time, remember, when it took 1,000 oaks to make a warship. As a result of which French forests were soon reserved for nothing but.

As a young sprig back in the 1720s, Duhamel had picked up this love of matters botanical during lectures he attended at the Jardin du Roi. There he also became great pals with one Bernard de Jussieu, who was running the garden's field trips at the time and winding up to yet another of the many and varied plant classification systems glutting the libraries. De Jussieu came from three generations of classifying botanists, the last of whom, Adrien-Henri-Laurent (son of Bernard's nephew), did his bit for the family with a piece rivetingly entitled "Vegetable Taxonomy." Adrien also set up a herbarium at the French Museum of Natural History, together with yet another scion of yet another noodler family, Adolphe-Théodore Brongniart.

Adolphe was a perfect example of what to do when every inch of your preferred research field is already crowded out with other workers. He dug deep and came up with something that would become virtually his own. Paleobotany (in Adolphe's case, the morphology of fossil plants) was a subject virtually untouched, except for some earlier research by a minor Scotsman whose publications were pretty thin on the ground. Not surprising, this. Around 1815 William Nicol (lecturer of natural philosophy at the University of Edinburgh) had used Canada balsam to cement pieces of fossil wood or minerals onto a glass plate and then ground the sample down to slices so fine you could see through them with a microscope and discover all kinds of good stuff—like bubbles in crystals, which told you something of the way the minerals had been formed, or the cell patterns that showed what kind of plant the sample had come from.

In 1828 Nicol stuck two bits of an Iceland spar crystal together and invented the Nicol prism. Iceland spar splits a beam of light into two polarized rays (a fact discovered, as it happens, by Ole Rømer's father-in-law, Erasmus Bartholin). If two Nicol prisms were used, when the second one was rotated, one of the polarized light rays coming through would dim and then cut off once it had rotated through 90 degrees.

Fascinating, but not everybody's cup of tea, right? Wrong. In the 1830s a Frenchman, Jean-Baptiste Biot, discovered that some liquids would twist the polarity of the ray and that the degree of twist would depend on the type and concentration of the material in solution. The twist in polarity was of course easily measured by a Nicol prism.

In 1845 a Parisian optician, Jean-Baptiste-François Soleil, perfected an instrument that would do all this and revolutionized life for the beverage drinker. Soleil's gizmo was known as a saccharimeter and could've told me in advance that the tea I was drinking at the start of this column would be too sweet. SA

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by Shawn Carlson

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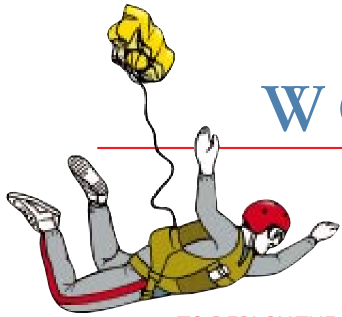
by Ian Stewart

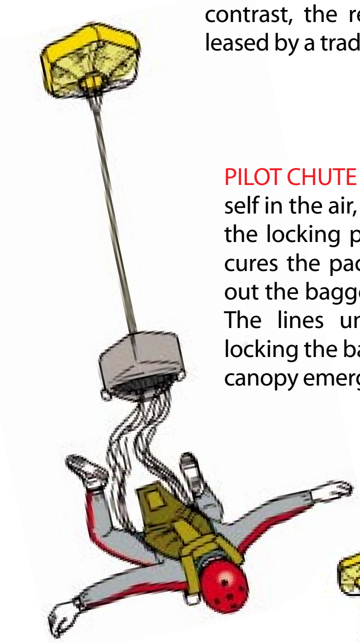
WORKING KNOWLEDGE

PARACHUTES

by Dan Poynter
Author of Parachuting: The Skydiver's Handbook



TO DEPLOY THE MAIN PARACHUTE, a skydiver typically pulls the small pilot chute from an outside pouch and throws it into the passing 110-mph wind. (In contrast, the reserve parachute is released by a traditional ripcord.)



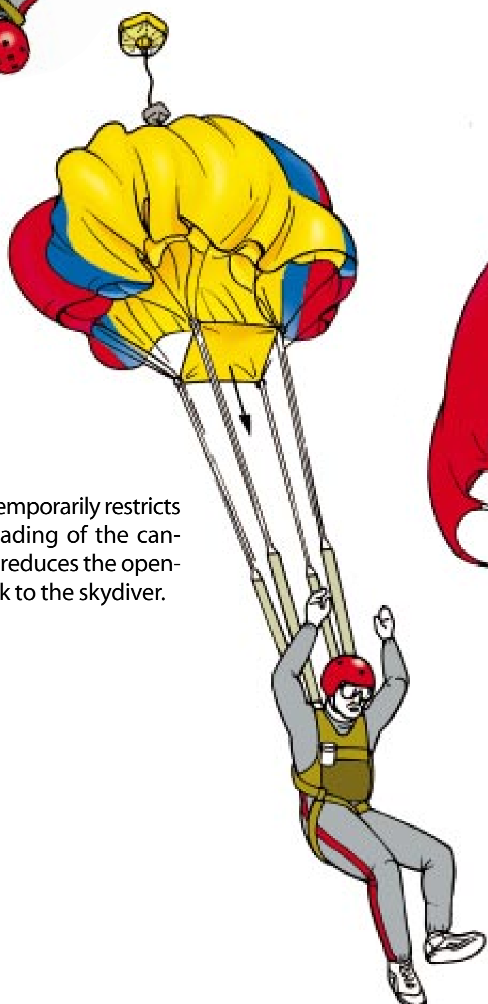
PILOT CHUTE anchors itself in the air, withdraws the locking pin that secures the pack and lifts out the bagged canopy. The lines unstow, unlocking the bag, and the canopy emerges.

Parachutes have changed over the past five centuries. The "round" (actually flat-circular) canopies of old depended on the air they captured (drag) to slow the descent of the suspended load or user. Today's skydivers use rectangular canopies with an airfoil shape that produce lift to further slow their descent. These new canopies fly forward at some 20 miles per hour and can be flared for tiptoe landings. Gone are the days when parachutists were at the mercy of the wind.

Over the years, sport parachutes have become smaller and lighter. Both weight and volume have been reduced through design changes, new materials and the elimination of some parts.

Canopy deployment must be orderly and sequenced so that the canopy will open quickly yet softly and reliably. The canopy has to be folded and stowed to accept the air properly, and the lines must be stowed in rubber bands so they will unstow bight by bight without tangling. This preparation helps to ensure predictable deployment of the canopy and makes the experience of jumping out of a plane exciting, fun and, most important, repeatable.

To find the skydiving school nearest you, call the U.S. Parachute Association at 703-836-3495.



SLIDER temporarily restricts the spreading of the canopy and reduces the opening shock to the skydiver.

STEERING LINES are used to guide the canopy and flare it for soft landings.

ILLUSTRATIONS BY GEORGE RETSECK