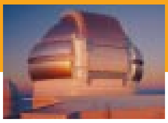


GEMINI: A NEW EYE OPENS ON THE HEAVENS

SCIENTIFIC AMERICAN

APRIL 1999 $4.95 www.sciam.com

GROWING NEW ORGANS

A SPECIAL REPORT ON TISSUE ENGINEERING

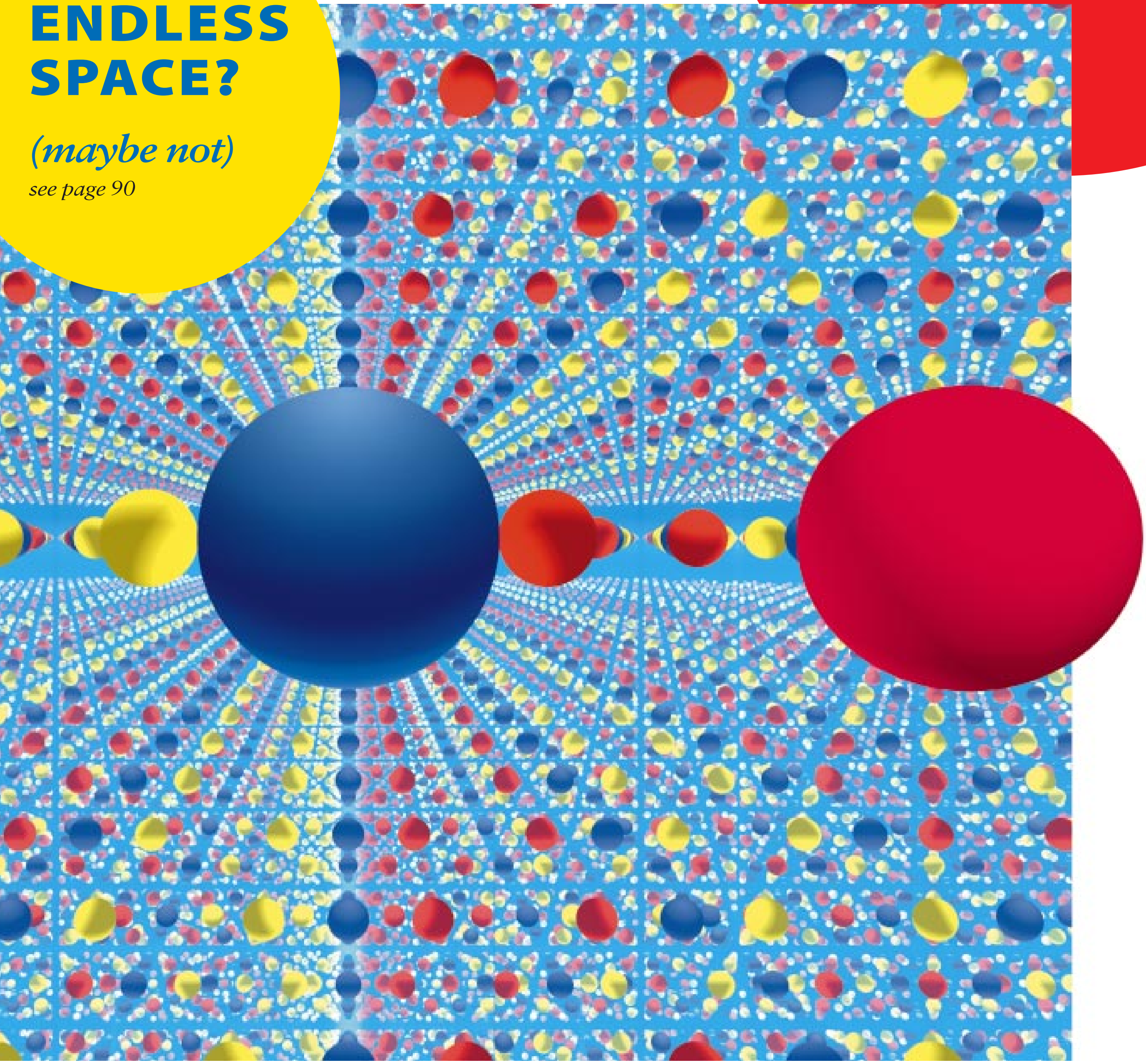
and

THE LOST BRAINSTORMS OF ALAN TURING

ENDLESS SPACE?

(maybe not)

see page 90



Mapping the Shape of Space

SCIENTIFIC AMERICAN

April 1999 Volume 280 Number 4

FROM THE EDITORS
8

LETTERS TO THE EDITORS
10

50, 100 AND 150 YEARS AGO
16

NEWS AND ANALYSIS

Colorless coral (page 30)

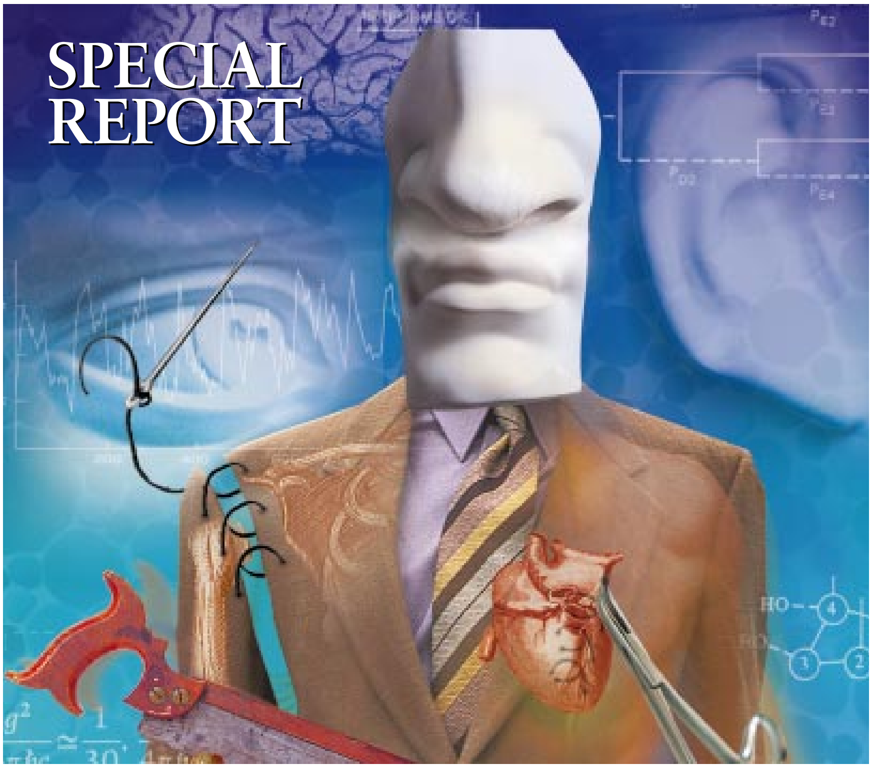
IN FOCUS
U.S. girds for the battle against bioweapons.
19

SCIENCE AND THE CITIZEN
Too many mutations.... Clocking an expanding universe.... The latest from Mars.
22

PROFILE
Mathematician John H. Conway, inventor of the game of Life.
40

TECHNOLOGY AND BUSINESS
A federal push does little for eco-friendly cars.... Electromagnetic machine gun.... The spy fly.
46

CYBER VIEW
The futility of on-line privacy.
55



THE PROMISE OF TISSUE ENGINEERING 59

"Bioartificial" pancreases, livers and kidneys. Freshly grown skin that can be bought by the yard. Honeycombs of collagen for breast reconstruction after mastectomy. Plastic-coated pellets of cells implanted in the spine to treat chronic pain. No, this isn't science fiction: it's tissue engineering, and as these pioneers in the field explain, it's already changing people's lives.

INCLUDES:

Growing New Organs 60
David J. Mooney and Antonios G. Mikos

Researchers have taken the first steps toward growing "neo-organs"—living, artificial human parts.

Embryonic Stem Cells for Medicine 68
Roger A. Pedersen

These remarkable human cells, only recently isolated, could help repair damaged tissues.

Encapsulated Cells as Therapy 76
Michael J. Lysaght and Patrick Aebischer

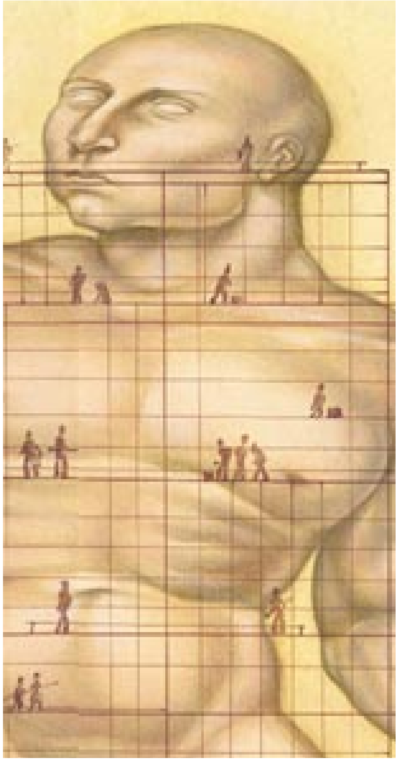
Many illnesses could be treated with cells packaged inside protective membranes.

Skin: The First Tissue-Engineered Products 83

Nancy Parenteau and *Gail Naughton* describe the manufacturers' technical and regulatory struggles.

Tissue Engineering: The Challenges Ahead 86
Robert S. Langer and Joseph P. Vacanti

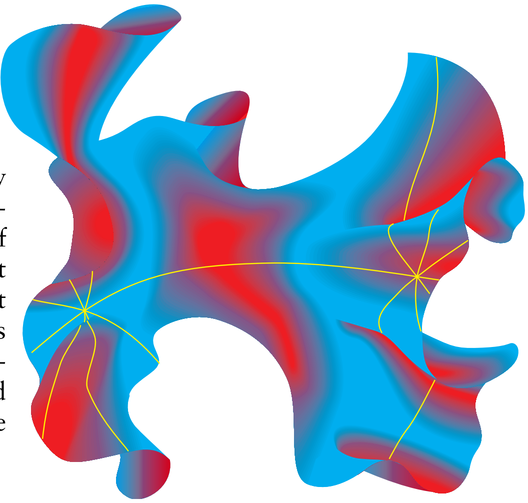
Ten obstacles to building organs from isolated cells.



90

Is Space Finite?

Jean-Pierre Luminet,
Glenn D. Starkman
and Jeffrey R. Weeks

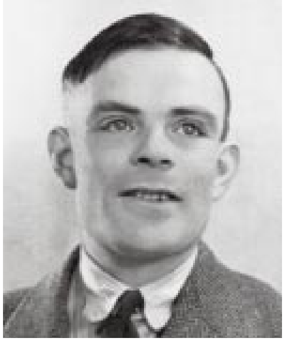


The universe may look infinitely large, but that could be an illusion. If space folds back on itself like the braids of a pretzel, it might be boundless, and light could spool around the cosmos endlessly. Astronomers are looking for patterns in the star field that could signal a finite volume for space.

98

Alan Turing's Forgotten Ideas in Computer Science

B. Jack Copeland and Diane Proudfoot



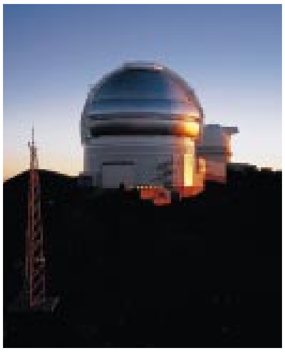
Neural networks and hypercomputation are hot ideas for transcending the limits of traditional algorithmic computing. What few realize, however, is that both concepts were anticipated in detail decades ago by Alan Turing, the British genius better remembered for laying the groundwork for artificial intelligence.

104

EXPEDITIONS

A New Eye Opens on the Cosmos

Gary Stix, staff writer

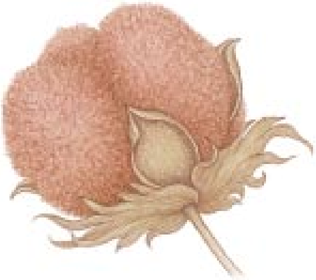


To build the mammoth Gemini North telescope, technicians had to manufacture a mirror and other optics to unimaginable tolerances, then gently haul the components up the side of a long-dormant Hawaiian volcano. An on-the-scene report about an astronomical marvel.

112

The Revival of Colored Cotton

James M. Vreeland, Jr.



Today's fashion craze for cotton fabrics made without artificial dyes owes a debt to the indigenous people of the Americas. For thousands of years, pre-Columbian Indians have been cultivating cotton plant stocks with fibers that are naturally green, red and other colors.

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THE AMATEUR SCIENTIST

A cloud detector for backyard astronomers.

120

MATHEMATICAL RECREATIONS

Why telephone cords get twisted.

123

REVIEWS AND COMMENTARIES

Physicist Brian Greene explains *The Elegant Universe.*

125

The Editors Recommend

The first spage age and more.

127

Wonders, *by the Morrisons*

Quick trips around the world.

129

Connections, *by James Burke*

Phrenologists and Lunatics.

130

WORKING KNOWLEDGE

The flight of the Frisbee.

132

About the Cover

Three objects in a mirrored box create an illusion of infinite depth. Yet patterns in the repeating images reveal the container's size and shape. Image by Bryan Christie.

THE SCIENTIFIC AMERICAN WEB SITE

Learn the cost of invasions by alien species:

GARY MESLAROS *Bruce Coleman, Inc.*

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Then browse this month's other features linked to science resources on the World Wide Web.
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FROM THE EDITORS

Attack of the Robo-Editor

Where would we be without technology? Waiting for buses that would never arrive, I imagine, but that's not the point. One year ago I wrote about the devices used in the editing of *Scientific American*. Not the computers and copiers and fax machines, which every office has. No, I discussed the peculiar tools of our trade: the Dejargonizing Passive Phrase Reallocator, the Implicit Inflection Remodulator. Little did I dream that someone out there would be inspired to create more advanced electronic tools aimed at—shudder—replacing editors altogether.

Oh, it hasn't happened yet, but that's clearly where things are going. The Educational Testing Service (ETS) has announced that to help with the grading of essays on the GMAT, it will employ an automated essay assessor. The E-Rater looks for linguistic cues that signify rich, well-ordered thinking. For example, it checks for phrases like, well, "for example." It also looks for words and phrases such as "consequently," "therefore," and "moreover," which denote logical connections between sentences and clauses.

Critics of the E-Rater howl that logical formalities of language do not necessarily reflect logical thinking. The system's defenders, on the other hand, maintain that it can help human graders plow through the volume of test essays more efficiently. (I think the E-Rater would have approved of my "on the other hand" there.)

That's right, the Spurious Analogy Delineator.

Nice try, ETS, but the E-Rater can't yet match the more sophisticated creations of the Scientific American Editorial Laboratories, based at the North Pole in our top-secret Fortress of Irritability. Just recently, we installed a slew of new gadgets highly pertinent to science editing, including:

The Spurious Analogy Delineator: It deletes comparisons that interpret complex phenomena in terms of other equally complex, unrelated phenomena. "To understand how a cyclotron works, imagine that every subatomic particle in your body is an ant carrying a stick of dynamite and running the Kentucky Derby at the speed of light."

The Ad Hominem-omulator: Most useful when editing biographical profiles, this unit flags weak attempts to identify a researcher's personal characteristics with his professional interests. "Having devoted 35 years of his career to hedgehogs, Professor Bledsote has become more than a little like them himself, with his warm-blooded metabolism and bristly determination to breathe oxygen."

The Grant Extension Appendicizer: It warns of paragraphs that justify requests for more money with poor data. "Thus far we have found no trace of the lost continent of Lemuria. Only further archaeological expeditions to Tahiti can determine whether that ancient and perhaps mythical civilization ever invented the toaster."

Trust us, when writing is down to a science, we'll know about it.

John Rennie

JOHN RENNIE, *Editor in Chief*
editors@sciam.com

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LETTERS TO THE EDITORS

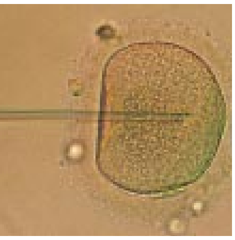
We know that many of our readers like to tinker. You might be the type to run chemistry experiments in the basement or perhaps build a seismograph in the garage. To encourage such pursuits, we offer the monthly column "The Amateur Scientist," by Shawn Carlson. So we were distressed by a letter from James W. Adams of Charlottesville, Va., sent in response to the December 1998 column, "Sorting Molecules with Electricity." Commenting that he found the article too elementary for his taste, Adams wrote that "a serious article on amateur electrophoresis would be in the same realm as some of the more ambitious projects written over 30 years ago, which entailed a fair degree of difficulty as well as a degree of electrical hazard that would require serious precautions." Adams suggested one factor influencing why this shift has occurred, and not just at SCIENTIFIC AMERICAN: "Litigation, overzealous regulations and paranoia over drugs, crime and terrorism have all but eliminated most branches of science for the modern amateur beyond computer simulations." We'll keep trying to balance safety, degree of difficulty and appeal in "The Amateur Scientist." And please keep sending us your opinions about all our articles.

FERTILITY FOR EVERYONE?

In "Cloning for Medicine" [December 1998], Ian Wilmut argues that cloning is not necessary to treat infertility, because "other methods are available for the treatment of all types of infertility." As a director of a support and advocacy group for infertility patients, I must point out that Wilmut is wrong. About 15 percent of humans are infertile, and most cannot be helped to have children who are biologically their own by any current medical technique. Cloning technology, once it is reasonably safe, will offer a new and legitimate way for infertile people to have their own genetic children. Our organization, RESOLVE of Northern California, supports research to make human cloning safe and effective, and we oppose government efforts to deny infertility patients the right to choose human cloning as a method—in many cases, the only method—of having children.

Reproductive freedom means much more than just the right to an abortion. Whether and how John and Mary Smith have a child is a private decision for them alone, not a political decision to be made by politicians or bureaucrats based on public opinion polls.

MARK D. EIBERT
Member, Board of Directors
RESOLVE of Northern California
Half Moon Bay, Calif.



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FERTILITY TREATMENTS ***available today, such as intracytoplasmic sperm injection, do not help everyone.***

TOO MUCH COVERAGE

On the cover of the December issue, a red banner at the top shouted out "Beating Prostate Cancer." A bit of an exaggeration, I thought. Was it just to hook a few more readers? Those who don't read the article inside—with the more conservative and realistic title "Combating Prostate Cancer"—will walk by thinking, "Ah, yes! Another cancer beaten by modern science. Great—I don't have to get involved." Of course, we are not "beating prostate cancer." If anything, we are just holding the beast at bay, and there are casualties.

SAM BATES
via e-mail

Editors' note:

It certainly wasn't our intention to mislead readers with our cover headline, and we regret if anyone interpreted it to mean the cancer had been cured. Rather we chose the wording because the article describes how improvements in diagnosis and treatment can help many more patients survive with a higher quality of life.

ALVAREZ AND THE ATOMIC BOMB

In their otherwise admirable memoir "Physicists in Wartime Japan" [December], Laurie M. Brown and Yoichiro Nambu misstate physicist Luis W. Alvarez's role in the atomic bombings. Alvarez flew in one of two backup B-29s that accompanied the *Enola Gay* on the Hiroshima mission, not the Nagasaki one, as the authors wrote. It is true, however, that on the Nagasaki mission, Alvarez, Philip Morrison and Robert Serber wrapped a letter to Japanese physicist Riokichi Sagane around the blast gauge deployed to measure the bomb's intensity (although it's unlikely they sent "photocopies"—carbon copies, probably).

Returning from Hiroshima, Alvarez wrote a letter to his four-year-old son, Walter. "What regrets I have about being a party to killing and maiming thousands of Japanese civilians this morning," he told his son presciently, "are tempered with the hope that this terrible weapon we have created may bring the countries of the world together and prevent further wars." So far, at least as far as world-scale war is concerned, Alvarez's hope seems to have been realized.

RICHARD RHODES
Madison, Conn.
author of *The Making of the Atomic Bomb* (1986)

ISLAMIC INHERITANCE

I enjoyed Madhusree Mukerjee's "The Population Slide" [News and Analysis, December], on the success of family planning in Bangladesh. But I found a factual error in her otherwise well-written report: the assertion that "under Islamic law, [a wife] gets no inheritance from her husband unless she has borne him a male child. . . . " I am certain there is no such law in Islam. Because I am from Bangladesh and I am a Muslim familiar with Bengali Muslim customs, I can assure you it is not a societal custom to deny women inheritance because of lack of a male child. Women are, however, denied inheritance for many flimsy excuses, which have more to do with societal greed than religious injunction.

MOHAMMAD G. SAKLAYEN
Wright State University

COMPUTERS IN CHINA

"Hello, Is This the Web?" by W. Wayt Gibbs [News and Analysis, "Cyber View," December], shows a certain, let's say, occidental bias. Certainly most of the speech-recognition software products on the market now, and in the near future, are merely expensive curiosities for Western Hemisphere computer users. Most of these languages have phonetic alphabets that are easy to type on current keyboards. In China, however, speech recognition may be the technology that decides which computer and software manufacturers dominate. There are more than 5,000 symbols commonly used in ordinary writing in Chinese. Typing out these symbols on a keyboard is a difficult skill to master, especially for the vast majority of Chinese citizens who are unfamiliar with modern computing technology. Even a limited ability to produce Chinese characters directly from speech will greatly accelerate the penetration of computers into the Chinese market. We may see that speech dictation is meant not for the wealthy corporate executive but for the struggling peasant.

CHRIS A. SMITH
Seoul, South Korea

Letters to the editors should be sent by e-mail to editors@sciam.com or by post to Scientific American, 415 Madison Ave., New York, NY 10017. Letters may be edited for length and clarity. Because of the considerable volume of mail received, we cannot answer all correspondence.

ERRATA

In "Cloning for Medicine" [December], the illustration on pages 60 and 61 incorrectly shows donor cells being injected into an egg. Wilmut's method fuses the donor and egg without injection.

"Proton Armageddon" [News and Analysis, "In Brief," January] contains an error. The lower limit for the lifetime of a proton is described as being 100 billion trillion years longer than the age of the universe. In fact, the lifetime of a proton is at least 100 billion trillion *times* longer than the age of the universe. We apologize for the confusion.

SCIENTIFIC AMERICAN

NEW YORK
Thomas Potratz
ADVERTISING DIRECTOR
212-451-8561
tpotratz@sciam.com

Timothy W. Whiting
SALES DEVELOPMENT MANAGER
212-451-8228
twhiting@sciam.com

Kevin Gentzel
212-451-8820
kgentzel@sciam.com

Randy James
212-451-8528
rjames@sciam.com

Stuart M. Keating
212-451-8525
skeating@sciam.com

Wanda R. Knox
212-451-8530
wknox@sciam.com

DETROIT
Edward A. Bartley
MIDWEST MANAGER
248-353-4411 fax 248-353-4360
ebartley@sciam.com

CHICAGO
Randy James
CHICAGO REGIONAL MANAGER
312-236-1090 fax 312-236-0893
rjames@sciam.com

LOS ANGELES
Lisa K. Carden
WEST COAST MANAGER
310-477-9299 fax 310-477-9179
lcarden@sciam.com

SAN FRANCISCO
Debra Silver
SAN FRANCISCO MANAGER
415-403-9030 fax 415-403-9033
dsilver@sciam.com

DALLAS
THE GRIFFITH GROUP
972-931-9001 fax 972-931-9074
lowcpm@onramp.net

CANADA
FENN COMPANY, INC.
905-833-6200 fax 905-833-2116
dfenn@canadads.com

EUROPE
Roy Edwards
INTERNATIONAL ADVERTISING DIRECTOR
Thavies Inn House, 3/4, Holborn Circus
London EC1N 2HB, England
+44 171 842-4343 fax +44 171 583-6221
redwards@sciam.com

BENELUX
RÉGINALD HOE EUROPA S.A.
+32-2/735-2150 fax +32-2/735-7310

MIDDLE EAST
PETER SMITH MEDIA & MARKETING
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JAPAN
NIKKEI INTERNATIONAL LTD.
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KOREA
BISCOM, INC.
+822 739-7840 fax +822 732-3662

HONG KONG
HUTTON MEDIA LIMITED
+852 2528 9135 fax +852 2528 9281

MARKETING
Laura Salant *MARKETING DIRECTOR*
212-451-8590
lsalant@sciam.com

Diane Schube *PROMOTION MANAGER*
212-451-8592
dschube@sciam.com

Susan Spirakis *RESEARCH MANAGER*
212-451-8529
sspirakis@sciam.com

Nancy Mongelli *PROMOTION DESIGN MANAGER*
212-451-8532
nmongelli@sciam.com

NEW YORK ADVERTISING OFFICES
415 MADISON AVENUE, NEW YORK, NY 10017
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SUBSCRIPTION INQUIRIES
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Spektrum der Wissenschaft
Verlagsgesellschaft mbH
Vangerowstrasse 20
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tel: +49-6221-50460
redaktion@spektrum.com

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Éditions Belin
8, rue Férou
75006 Paris, FRANCE
tel: +33-1-55-42-84-00

Le Scienze
Piazza della Repubblica, 8
20121 Milano, ITALY
tel: +39-2-29001753
redazione@lescienze.it

Investigacion y Ciencia
Prensa Científica, S.A.
Muntaner, 339 pral. 1.ª
08021 Barcelona, SPAIN
tel: +34-93-4143344
precisa@abaforum.es

Majallat Al-Oloom
Kuwait Foundation for
the Advancement of Sciences
P.O. Box 20856
Safat 13069, KUWAIT
tel: +965-2428186

Swiat Nauki
Proszynski i Ska S.A.
ul. Garazowa 7
02-651 Warszawa, POLAND
tel: +48-022-607-76-40
swiatnauki@proszynski.com.pl

Nikkei Science, Inc.
1-9-5 Otemachi, Chiyoda-ku
Tokyo 100-8066, JAPAN
tel: +813-5255-2821

Svit Nauky
Lviv State Medical University
69 Pekarska Street
290010, Lviv, UKRAINE
tel: +380-322-755856
zavadka@meduniv.lviv.ua

Ke Xue
Institute of Scientific and
Technical Information of China
P.O. Box 2104
Chongqing, Sichuan
PEOPLE'S REPUBLIC OF CHINA
tel: +86-236-3863170

50, 100 AND 150 YEARS AGO

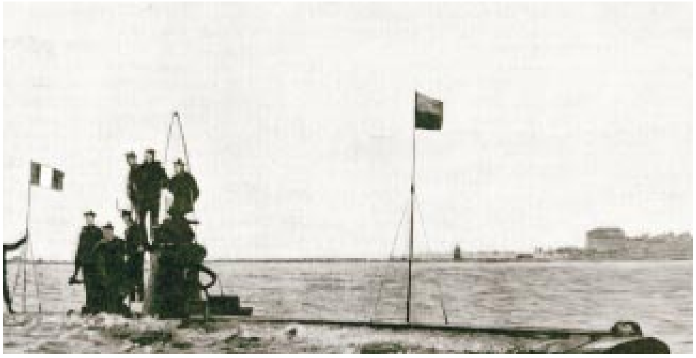
APRIL 1949

BEFORE PLATE TECTONICS—“Large undersea canyons exist off the shores of every major continent, but nothing in traditional geological knowledge explains clearly how they could have formed. The most obvious suggestion is that they were cut by streams when the oceanic slopes were above water. Could the glaciers of the Ice Age have been big enough to reduce the oceans to such an extent by piling up water on the land to the height of many miles? Most geologists doubt it. Alternatively, the continents and ocean basins might have undergone vast shifting movements that exposed the margins to river erosion. The implications of these ideas may lead to radical changes in supposedly well-established geological concepts.”

WAR ON MALARIA—“A major offensive against malaria is to be launched by the World Health Organization, International Children’s Emergency Fund, and the Food and Agriculture Organization. DDT has now made it possible to control the disease. WHO teams have been in Greece for a year, battling malaria with DDT and synthetic antimalarials. Demonstration units have just arrived in Indo-China and Siam. Similar teams will be sent to Burma, Ceylon, India, Indonesia, Malaya, Pakistan and Yugoslavia. In southern Greece, three years of DDT treatment to eradicate malaria-bearing mosquitoes have reduced the malaria incidence from one million to 50,000 a year at an annual cost of 30 cents per person.”

APRIL 1899

EARLY SUBMARINE—“The widespread interest which has been aroused by the performances of the submarine torpedo boat *Gustave Zédé* is out of all proportion to the actual fighting value of this type of vessel. There is evidently something which takes the popular fancy in the idea of a fighting ship that can move unseen in the depths of the ocean, and strike a fatal blow unsuspected by the enemy. However, Vice-Admiral Dupont, an old and experienced naval officer, has warned that the public should understand that, in a naval war, submarine boats have no other mission than rendering it dangerous for the enemy to blockade a friendly port. Our illustration shows a longitudinal section and a view of the vessel near Toulon after the addition of a conning tower.”



The new submarine torpedo boat Gustave Zédé

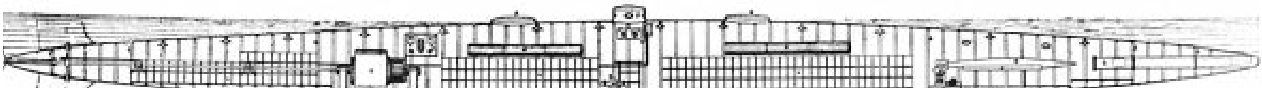
THE CANCER MICROBE—“The Paris *Figaro* has announced that Dr. Bra has found the microbe of cancer, and that there is reason to hope that the discovery may soon lead to a certain cure of that dread disease. Dr. Bra is modest and cautious in his statement, saying that it must be months before a definite announcement is possible. What he has succeeded in doing, however, is to isolate and cultivate a parasite from cancerous tumors and to produce therefrom cancer in animals. The parasite is fungus-like and is certainly the specific agent of cancer. Dr. Bra has spent four years researching the origin of cancer.”

MARCONI—“My company has been anxious for some time to establish wireless communication between England and France across the Channel in order that our French neighbors might have an opportunity of testing for themselves the practicability of the system, but the promised official consent of the French government has only just been received. The positions for the stations chosen were at Folkestone and Boulogne, the distance between them being 32 miles. —G. Marconi”

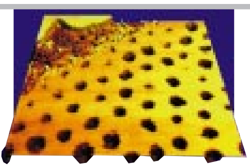
APRIL 1849

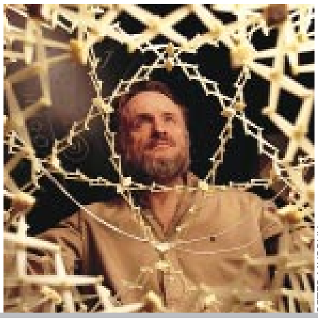
FASTEST WORLDWIDE COMMERCE — “The ship *Sea Witch,* with Captain Robert Waterman, which arrived at this port [New York] last week from Canton, in the unusually short space of 74 days and 14 hours, has, it appears, made a series of passages on her course out and home again, surpassing in quickness any previously made by a sailing vessel. These passages make a voyage ’round the world, which he effected in 194 sailing days.”

RUINED MINDS—“From the Mount Hope Institute on the Insane, Dr. W. H. Stokes says, in respect to moral insanity: ‘Another fertile source of this species of derangement appears to be an undue indulgence in the perusal of the numerous works of fiction, with which the press is so prolific of late years, and which are sown widely over the land, with the effect of vitiating the taste and corrupting the morals of the young. Parents cannot too cautiously guard their young daughters against this pernicious practice.’ ”

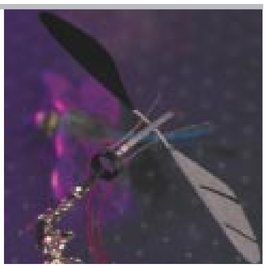


NEWS AND ANALYSIS





PETER MURPHY



IN FOCUS

FACING AN ILL WIND

The U.S. gears up to deal with biological terrorism

MICHAEL CONROY *AP Photo*

DECONTAMINATION PROCEDURES* *were followed by emergency workers after an anthrax scare in Indianapolis.

The specter of mass civilian casualties resulting from an attack with biological weapons has long been a worst-case scenario mulled over by defense planners. But in recent years the threat has moved to the front of the U.S. policy agenda, driven by a series of unwelcome revelations. Soviet émigré Ken Alibek, former deputy head of the secret laboratory known as Biopreparat, has recounted how the former Soviet Union manufactured tens of tons of "weaponized" smallpox virus, which is highly contagious and would likely spread rapidly in the now largely unimmunized U.S. population. The Soviets also produced weapons based on pneumonic plague and anthrax, Alibek has charged, and they experimented with aerosolized Ebola and Marburg viruses, which cause massive hemorrhaging.

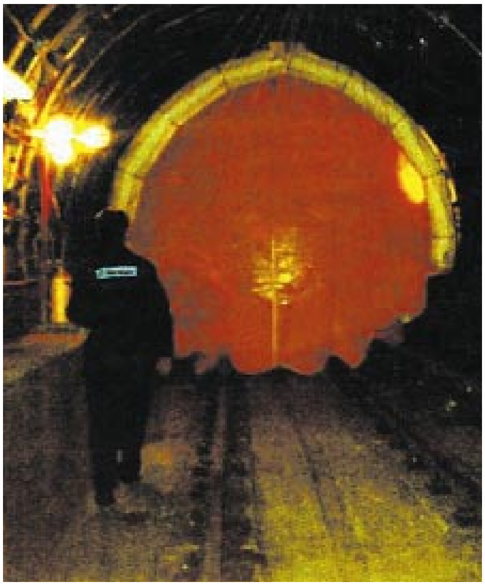
Disclosures about sophisticated anthrax-based biological weapons developed by Iraq have also contributed to growing apprehension, as did the discovery that the Aum Shinrikyo cult in Japan released anthrax spores and botulinum in Tokyo nine times before it carried out its deadly 1995 subway attack with the nerve gas Sarin. The Aum's attempted germ attacks failed because the group's biologists cultured the strain of anthrax used to make vaccine, which is harmless; had they used a potent culture, the outcome might have been very different. (No one knows why the botulism attack failed.)

The Aum's lack of success in making biological weapons suggests that making a lethal device is difficult. Some specialists, such as Alan P. Zelicoff of Sandia National Laboratories, maintain that developing a system to spread anthrax or other agents so as to achieve mass fatalities is a serious challenge in its own right. Zelicoff has done experiments with simulated weapons and was unable to achieve good dispersal.

Others are less confident. Donald A. Henderson of Johns Hopkins University, who spearheaded the World Health Organization's successful campaign to eradicate smallpox, counters that widely known advances in fermentation and dispersion technology make it easier than ever for a malefactor to grow substantial quantities of some deadly agents and use them. Unlike nuclear or chemical weapons, biological weapons can be made with readily available materials or equipment. Many deadly agents, including plague and anthrax, can be found in nature. (Only two declared locations in the world hold the smallpox virus, but Henderson says he is "persuaded" that smallpox is being worked on at undeclared laboratories in Russia and possibly elsewhere.) Henderson believes 10 to 12 countries are now researching biological weapons. Moreover, thanks to domestic economic woes, Russian microbiologists are often targets for recruitment by foreign powers.

Advances in molecular biology could make engineering a superpathogen more feasible, according to Steven M. Block of Princeton University, the only molecular biologist on the panel of defense advisers known as the Jasons. Block says smallpox or anthrax engineered for extra lethality is "very credible indeed."

Most agents produce flulike symptoms in the early stages of infection, so the first victims would most likely be sent home with a diagnosis of a nonspecific viral syndrome. Only when authorities noticed unusual deaths would the alarm be raised. At that point, public demand for prophylactic medications would quickly become intense. Yet at present there are only some seven million doses of smallpox vaccine in the U.S., and scaling up production would take at least 36 months, according to Henderson. He estimates that an attack with aerosolized smallpox virus that initially infected just 100 people would within a few weeks paralyze a large part of the country: by the time the first cases had been diagnosed, people would have carried the infection to other cities.


COURTESY OF MELBA BAYNE

TUNNEL-BLOCKING BALLOON
is being evaluated to counter a subway attack.

Dozens of different agents might conceivably be employed as a weapon. Indeed, the only successful biological attack in the U.S., which was not recognized as such at the time, was with salmonella. Followers of Bhagwan Shree Rajneesh put the bacteria in salad bars in restaurants in The Dalles, Ore., in 1984, sickening several hundred people. But Henderson says anthrax, smallpox and plague represent by far the greatest threats.

The administration has proposed steep budget increases to counter biological threats against civilians. Surveillance for odd outbreaks of disease is being stepped up by 22 percent, to $86 million, regional laboratories are being established, and funds are being sought for 25 new emergency metropolitan medical teams. Research on vaccines is being boosted by $30 million, and specialized medicines are being stockpiled. The Department of Energy is working on new and better sensors and is studying airflow patterns in cities and around subways.

One focus is an attempt to prevent the spread of deadly agents with water curtains and giant balloons that would block off tunnels. Sandia scientists have also developed a noncorrosive foam that neutralizes chemical agents and effectively kills spores of a bacterium similar to anthrax. Some of the most far-out research is being funded by rapidly growing programs at the Defense Advanced Research Projects Agency (DARPA), which is researching sensitive detection devices and countermeasures that would work against a wide spectrum of agents. Many pathogens employ similar molecular mechanisms in the early stages of infection, notes Shaun B. Jones, head of DARPA's Unconventional Pathogen Countermeasures program. Many, too, share similar mechanisms of damage. Those insights make a search for broad-spectrum agents worthwhile, Jones maintains. One promising molecule for suppressing inflammation is now being tested.

DARPA is also funding projects in which red blood cells are modified. Mark Bitensky of Boston University and Ronald Taylor of the University of Virginia have shown that enzymatic complexes and antibodies can be added to the surfaces of red blood cells that give them the ability to bind pathogens. The antibodies carry the pathogens to the liver to be destroyed, and, remarkably, the lifetime of the red blood cells in the body is not affected. Maxygen in Santa Clara, Calif., is using a technique called DNA shuffling, which randomly combines potentially useful gene fragments to evolve potential DNA vaccines. James R. Baker, Jr., of the University of Michigan is developing liposomes and dendritic polymers that are safe to apply to the skin yet dissolve pathogens.

Some critics, however, maintain that high-tech may not be the best answer. The government has approached biological weapons "from the standpoint of vulnerability assessment, not threat assessment," says Jonathan B. Tucker of the Monterey Institute of International Studies. What is needed, he believes, is "a much better understanding of what might motivate a group to use these weapons" so that terrorists can be stopped before they strike. Block of Princeton likewise emphasizes the great importance of human intelligence. Civil libertarians, however, worry about giving the military any permanent counterterrorist role in the homeland.

If covert operations face difficulties, perhaps overt ones would be easier. Leonard A. Cole of Rutgers University at Newark asserts that simple moral suasion could deter many political terrorists from following the biological route, because such weapons would alienate them from their constituencies. And Barbara Hatch Rosenberg of the Federation of American Scientists argues that the U.S. could participate more constructively in the negotiations under way in Geneva aimed at strengthening the 1972 Biological and Toxin Weapons Convention. Senior officials "say the right things" about the convention, Rosenberg indicates. But she charges that the U.S. has repeatedly objected to a proposed inspection regime that would give it teeth, on the grounds that surprise visits by international inspectors might imperil commercial secrets—or compromise national security.

Some feel, moreover, that scientists themselves could do more to oppose biological terrorism. Just as physicists became active in the movement to prevent nuclear war in the past century, Block notes, "I would hope and expect biological scientists will take a leading role in anti–biological weapons activity."

—Tim Beardsley in Washington, D.C.

ASTRONOMY

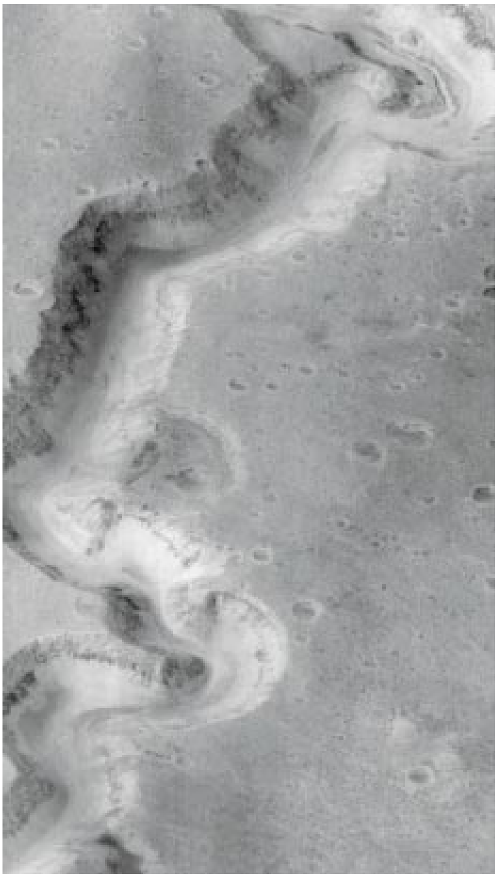
A PROBING PRELUDE

Global Surveyor bolsters the theory that water persisted on Mars

Thanks to a crack in a yoke supporting one of its two solar panels, the Mars Global Surveyor settled into its intended orbit only a month ago, after a year and a half of trajectory adjustments. But as controllers slowly maneuvered the spacecraft to prevent further damage, researchers operating the craft's extensive suite of instruments used the delay to come up with an impressive résumé of discoveries about the status and history of water on Mars.

In February, for example, researchers described an image made by the orbiter's camera, which can resolve objects as small as about five meters, or 16 feet (the best resolution of any previous mission was 35 meters). The image showed a deeply cut, sinuous channel in Mars's Nanedi Vallis. Many scientists consider the finding the strongest single piece of evidence to date that water existed on the planet's surface for prolonged periods.

Of course, researchers have long known that liquid water once sculpted Mars's surface. But they debated whether that water came from stable, long-lasting sources on the planet or from permafrost that was occasionally but only temporarily converted to liquid water—and even massive flash floods—by catastrophic events such as lava flows and meteorite strikes. The distinction is important because most scientists believe that stable liquid water is necessary for life as we know it.



MALIN SPACE SCIENCE SYSTEMS/NASA

SINUOUS CHANNEL in Mars's Nanedi Vallis is considered to be strong evidence of sustained water flow.

The image of the deeply cut channel seems to support the stable-water theory, because it appears extremely unlikely that erosion could have quickly carved the waterway. "It's a spectacular picture," says Michael H. Carr, a geologist with the U.S. Geological Survey and co-author of a paper describing the Nanedi Vallis finding and other water-related discoveries. "Upstream of this area in the image there had to be a source of water, and this source had to be sustained to incise the channel deep into these volcanic plains."

Scientists were also interpreting data from the orbiter's thermal emission spectrometer as evidence of long-lasting water on Mars. Philip R. Christensen, a geologist at Arizona State University, disclosed that it had located a vast deposit of coarse-grained hematite, an iron-bearing mineral. The oblong-shaped lode, which measures about 500 kilometers long and 300 kilometers wide, is close to the equator. "On Earth, at least, most of the iron we get from mines comes from hematite deposits that precipitated out of oceans," Christensen explains. Nevertheless, he speculates that the Martian hematite was actually created through hydrothermal activity—the other major formation mechanism for the mineral on Earth—and was transported a short distance to its present location, where it was deposited in layers. In any event, "what has us so excited is that any good model for how hematite forms involves water," Christensen says.

Global Surveyor's laser altimeter contributed an important finding about the planet's northern polar ice cap. Scientists had long assumed that this cap held a significant amount of Mars's water. But the altimeter showed that it in fact contains no more than about 1.2 million cubic kilometers of ice—which, if melted, would cover the planet to a depth of only nine to 12 meters. Scientists had previously estimated from surface features that Mars once had an amount of water corresponding to coverage 500 to 1,000 meters deep.

"If there was this huge amount of water, it has gone someplace else besides the poles," says Maria T. Zuber, the deputy principal investigator for the altimeter. She adds that the consensus is that some of the water may be in permafrost below the planet's surface and that some of it may have been lost to space.

From the Global Surveyor's magnetometer came the revelation that Mars does not have a global magnetic field. Subsequently, the spacecraft found that the planet has many small magnetic fields, oriented differently and scattered all over its surface. Even this discovery bears on the water question because it may help scientists understand how the planet cooled, thereby placing constraints on the history of water on Mars.

Earth's single magnetic field is generated by the motion of an electrically conductive fluid core, which acts as a kind of dynamo. Mars's many fragmentary fields are believed to be what was left when the planet's fluid dynamo stopped working, probably because it had solidified. Further study of the remnant fields may reveal when the dynamo became extinguished and how the planet's crust evolved.

Looking back over the 34-year history of Mars probes, project manager Glenn E. Cunningham remarks, "Every one of these missions has completely changed our picture of Mars." But Global Surveyor has clearly upped the ante. After all, its many revelations have come during what amounts to the mission's prelude, leaving scientists with high hopes for an unusually thrilling main event. *—Glenn Zorpette*

COSMOLOGY

A HUNDRED BILLION YEARS OF SOLITUDE

Evidence for an accelerating universe continues to pile up

If astronomers are right and the universe is expanding at a quickening pace, the cosmos will grow to untold size. But our world will shrink. The vast distances between galaxies will become ever vaster, until not even a spaceship traveling at the speed of light could cross them. The relatively nearby Coma cluster of galaxies, for instance, will be cut off from the Milky Way after some 60 billion years. Eventually we will be solitary prisoners in our cosmic neighborhood. “If you want to see Coma, go now,” recommends cosmologist Glenn D. Starkman of Case Western Reserve University. “Time is running out.”

A year and a half ago few scientists thought about the oddities of life in an accelerating universe, as opposed to in the traditional, decelerating one. But observations of distant supernovae, as well as confirmation of discrepancies in the amount of matter in space, have stretched cosmologists’ minds. The latest finds have boosted the two main arguments for acceleration and hinted at its exotic antigravitational causes.

The supernovae, acting as rafts on the cosmic currents, provide the most direct probe of the expansion rate. Acceleration could account for the anomalous faintness of these stellar explosions. But might not they seem dimmer for more prosaic reasons, such as dust absorption and changes in stellar composition over time?

Last October’s detection of SN1998eq helps to allay this concern. Nicknamed for the composer Tomaso Albinoni by the Supernova Cosmology Project—whose leader, Saul Perlmutter of Lawrence Berkeley National Laboratory, plays the violin—the supernova is the most distant yet found. It is not as anomalously dim as nearer explosions, and that is difficult to attribute to prosaic effects, which should steadily increase with distance. But it is easy to explain in an accelerating universe, because acceleration decreases with distance: earlier on in cosmic history, the density of matter was higher and gravity stronger.

To address unorthodox speculation that the anomalous dimness might be caused by light getting “tired” on its long journey, Perlmutter and other supernova hunters point out that distant supernovae appear to fade more slowly than nearby ones. This “time dilation” is a natural consequence of cosmic expansion, which, by stretching light waves, both reddens them and drags out their arrival on the earth. The putative tiring of light might change its color and predicted brightness, but not the apparent passage of time.

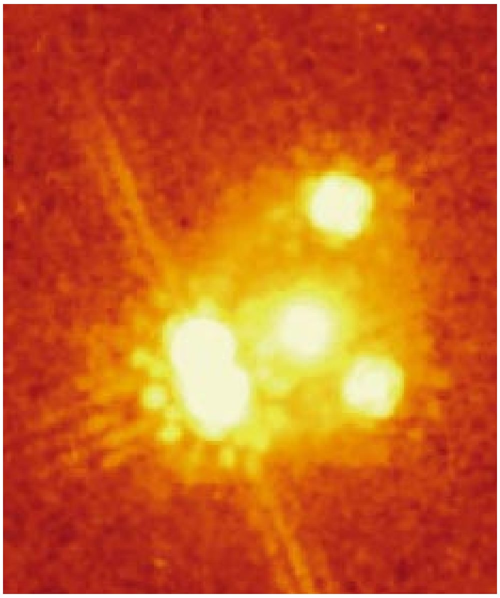
The second main argument for acceleration is the discrepancy between the observed amount of matter in the universe and the amount needed to give space a Euclidean geometry. A hitherto unknown type of energy may plug this gap, perhaps the infamous cosmological constant or its inconstant cousin, “quintessence,” either of which could exert an antigravity force.

The weak link in this second argument has been the assumption that space is Euclidean [see “Is Space Finite?” on page 90]. Observations of the cosmic microwave background radiation at a telescope in Saskatoon, Canada, several years ago suggested that it is. Since then, the case has been solidifying. The latest evidence comes from two South Pole telescopes, Python and Viper, run by scientists at Carnegie Mellon University and the University of Chicago; from the California Institute of Technology’s Owens Valley Radio Observatory; and from a reanalysis of the balloon-borne Medium Scale Anisotropy Measurement (MSAM), sent aloft by researchers at Chicago and the National Aeronautics and Space Administration Goddard Space Flight Center.

Some data, however, refuse to go along quietly with the accelerating scenario. The main counterevidence involves gravitational lensing, the bending of light from one celestial body by the gravity of another. One type of distortion, multiple galaxy images, should be common if the volume of space is large, as in an accelerating universe. Yet various studies, most recently by Emilio E. Falco and his colleagues at the Harvard-Smithsonian Center for Astrophysics, have found only a handful of image clones. Another type of distortion, sweeping arcs of light, depends on the concentration of galaxy clusters and should be fairly rare in an accelerating universe. But according to Matthias Bartelmann of the Max Planck Institute for Astrophysics in Garching and his colleagues, such arcs are widespread.

The lensing observations might be easier to reconcile if the accelerating force varies with position or time—a scenario that quintessence conveniently brings about. Groups led by Perlmutter, by Peter M. Garnavich of Harvard and by Limin Wang of Columbia University have combined all the available data to deduce what properties quintessence could have. If the force does differ from place to place, the local universe might be just a small pocket of accelerating space, as Starkman and his colleagues have described. As galaxies are pushed apart, they eventually leave the pocket and begin to decelerate.

But if the observers find that the acceleration persists out much farther than Albinoni, any variations will matter little to us. Almost all the galaxies we now see will come to recede at light speed, and solitude will indeed be our fate. Because of time dilation, we will watch the ghosts of departed galaxies slow to an adagio. “The galaxies will rotate more and more sluggishly, stars will evolve more slowly, and everything will look redder,” Starkman says. The cosmos will have been paralyzed by its haste. —*George Musser*



CHRISTOPHER D. IMPEY *University of Arizona;* SPACE TELESCOPE SCIENCE INSTITUTE

***GRAVITATIONAL LENS** creates four images of a single quasar. The paucity of such lenses may mean that the cosmological constant, if it exists, is not really constant.*

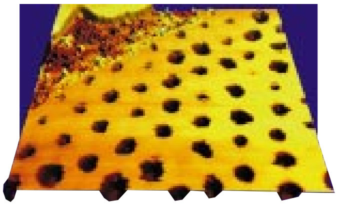
IN BRIEF

Origin of AIDS Identified

Beatrice H. Hahn of the University of Alabama at Birmingham and her colleagues describe in the February 4 *Nature* how they traced HIV-1 to a similar, simian virus that harmlessly inhabits a subspecies of chimpanzees, *Pan troglodytes troglodytes*. The researchers think, based on mutations in the virus, the simian virus has infected the chimps for 100,000 years and has jumped to humans at least three times. It probably occurred during butchering—a practice common in the animal's west-central African home. The chimps, which could provide clues for new HIV treatment, are unfortunately near extinction because of human predation. *—Philip Yam*

Self-Organizing Sulfur

With a scanning tunneling microscope, Karsten Pohl and colleagues at Sandia National Laboratories watched sulfur atoms embed themselves as islands on a one-atom-thick layer of silver on a substrate (*image*). The mystery has been how the spontaneous organization takes place—the atoms are 25 times too far apart to be influenced by interatomic forces. The researchers conclude in *Nature* that the distorting substrate caused the sulfur islands to repel one another, producing a lattice pattern. *—P.Y.*



Nanoscale sulfur pattern

SANDIA NATIONAL LABORATORIES

Reattaching the Head to the Neck

In the premier issue of the *Journal of Neurosurgery: Spine,* T. Glenn Pait of the University of Arkansas for Medical Sciences describes an inside-out way to reattach the skull to the neck. Such breaks, which can occur in accidents or illness, have been tough to repair, because the base of the skull is thin and cannot fully accommodate supports needed for a bone graft. In Pait's method the head of a screw is placed in the skull first, so that the threads face the outside. A special bone plate is secured with nuts, and the plate is then screwed to the neck bones, resulting in a connection three times stronger than screwing bolts from the outside in. *—P.Y.*

More "In Brief" on page 30

ANTI GRAVITY

Diamond Reflections

Who better than Roald Hoffmann to share my symmetry theory with, I thought. Hoffmann, professor of chemistry at Cornell University, is one of symmetry's great mavens. His Nobel Prize was for showing that symmetry relations play a fundamental role in chemical reactions. My particular symmetry theory was less magnitudinous, but I thought he might enjoy it.

The idea came in a blinding moment of insight last fall, the kind of epiphany that caused Archimedes to shout from his tub, "Give me a place to stand, and I will take a shower!" Symmetry was behind baseball's subtlety and complexity, I realized. Football and basketball, for example, have a simple spatial symmetry. The playing areas are bilaterally symmetrical, and the teams are of equal numbers. But in baseball, the symmetry is temporal: teams alternate their use of the same space. And symmetry is broken in the numbers of players—always nine on defense, anywhere from one to four at any time on offense. These conditions of symmetry, I argued to Hoffmann, give baseball its depth and texture. He listened patiently. Then he squinted slightly and threw me an exploding, knee-high slider. "But it's so slow," he said.

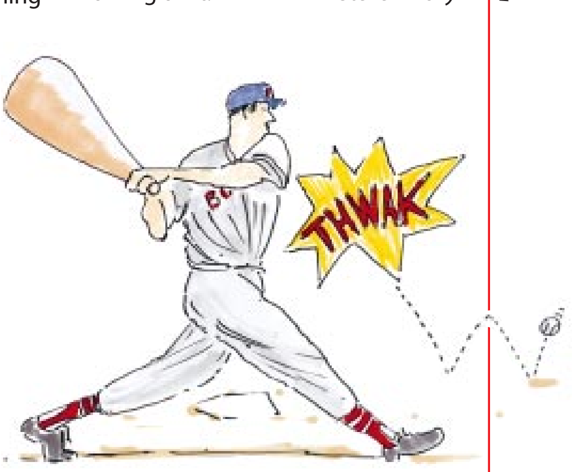
Hoffmann, as usual, happens to be correct. The game can be downright torpid at times. But the inactivity is punctuated by moments of blinding speed: balls may zoom to the plate at close to 100 miles per hour—and get batted back even faster. In the college game, baseballs have been returning to the mound so fast, in fact, that scientists have been called in to help protect pitchers from being hoisted on their own petards. (A baseball, by the way, exhibits D_{2d} point group symmetry, for you chemists keeping score at home.)

According to the National Collegiate Athletic Association (NCAA), as many as 20 college pitchers each season have to leave games because they are hurt badly enough by shots from aluminum and other almost unbreakable, nonwood bats. The NCAA, therefore, announced last year that it wants to impose a speed limit on the belt-high way between batter and pitcher. The moundsmen will still be able to fling the ball to the plate as fast as they can, but the batters will not be allowed to hit the ball with an initial velocity exceeding 93 miles per hour.

Of course, asking hitters to ease up would be contrary to every healthy American's competitive instincts. No guidelines will deny any individual batsman the right to swing as hard as he wants. The laws of physics are being trusted to slow the ball down, as new bat specifications now being tested should impose the NCAA's will. A batter may still hit a fly, but he wouldn't hurt one.

Although maximum diameters and relations between length and mass come into play, the bottom line is straightforward: heavier bats. Obviously, players cannot uncoil cumbersome clubs quite as quickly. The drop in swing speed translates to slower slaps back to the mound. That in turn means that student-athletes won't have their brains scrambled by anything other than deciphering why Hoffmann has suggested that the *endo* preference in Diels-Alder reactions is a secondary effect of orbital symmetry.

One other launched projectile note: just a Mark McGwire moonshot away from Yankee Stadium sits the Bronx Zoo, home to Tunuka, a gorilla pegged by the *New York Daily News* as the "primate suspect" in a 1995 rock-throwing incident in which an eight-year-old boy was allegedly beaned. The boy's family is now suing the zoo for a million bananas. The *News* story was written by someone actually named FitzGibbon. I have yet to figure out all the symmetry rules in play here, but I'm working on it. *—Steve Mirsky*



MICHAEL CRAWFORD

In Brief, *continued from page 26*

Long-Lasting Element 114

Through e-mail, scientists at the Joint Institute for Nuclear Research in Dubna, near Moscow, reported strong evidence that they have created the heaviest element yet, one with 114 protons and 184 neutrons. In work that has yet to be published, a team led by Yuri Oganessian and Vladimir Utyonkov smashed a rare isotope, calcium 48, with a plutonium 244 target to make the element. It lasted an astonishing 30 seconds, far longer than the 280 microseconds of the last new element found, element 112 (113 has yet to be created). The long lifetime proves that "islands of stability" exist in the superheavy-element range. (See September 1998, page 72.) *—P.Y.*

Seal-Cam

Filming the predatory behavior of highly mobile marine mammals like seals is hard enough without having to contend with the frigid gloom beneath the Antarctic fast ice. The solution? Give the cameras to the seals. As they report in the February 12 *Science,* Randall W. Davis of Texas A&M University and his colleagues fitted four Weddell seals with audio-video headsets and data recorders to see how the seals pursue Antarctic cod and other fish. Despite the dim light, the seals rely primarily on vision to locate their prey, looking upward to find fish backlit against the ice. The cameras also recorded a hitherto unknown hunting technique—blowing bubbles into icy crevices to flush their quarry out of hiding (*photograph*). *—Jessa Netting*

Seal's-head view

RANDALL W. DAVIS

Salt-Free Spit

Drooling isn't socially acceptable, but medically it's a great prophylactic: saliva has antimicrobial proteins and antibodies, helping to explain why HIV is not easily transmitted by kissing or dental procedures. Now Samuel Baron of the University of Texas Medical Branch at Galveston and his co-workers report in the *Archives of Internal Medicine* that saliva's antimicrobial action also derives from its lack of salt, a necessary component of cells. Placed in a salt-free liquid, cells swell up and explode. Saliva, which is one seventh as salty as other body fluids, doesn't protect during oral sex or breast-feeding, however—the addition of saltier fluids from those activities counterbalances saliva's low salinity. *—P.Y.*

More "In Brief" on page 32

ENVIRONMENT

WHITEOUT

Widespread coral bleaching, even in deep waters, continues to perplex scientists

Mention a hot tub to most people, and images of relaxation, perhaps a little romance, probably come to mind. But when marine biologist Thomas J. Bright, who works at Glover's Reef Marine Research Station off the coast of Belize, uses the term, he is anything but content. As head of the station, which is run by the Wildlife Conservation Society, Bright spends a fair bit of time in the water monitoring the health of Belize's coral reefs. Some of his most recent observations, particularly of deepwater reefs, have been surprising—and troubling.

It all started last September, Bright recalls, as he was sailing back to Belize from a research trip to Honduras, when he stopped to examine one of the Caribbean's abundant coral reefs. "The water felt like a hot tub," Bright says, and he immediately knew something was amiss. Just as he suspected, the coral reef where he was snorkeling had suffered heavy damage as a result of a process called coral bleaching. Bleaching occurs when coral—often in response to an increase in water temperature—expel algae that typically live on the reef. The algae, known as zooxanthellae, exist in a symbiotic relationship with the coral, providing nutrition to the reef. The algae also give the reef its color. Without the zooxanthellae, the coral's calcium carbonate skeleton is exposed, and the reef appears pure white and will eventually die.

As it turns out, the coral reef in Belize was just one of countless others to have also discharged its zooxanthellae recently. Bright indicates that throughout last fall, he and other researchers made "innumerable observations [of bleached coral] all over the Caribbean." Indeed, according to the International Society for Reef Studies (ISRS), over the past two years scientists around the world have documented "the most geographically widespread bleaching ever recorded."

Bleaching often occurs in surface waters—say, the top two meters (around seven feet)—where the ocean is the warmest. (Notably, some researchers have suggested that recent increases in sea-surface temperatures in the tropics are a consequence of global warming.) So imagine Bright's astonishment when he saw coral bleaching in Belize waters all the way down to some 30 meters (100 feet) below the surface. Was the water particularly warm at such depths? "It shouldn't be," Bright admits. He offers one speculative explanation for the phenomenon: during a dive with another scientist, Bright and his colleague "ran into warm layers of water at about 30 feet." So the bleaching may have resulted from warm, more saline layers traveling down to the deep water.

John C. Ogden, director of the Florida Institute of Oceanography and former president of the ISRS, notes that bleaching of coral even deeper than 30 meters has been reported. He goes on to say that the complex patterns of when and where deep bleaching has been observed offer "further evidence of the fact that we don't know enough about the physiological relationship between corals and zooxanthellae." For instance, another bleaching culprit could be ultraviolet solar radiation, which, like warm waters, causes the coral to expel zooxanthellae—but not many UV rays penetrate down to the coral and zooxanthellae residing at depths of 30 meters or below.

KELVIN AITKEN *Peter Arnold, Inc.*

CORAL BLEACHING, occurring here only on the outer edge, has been seen worldwide in record quantities over the past two years.

As scientists puzzle over what is happening to coral around the world—whether deeper waters are starting to warm or whether some new agent is to blame for coral bleaching—the Belize coral, at least, is recuperating somewhat during these cooler months. But parts of the reef have been permanently damaged. Bright estimates that only 50 percent of the deepwater reefs have recovered. And conditions on the shallow reefs appear especially grim, in large part because many were torn to pieces by Hurricane Mitch, which devastated much of the Caribbean region in October. Bright estimates that some 60 to 70 percent of the coral above nine meters has died as a result of what he calls "a triple whammy"—first bleaching, then the hurricane, and finally infections, which moved quickly through the already vulnerable reefs. If global warming is truly heating up the oceans and rocking the fragile ecosystems of coral reefs, the resulting sea sickness just might continue to spread. —*Sasha Nemecek*

In Brief, *continued from page 30*

Killer Headaches

It may not just be the morning after when you regret having one too many. When the body processes ethanol, it produces acetaldehyde, a chemical that leads to hangovers. It is rendered harmless by the enzyme aldehyde dehydrogenase 2. But prolonged alcohol intake overloads the detoxification process. In the January 19 *Biochemistry,* Shinya Shibutani of the State University of New York at Stony Brook and his colleagues show that residual acetaldehyde can damage a nucleotide, possibly leading to mutated DNA. Previous studies have linked this mutation to cancers of the esophagus, larynx and liver.—*Gary Stix*

Hangovers and mutations?

ADAM WOOLFITT *Corbis*

Single-Strain Vaccine Danger

A new model described in the January *Proceedings of the National Academy of Sciences* suggests that single-strain vaccines—such as some of those in testing to combat HIV—may actually increase the risk of contracting disease. Many viruses exist as complexes of several related strains. Usually infection or vaccination with one virus family member causes the body to produce antibodies that also fight subsequent infection by closely related strains. In a sinister variation on this script, certain viruses, such as the strains that cause dengue fever, respond to the presence of such "cross-reactive" antibodies by mounting an even more severe attack. Such a sequence of infection could lead to cyclical or chaotic outbreaks of disease that are hard to combat. —*J.N.*

IT Gets the Bucks

Funding for information-technology research is likely to get a big boost. On February 1, President Bill Clinton submitted to Congress a $1.8-trillion budget for 2000. The plan contains a proposal for $366 million to back a so-called Information Technology for the 21st Century, or IT^2. The money is to be funneled through six federal agencies; the National Science Foundation and the Defense and Energy Departments get the bulk—$146 million, $100 million and $70 million, respectively. The funds will go to long-term projects aimed at developing faster computers. —*P.Y.*

GENETICS

MUTATIONS GALORE

Humans have high mutation rates. But why worry?

All living things slowly accumulate mutations, changes in the string of chemical units in the famous DNA double helix that may in turn alter the form and function of a protein. A mutation that does affect a protein, if passed on to an offspring, might improve the progeny's chances in life—or, more likely, harm them. Deleterious mutations, which can cause genetic diseases, are unfortunately more likely than beneficial ones, for the same reason that randomly retuning a string on a piano is likely to make the instrument sound worse, not better.

Despite the hazard of harmful mutations, researchers until recently had only the vaguest notion of how often they occur in humans. Many mutations are thought to produce no obvious effect, yet they might still represent a subtle disadvantage to an organism carrying them. Adam Eyre-Walker of the University of Sussex and Peter D. Keightley of the University of Edinburgh recently examined the frequency of mutations in humans by studying how many have occurred in a sample of 46 genes during the six million years since humans and chimpanzees last shared an ancestor. The results, published in *Nature,* were surprising: a minimum of 1.6 harmful mutations occurs per person per generation, and the number is more likely close to three. That number is high enough to pose a challenge to theorists.

Eyre-Walker and Keightley's approach was subtle. They first assessed how many human mutations occurred in the sample of genes that could not have produced any alteration in a protein and so must have been invisible to natural selection. (A fair proportion of mutations, even those occurring in active genes, do not cause any change in the protein that they encode.) They judged which differences in gene sequences between humans and chimpanzees were caused by mutations in humans by comparing discrepant sequences with the equivalent gene sequence in a third primate group. If the third group's sequence matched up with that of the chimpanzees, the change was surmised to have occurred in the human line.

From this observed number of "invisible" human mutations, Eyre-Walker and Keightley could calculate the theoretical number of mutations that should have resulted in altered proteins. The answer was 231. But only 143 such protein-changing human mutations were actually seen in the sample. The missing 88, they concluded, did occur at some point but were harmful enough to be eliminated by natural selection. That number leads to the estimate of perhaps three harmful mutations per person per generation.

The proportion of mutations that is clearly harmful seems lower than most geneticists would have guessed. But the overall rate of human mutations is very high, and as a result the actual rate of bad mutations is disturbingly high, too.

According to standard population genetics theory, the figure of three harmful mutations per person per generation implies that three people would have to die prematurely in each generation (or fail to reproduce) for each person who reproduced, in order to eliminate the now absent deleterious mutations. Humans do not reproduce fast enough to support such a huge death toll. As James F. Crow of the University of Wisconsin asked rhetorically, in a commentary in *Nature* on Eyre-Walker and Keightley's analysis: "Why aren't we extinct?"

Crow's answer is that sex, which shuffles genes around, allows detrimental mutations to be eliminated in bunches. The new findings thus support the idea that sex evolved because individuals who (thanks to sex) inherit several bad mutations rid the gene pool of all of them at once, by failing to survive or reproduce.

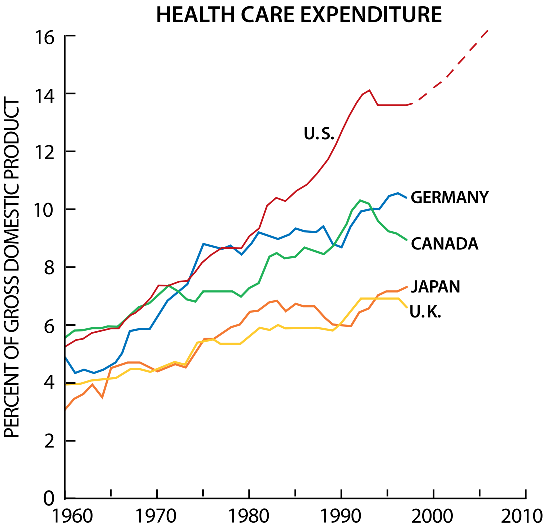
Yet natural selection has weakened in human populations with the advent of modern medicine, Crow notes. So he theorizes that harmful mutations might now be starting to accumulate at an even greater rate, with possibly worrisome consequences for health. Keightley is skeptical: he thinks that many mildly deleterious mutations have already become widespread in human populations through random events in evolution and that various adaptations, notably intelligence, have more than compensated. "I doubt that we'll have to pay a penalty as Crow seems to think," he remarks. "We've managed perfectly well up until now."

—Tim Beardsley in Washington, D.C.

BY THE NUMBERS

Health Care Costs

Rising medical costs are a worldwide problem, but nowhere are they higher than in the U.S. Although Americans with good health insurance coverage may get the best medical treatment in the world, the health of the average American, as measured by life expectancy and infant mortality, is below the average of other major industrial countries. Inefficiency, fraud and the expense of malpractice suits are often blamed for high U.S. costs, but the major reason is overinvestment in technology and personnel. America leads the world in expensive diagnostic and therapeutic procedures, such as organ transplants, coronary artery bypass surgery and magnetic resonance imaging. Orange County, California, for example, has more MRI machines than all of Canada.



SOURCE: Organization for Economic Cooperation and Development, Health Data 1997. Dashed line shows projections for U.S. made by Sheila Smith, Mark Freeland, Stephen Heffler et al., "The Next Ten Years of Health Spending," in Health Affairs, *Vol. 17, No. 5, pages 128–140; September–October 1998.*

Federal policy since World War II has emphasized medical technology and the widespread building of hospitals, even in rural areas. Other industrial countries, in contrast, followed the more cost-effective alternative of building up regional centers. The U.S. has long overinvested in the training of specialists at the expense of primary physicians, leading to a large surplus of specialists. Because specialists have economic incentives to perform unnecessary procedures, they may contribute to cost inflation.

Other industrial countries have managed to slow the growth in costs while achieving near-universal coverage. These include Britain, France and Italy, which have heavily centralized systems; Canada and Germany, which have decentralized systems but whose provinces play a key administrative role; and Japan, which combines strong national policy making with health care administration left largely in private hands. In each instance, central governments imposed strict fiscal controls even though they resulted in long waiting times for elective treatment and considerable delays in seeing specialists.

President Bill Clinton attempted to impose central fiscal controls as a part of his 1994 health care plan but was unable to put together a solid supporting coalition. Insurance firms, pharmaceutical companies, small business operators and academic medical centers were opposed to the plan. Labor unions and Medicare beneficiaries generally favored it but lobbied vigorously for changes that would improve their benefits. Republicans opposed the plan on the grounds that it called for new taxes.

According to political scientist Lawrence R. Jacobs of the University of Minnesota, universal access is a key to the success of other countries in imposing fiscal controls because it helps to lessen friction between groups. The American system encourages discord, for example, between health care insurers and high-risk people whom they exclude from coverage. Americans who receive adequate care through employers have little economic interest in seeing coverage extended to the more than 43 million Americans now uninsured.

In recent years U.S. health care expenditures as a percent of gross domestic product have leveled off, probably as a result of the expansion of managed care. The projected increase to 16.6 percent of GDP in 2007 shown on the chart assumes that managed care will grow more slowly, that increasing consumer income will boost the demand for medical services and that medical cost inflation will accelerate. But the period of greatest stress will come after 2010, when baby boomers begin to retire. Not only will federal budgets be strained, but also employers, already paying far more in medical costs than foreign competitors, will be put at a further disadvantage in world trade.

How can the federal government ever assert fiscal control over medical costs? Victor R. Fuchs of Stanford University, a longtime observer of the medical economy, believes that comprehensive reform of the U.S. medical system will come only after a major political crisis as might accompany war, depression or widespread civil unrest. Such a crisis might arise as medical costs reach ever higher and threaten Social Security, Medicare and other popular programs; there could be political upheaval of such magnitude that medical reform will seem to be the easy solution.

—Rodger Doyle (rdoyle2@aol.com)

RODGER DOYLE

PROFILE

Not Just Fun and Games

Best known for inventing the game of Life, John H. Conway is adept at finding the theorems hidden in simple puzzles

Stepping into John H. Conway's office at Princeton University is like stepping into a mathematician's playpen. Dozens of polyhedra made of colored cardboard hang from the ceiling like mirror balls at a discotheque. Dangling among them is a Klein bottle constructed from chicken wire. Several models of crystal lattices sit beside the window, and a pyramid of tennis balls rises from the floor. At the center of it all is Conway himself, leaning back in his chair, his face obscured by oversize glasses and a bushy, gray beard. The eclectic 61-year-old mathematician is clearly in his element.

"What's your date of birth?" he asks me soon after we shake hands.

"April 19, 1961," I reply.

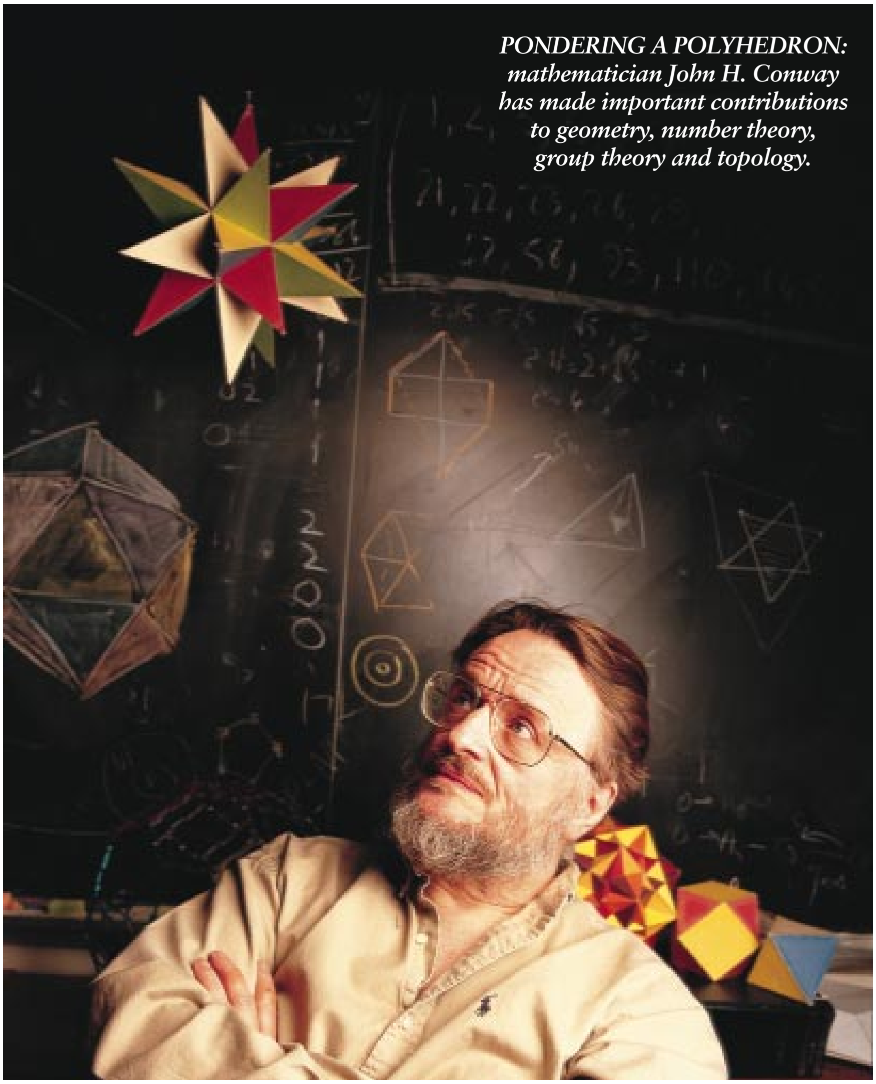
"Tuesday!" he shouts immediately. Then he corrects himself. "No, damn! Wednesday!" Slightly irritated by his error, he explains that long ago he devised an algorithm for determining the day of the week that any given date falls on. Called the Doomsday Rule, the algorithm is simple enough for Conway to do the calculations in his head. He can usually give the correct answer in under two seconds. To improve his speed, he practices his calendrical calculations on his computer, which is programmed to quiz him with random dates every time he logs on.

At this point, I begin to wonder why Princeton University is paying this man a salary. But over the past three decades Conway has made some of his greatest contributions to mathematical theory by analyzing simple puzzles. "It's impossible for me to go into the office and say, 'Today I'll write a theorem,'" Conway admits. "I usually have half a dozen things running through my head, including games and puzzles. And every so often, when I feel guilty, I'll work on something useful." Conway's useful work spans the gamut of mathematical disciplines, ranging from theorems about knots and sphere packing to the discovery of a whole new class of numbers—the aptly named surreal numbers.

Born in Liverpool, England, in 1937, Conway showed an early interest in mathematics. At the age of four, according to his mother, he began reciting the powers of two. Liverpool was being bombed by the German Luftwaffe at the time, and Conway has a lasting memory of one of the air raids. "While my father was carrying me to our backyard shelter one night, I happened to look up at the sky. There were spotlights overhead, and I saw the bombs falling from the planes. They were chained together and whirling around. It looked so beautiful, I said, 'Look, Daddy! That's so nice!'"

Conway attended the University of Cambridge, where he studied number theory and logic and eventually joined the faculty of the mathematics department. In his spare time he became an avid backgammon player. "I used to play backgammon in the common room at Cambridge," Conway recalls. "My more sedate colleagues would come in occasionally for a cup of coffee or tea, but I'd be there all day long."

Conway's career didn't really take off until the late 1960s, when he became intrigued by a theoretical lattice that extends into 24 dimensions. By contemplating this lattice, Conway discovered a new finite group, which is the set of symmetries of a geometric object. A cube, for example, has 24 symmetries—there are 24 ways to rotate it to an identical position. But the Conway group, as it became known, has more than 10^{18} symmetries, making it the largest finite group known at the time of its discov-



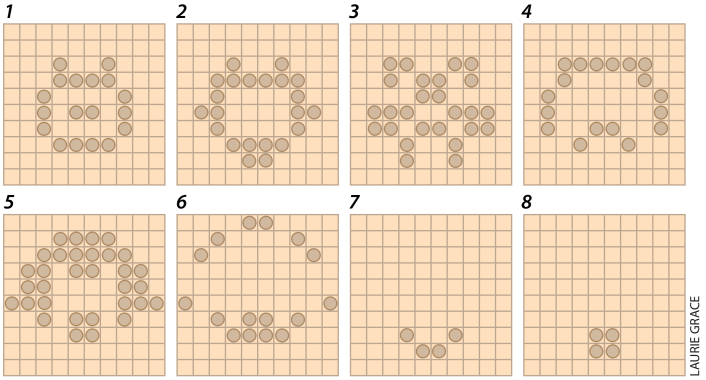
PONDERING A POLYHEDRON: mathematician John H. Conway has made important contributions to geometry, number theory, group theory and topology.

PETER MURPHY

ery. (It was later superseded by the so-called Monster group, which has more than 10^{53} symmetries.) Finding a new group is an extraordinarily difficult achievement, and Conway's colleagues soon began to hail him as a genius.

At about the same time, Conway was exploring the idea of the universal constructor, which was first studied by American mathematician John von Neumann in the 1940s. A universal constructor is a hypothetical machine that could build copies of itself—something that would be very useful for colonizing distant planets. Von Neumann created a mathematical model for such a machine, using a Cartesian grid—basically, an extended checkerboard—as his foundation. Conway simplified the model, and it became the now famous game of Life.

In the game, you start with a pattern of checkers on the grid—these represent the "live" cells. You then remove each checker that has one or no neighboring checkers or four or more neighbors (these cells "die" from loneliness or overcrowding). Checkers with two or three neighbors remain on the board. In addition, new cells are "born"—a checker is added to each empty space that is adjacent to exactly three checkers. By applying these rules repeatedly, one can create an amazing variety of Life forms, including "gliders" and "spaceships" that steadily move across the grid.



LAURIE GRACE

CHESHIRE CAT, A LIFE PATTERN,
transforms into a grin (7) ***and finally a paw print*** (8).

Conway showed the game of Life to his friend Martin Gardner, the longtime author of *Scientific American*'s Mathematical Games column. Gardner described the game in his October 1970 column, and it was an immediate hit. Computer buffs wrote programs allowing them to create ever more complex Life forms. Even today, nearly 30 years after the game's introduction, Conway receives voluminous amounts of e-mail about Life. "The game made Conway instantly famous," Gardner comments. "But it also opened up a whole new field of mathematical research, the field of cellular automata."

Conway, though, moved on to other pursuits. Some of his Cambridge colleagues were skillful at the ancient game of Go, and as Conway watched them play he tried to develop a mathematical understanding of the game. He noticed that near the end of a typical Go match, when the board is covered with snaking lines of black and white stones, the game resembles the sum of several smaller games. Conway realized that certain games actually behave like numbers. This insight led him to formulate a new definition of numbers that included not only the familiar ones—the integers, the rational numbers, the real numbers and so on—but also the transfinite numbers, which represent the sizes of infinitely large sets.

Mathematicians have long known that there is more than one kind of infinity. For example, the set of all integers is infinitely large, but it is smaller than the set of all real numbers. Conway's definition encompassed all the transfinite numbers and, better still, allowed mathematicians to perform the full array of algebraic operations on them. It was a theoretical tour de force: by defining finite and transfinite numbers in the same way, Conway provided a simpler logical foundation for all numbers. Stanford University computer scientist Donald E. Knuth was so impressed by Conway's breakthrough that he wrote a quirky novella, called *Surreal Numbers,* that attempts to explain the theory. In the story, Conway is cast as God—there is a character named "C" whose voice booms out of the sky. Although the comparison may seem a little extreme, Conway acknowledges that he has a healthy ego. "After I make a discovery, my feelings are a bit of a mix," he says. "I admire the beauty of the thing I've discovered, how it all fits together. But I also admire my own skill at finding it."

Conway's interest in games culminated in 1982 with the publication of *Winning Ways for Your Mathematical Plays,* a two-volume work he wrote with Elwyn R. Berlekamp of the University of California at Berkeley and Richard K. Guy of the University of Calgary. The book has become the bible of recreational mathematics; it describes dozens of brain-teasing games, most of them invented by the authors, with outlandish names such as Toads-and-Frogs and Hackenbush Hotchpotch. But the main purpose of the book, Conway insists, is not entertainment. "The book is really more about theory than games," he says. "I'm much more interested in the theory behind a game than the game itself. I got the theory of surreal numbers from analyzing the game of Go, but I never really played the game." In fact, the only game Conway plays regularly is backgammon—a pastime that defies mathematical analysis because it involves the element of chance.

Unfortunately, Conway's personal life has not been as orderly as his mathematical theorems. He has endured bouts of depression and a heart attack. In the mid-1980s Conway moved from Cambridge to Princeton, and since then much of his work has focused on geometry. He is currently exploring the symmetries of crystal lattices—which explains the presence of the lattice models in his office. He is also pursuing what he calls his "grandiose project," a rethinking of the fundamental axioms of set theory. Conway recognizes, however, that he is slowing down. "I used to go through these white-hot phases when I couldn't stop thinking about a problem," he admits. "But now those phases are not so common. It's been ages since I had one."

Among mathematicians, though, Conway's reputation is already assured. "It's hard to predict which of his many major achievements will most impress mathematicians of the future," says Martin Kruskal of Rutgers University, who has spent years investigating the surreal numbers that Conway discovered. Conway himself worries a little that his work on games and puzzles may overshadow his more significant accomplishments, such as the discovery of surreal numbers and the Conway group. But his career is strong evidence that playful thinking can often lead to serious mathematics. "Games usually aren't very deep," Conway muses. "But sometimes, something you thought was frivolous can turn out to be a deep structural problem. And that's what mathematicians are interested in." *—Mark Alpert*

TRANSPORTATION

WAITING FOR THE SUPERCAR

Overly ambitious goals may have hurt the Partnership for a New Generation of Vehicles

Announced to notable fanfare in a Rose Garden ceremony at the White House in 1993, the Partnership for a New Generation of Vehicles was heralded as a linchpin of the Clinton administration's technology strategy. In a collaboration of unusual scale, the government's national laboratories and the Big Three U.S. automakers and their many subcontractors would work together to build, within a decade, a "supercar" that had a fuel efficiency of 80 miles per gallon (three liters per 100 kilometers), low pollutant emissions and essentially the same performance, safety, comfort and cost as a midsize five-passenger sedan.

The rationale underlying the partnership (known as the PNGV) was a good one. It was to jump-start innovation by funding research and development at the national laboratories (which were then searching for a new mission after the cold war) on technologies that were too risky, or whose payoff was believed to be too far in the future, to be pursued by the automakers on their own.

The reality, however, has not lived up to the rationale. Today, halfway through the intended 10-year mission, some experts in advanced automotive technologies say the PNGV has delivered too little for the roughly $2 billion that has been spent so far on the program, about half of which came from the government. Meanwhile PNGV officials themselves are already conceding that a production-ready prototype of an 80-mpg car that meets all the other criteria is unlikely to be built by 2004. The shortcomings seem all the more stark in view of Toyota's success a year ago in bringing an advanced hybrid vehicle to market.

At the same time, the PNGV is wrestling with a number of problems, including an unwieldy administrative structure and uncertainty about German-based DaimlerChrysler's future in the federally supported program. But most notable, perhaps, among those difficulties are several stemming from the PNGV's ambitious 80-mpg target—a goal that some critics say was unrealistic all along.

According to the critics, the all but unattainable fuel-efficiency goal compelled researchers to pursue far-fetched technologies, such as flywheels and ultracapacitors, longer than they should have. "There was an unnecessary bias toward far-out technologies that didn't have a very good chance of success," according to the noted hybrid- and electric-vehicle designer Alan Cocconi. "They stuck to some of the requirements in such a dogmatic manner that they wound up with nothing at all."

COURTESY OF DAIMLERCHRYSLER CORPORATION

HYBRID DODGE INTREPID WOULD COST $15,000 more than a conventional car, DaimlerChrysler estimates.

Tom Gage, a former Chrysler executive, says the PNGV set out in the early 1990s with an overly ambitious goal partly to appease environmentalists. "Industry had just survived a strong attempt to increase [average fuel-efficiency] laws to 40 miles per gallon," he explains. The PNGV, he adds, succeeded in placating the environmentalists, but it did so with a goal that he is not sure "was even thermodynamically possible. It depends on the assumptions you make. The assumptions I make indicate it wasn't, not with five passengers in a full-size car. PNGV has been a surrogate for a real, effective fuel-economy policy," Gage concludes. "While PNGV was going on, light trucks captured 50 percent of the market, with their fuel economy in the 13- to 17-mpg range. We're back to the 1970s again."

Victor Wouk, a veteran hybrid-vehicle consultant, also criticizes the PNGV's ambitious goals, but for a different reason. "Ford, GM and Chrysler are going for the gold ring the first time around," Wouk declares. "And while we were talking about hybrids, the Japanese were building one," he adds, referring to Toyota's Prius. On sale only in Japan, the vehicle is not quite the supercar envisioned by the PNGV; it is a compact sedan that gets between 50 and 66 mpg. Nevertheless, Wouk says, it is "a solid basis from which to build." (Honda plans to introduce a hybrid in the next few months that it claims is even more efficient than Toyota's.) A Big Three executive, meanwhile, insists that "the focus on 80 miles per gallon, if anything, has taken some pressure off the nearer-term technologies that we need to get to market."

But to PNGV proponents, the ambitious goals were galvanizing. Al Murray, an executive in Ford's PNGV effort, says of the 80-mpg objective: "We all had a hard time swallowing that goal to begin with. But it forced us to rethink every aspect of the vehicle, so there was some merit in [it]." George Joy, head of the PNGV technical task force for the Department of Commerce, the lead government agency in the program, argues that the PNGV will be a triumph "if we manage to get an affordable, clean-running vehicle" that gets 55 to 65 rather than 80 mpg but otherwise meets the supercar goals. In addition, PNGV executives emphasize the program's two other, lesser-known targets: improving manufacturing competitiveness in general and getting new technologies into ordinary production vehicles to improve their fuel efficiency and emissions levels.

Unfortunately for these executives, however, they still do not know the pollutant emission standards they must work toward—and will not until the end of this year at the earliest. These so-called Tier 2 standards, most significantly for particulate matter and nitrous oxides ("NO_x"), are now being formulated by the Environmental Protection Agency and will be incorporated into the PNGV's goals.

The EPA's recommendation for NO_x emissions is expected to be somewhere below 0.2 gram per mile, and for particulate emissions, not greater than 0.04 gram per mile. (The U.S. has the puzzling custom of mixing metric and British imperial units in pollutant emission rates.) And there is mounting pressure for the Tier 2 emission limits to match those for the latest "ultralow-emission vehicles" (ULEVs) set forth by the California Air Resources Board, which are 0.05 gram per mile for NO_x and 0.01 gram per mile for particulates. Starting in 2001, an increasing percentage of the vehicles sold in California will have to be ULEVs; basically by 2010 the vast majority of cars sold in the state will be no more polluting than ULEVs. This fact presents a problem for the PNGV, because the ULEV emission rates would be impossible to meet in a supercar that had the other desired attributes.

For a hybrid-electric car even to approach a fuel efficiency of 80 mpg would most likely require the use of a diesel engine, which is notorious for its emission of particulates. The traditional spark-combustion engine, on the other hand, might satisfy particulate emission goals but would be unlikely to meet both the fuel-efficiency and the low-NO_x requirements. "The combination of low NO_x and low particulate emissions is going to be one heck of a technical hurdle for us," Joy concedes.

In the meantime, each Big Three automaker is now working on a hybrid vehicle, to be unveiled early in 2000 as evidence of its progress. When asked how, exactly, the program benefited these concept cars, none of the PNGV directors could immediately identify a specific technology in their vehicle that emerged directly from their collaborative work with the government. All, however, staunchly support the PNGV, insisting that its technologies will be more important in the program's next half a decade.

More significant, they maintain that the alliance has had major benefits outside the technical arena. At Ford, PNGV director Vincent Fazio says the program has been instrumental in fostering "a significant amount of trust between Washington regulators and the industry." Steven Zimmer of DaimlerChrysler agrees, adding that because regulatory bodies such as the EPA are represented in the PNGV, "we have an ability to at least have a dialogue on the agendas that each of the [government] departments has." At GM, PNGV director Ron York says that because of the program, "we have learned to use collaborative work and competitive work in combination to get the job done." The Big Three were prohibited from collaborating until the mid-1980s. Critics of the PNGV, however, insist that these accomplishments could have been achieved with less money. This year's government allocation is $240 million.

The technical hurdles notwithstanding, one of the most difficult challenges for automakers in coming years will be marketing. With gas prices at historic lows, car buyers seem less willing than ever to pay a premium for fuel efficiency. "The bottom line is, we're trying to develop technology with no cost penalty to the consumer," Fazio notes. "That will be the biggest strategic issue we face."

Six years ago, when Al Gore's advocacy helped make the PNGV a reality, the vice president often compared the program with the Apollo project. The comparison was not lost on Fazio, who has his own version of the analogy. "This project is tougher than going to the moon," he says, "because we're trying to take 200 million Americans with us."

—*Glenn Zorpette*

WEAPONRY

TAKING BALLISTICS BY STORM

An electronic gun with no mechanical parts fires a million rounds per minute

When you first hear of a gun without any moving mechanical parts, you tend to laugh. I know I had to withhold my giggles," recalls physicist Adam Drobot of Science Applications International Corporation (SAIC), a company based in San Diego that evaluates new technologies. "But once you see the videotape of this test-firing, the giggle factor goes away."

The gun in question is something that even its inventor says comes out of left field. Termed Metal Storm, the weapon has no hammer, no trigger, no breechblock and no shell casings to eject. Equally unusual, a single barrel fires at a rate equivalent to one million rounds per minute. In comparison, the fastest conventional firearms (Gatling guns) fire only 6,000 rounds per minute.

Metal Storm's origins are unorthodox as well. It was invented by former grocery wholesaler Mike O'Dwyer, a lone Australian tinkerer with no formal education in ballistics or engineering. His previous patents are for devices such as air-cooled sneakers. ("They pump air through as you jog," he explains.) Yet after 15 years of trial and error in his tropical Queensland home, O'Dwyer came up with a gun prototype that recently fired 180 rounds of nine-millimeter bullets in 0.01 second during a demonstration before military officials in Adelaide. Metal Storm's bullets leave its barrel so quickly that they are only microseconds apart—when one bullet is flying through the air, the next is just 10 centimeters (four inches) behind. For current machine guns, the gap between bullets is 30 meters.

"It could replace our existing technology on the battlefield," says Maj. David Goyne, a weapons specialist at Australian Defense Headquarters. The gun is ideal for close-in situations, such as defending ships against incoming missiles. Goyne comments that it could also eliminate land mines in open areas such as Kuwait's deserts: a helicopter using the gun could hover above the sands and clear a minefield by spraying it from a distance, exploding mines harmlessly.

The gun works through a combination of specially designed bullets and an electronic firing mechanism, which O'Dwyer describes as "a barrel tube with an electrical wire attached." Jacketless bullets are lined up inside, nose to tail, and are separated from one another by a layer of propellant. When an electric current makes its way down the strip, the bullets are set off one by one. To stop them from going off simultaneously—a problem previously encountered when putting many bullets in a single barrel—O'Dwyer designed the bullets to work together. The high pressure caused by the firing of the first projectile makes the nose of the next one in line swell against the walls, temporarily sealing off the rest of the barrel. (In ballistics terms, the nose of the second bullet effectively acts as a breechblock to prevent an uncontrolled sympathetic ignition.) After the first bullet exits, the pressure drops, and the nose of the second one loosens up, enabling the bullet to be fired. This process continues for each successive bullet.


NewsPix

MULTIBARREL ELECTRONIC GUN is displayed by its inventor, Mike O'Dwyer.

Other than the projectiles themselves, there are no moving parts. To get even more firepower, several loaded barrels can be set up side by side. Once a barrel is used up, it can be discarded or sent back to the factory for reloading.

Variations of electrically fired weapons have been tried before. For instance, Sandia National Laboratories developed an electromagnetic coil gun designed to hurl 100-kilogram (220-pound) satellites into orbit. But a number of differences separate the two approaches, observes Vinod Puri, senior research scientist with the Australian Defense Science and Technology Organization: "The electromagnetic coil gun demands lots of energy, achieves high velocities and sends large objects great distances. In contrast, Metal Storm requires less energy, works at lower velocities, uses normal gun propellant and sends out more, smaller projectiles per minute for shorter distances."

O'Dwyer points out another feature of guns like Metal Storm: because electronics are such an integral part of their makeup, they offer a good opportunity for built-in electronic safeguards, such as security keypads. If an unauthorized user tried to bypass the gun's security system by disabling the electronics, the gun simply couldn't fire. The device has many nonmilitary uses, too, Drobot notes. A slower version could replace the nail guns used by carpenters and roofers and may find a use in riveting and other industrial applications.

Goyne remarks that the technology still needs fine-tuning—it fires relatively small caliber bullets, for example. But physicists such as Puri say its basic design is "very solid." The Australian Trade Commission is promoting the weapon, which has attracted attention in Australia and Britain.

In the U.S., General Dynamics has tested it, and SAIC has been contracted to help develop it further. A. Fenner Milton, previously in charge of weapons acquisition for the U.S. Army and now running the army's night-vision lab, attended a test-firing of a Metal Storm prototype in Australia last year. "In my opinion, Metal Storm represents a truly innovative approach to lethality, that if further developed has great potential for defensive weapon systems that can take advantage of its extraordinarily high burst rate of fire," an impressed Milton says.

What seems to surprise most experts about the technology is its source. "It sometimes takes someone who isn't very conventional to come up with new ideas," Drobot observes. "My amazement is at the process—O'Dwyer didn't blow up a barrel or kill himself while making it."

—Dan Drollette in Canberra, Australia

DAN DROLLETTE described how wallabies could replace the lab rat in the October 1997 issue.

AERODYNAMICS

A BUG'S LIFT

The Defense Department is looking for a few good mechanical insects

Who hasn't wanted to be a fly on a wall during a closed-door meeting or even a certain infamous tryst? Now a breakthrough in the understanding of insect flight and fortuitous funding by the U.S. Department of Defense have inched a colorful adage closer to reality.

Not long ago insect flight seemed to defy the conventional laws of aerodynamics. In a typical aircraft the wing's camber (or shape) and its angle of attack create an area of low pressure over the top of the wing—otherwise known as lift. Conventionally speaking, insects can't generate enough lift to stay in the air. And yet they do. In 1994 Charles Ellington, a zoologist at the University of Cambridge, and his colleagues built a large, slow-motion insect model for wind-tunnel tests. Confirming the group's theory, the experiment revealed a microscale vortex sticking to the wing's leading edge during the downstroke. The swirling produced low pressure over the wings, generating copious volumes of lift.

At least as far as bugs go. "We don't know how big you can build a device and still get this effect," Ellington adds. "We suspect it will break down as you get to the size of small birds."

Interesting science but seemingly impractical for flight on a human scale, Ellington's results were published in *Nature* in late 1996. "In the past when someone asked whether understanding insect flight would help us build a better man-made flying machine, we scoffed at the idea," Ellington remarks. "We would say, 'Yes—if you want to build an airplane with a three- to four-inch wingspan.' But that was all before all this interest in micro air vehicles."

Ellington's research came to the attention of the DOD's Defense Advanced Research Projects Agency (DARPA), which had begun a $35-million program to develop micro air vehicles, or MAVs. The concept: equipping soldiers with tiny airplanes and helicopters that carry miniature remote sensing devices to observe enemy troops on their side of the bat-

HARRISON McCLARY

***ARTIFICIAL FLAPPING INSECT** built by Adam Cox and his colleagues at Vanderbilt University draws power through a tether. Such vehicles might fly freely in three years.*

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It may never win a beauty contest, but our bed consistently wins SLEEPING CONTESTS. Contests conducted by thousands of skeptics who *try* it in their own homes, at our risk, for 3 full months. They find out firsthand that Tempur-Pedic's plain, *ultralight* terry cover is *supple* enough to allow billions of viscoelastic MEMORY CELLS inside the bed to work as "molecular springs" (see cut-away photo) conforming *exactly* to their bodies' every curve and angle.

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83% better sleep!

SLEEP-LAB TESTS reveal that our Swedish Sleep System cuts nighttime tossing and turning by an astounding 83%, ensuring a new level of restorative, energizing, *life-changing sleep!*

The viscoelastic Tempur® material inside our beds fights gravity, relieves pressure. It uses your own BODY MASS—and skin temperature—to form a super-resilient, infinitely variable "mold" that *adjusts* to your body's precise shape, position, and weight. A pressureless matrix that's soft and yielding, yet gives you EXTRA-FIRM SUPPORT! Much better support than *any* innerspring, inflatable, foam rubber, or water bed.

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Despite its glovelike "whole-body fit," Tempur material is intrinsically SELF-VENTILATING. Its *microporoscopic* structure promotes efficient heat dissipation—keeping you cool and perspiration-free.

Our bed is *automatically* self-regulating. No need to adjust or inflate anything. Your Tempur-Pedic *never* needs turning or rotating. And there are no switches, motors, or pumps to break down!

Free sample...Free video...Free info!

Right now—at no cost or obligation—we'll send you an eye-opening DEMONSTRATION KIT containing (1) a real lab sample of Tempur material, (2) our *Better Sleep* video, (3) detailed product information, (4) a duty-free Direct Import Price List, and (5) a *3-MONTH IN-HOME TRYOUT* certificate.

Our Swedish scientists, starting where *NASA's* early spacecraft seating experiments ended, *perfected* this unique (patent pending) sleep product. Their achievements have won RAVE REVIEWS FROM THE MEDIA...

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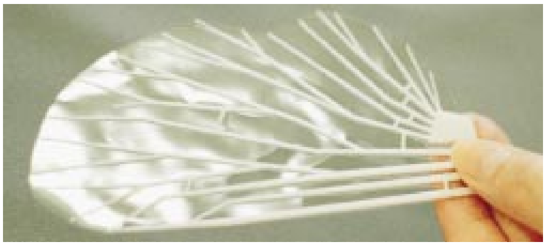


GEORGIA INSTITUTE OF TECHNOLOGY

“ENTOMOPTER” WING developed at Georgia Tech benefited from work on how insects achieve lift.

tlefield. Such flying machines, however small, could not do well in urban combat—in narrow city canyons and inside buildings. They are either too noisy to remain undetected or fly too fast to maneuver in such an environment. But that is not true of insects, which can fly fairly quietly in all directions yet can blast into a wall at full speed and then fly—or crawl—away unscathed.

As part of an overall effort to create such hardy and versatile reconnaissance bugs, last fall DARPA began its Mesoscale Machines for Military Applications program, bestowing $20 million in funding and a three-year deadline on a handful of research institutions across the U.S. Ellington himself is working with a design team at the Georgia Institute of Technology, headed by research engineer Robert Michelson. “We’re still in phase one,” says Michelson, whose team is working to develop the “reciprocating chemical muscle”—a chemical power source—that will energize the wings, navigation and steering instruments, and various payload accessories of his group’s device, called an entomopter, for at least three minutes. Although the team has not yet achieved sustained powered flight, a rubber band–driven model with a 25-centimeter (10-inch) wingspan—a kind of Robomoth—has managed to lift its 50-gram (1.8-ounce) weight into the air for 15 seconds.

Meanwhile Vanderbilt University is home to an effort led by principal investigators Ephrahim Garcia and Michael Goldfarb. Graduate student Adam Cox is nearing sustained tethered flight with his five-gram, 15-centimeter-wingspan artificial insect. Actuators made from piezoelectric material—a ceramic that strains when a voltage is applied to it—flap the insect’s wings. Electric power for the moment arrives from an external source: a lithium battery. An onboard battery would add 15 grams. “With the amounts of lift that we are expecting, we can pretty much tweak it and get the thing to hover by itself autonomously,” Cox explains.

Still, getting the right stroke out of the actuators remains a very high hurdle, as does shrinking the entire machine to real-insect proportions. But the Vanderbilt and Georgia Tech teams are optimistic that they can bring their bugs to life. “By the end of the three years we’ll have it flying in stable, trimmed flight,” says a confident Ellington. “I’ll be able to walk out of my office and toss it down the hallway and have it fly away.” *—Phil Scott*

PHIL SCOTT, a New York City–based writer, described space construction tools in last month’s issue.

OPTICS

Japan Fields a Big-League Light Gatherer

On January 28 the National Astronomical Observatory of Japan exhibited the “first light” snapshots from Subaru, a new, world-class optical and infrared telescope built atop Mauna Kea, the 4,205-meter (13,796-foot) dormant volcano on Hawaii’s Big Island. Subaru joins about a dozen telescopes with mirrors that measure at least eight meters in diameter that are achieving first light through the turn of the century. These giant light-collecting machines include another Mauna Kea resident, the Gemini North Observatory, backed by the U.S. and six other nations, which is nearing its own first-light images [see “A New Eye Opens on the Cosmos,” on page 104].

Subaru, the Japanese word for the Pleiades star cluster, boasts the planet’s largest single-piece mirror, an 8.3-meter-diameter wonder (others are larger but consist of separate pieces). Shaped like a contact lens, the 20-centimeter-thick meniscus mirror maintains its shape via 261 computer-controlled supports that continually adjust the surface to prevent flexing or sagging. The instrument, which marks Japan’s entrance into big-time infrared and optical astronomy, is the most expensive ground-based telescope ever built. The telescope, eight years in construction, cost some $350 million—and took the lives of three workers, who died in a fire in the dome in 1996.

The first targets imaged were planets, star clusters, quasars and the ever popular Orion nebula. The photographs already compare favorably with those from some of the best ground-based telescopes. Once scientists deploy systems to nullify image-degrading atmospheric turbulence, Subaru could prove superior at near-infrared wavelengths even to the Hubble Space Telescope. *—Gary Stix on Mauna Kea*

SUBARU LOOKS SKYWARD through the observatory dome.

ORION NEBULA, a star-forming region, is captured by Subaru.

PHOTOGRAPHS COURTESY OF SUBARU TELESCOPE, NATIONAL ASTRONOMICAL OBSERVATORY OF JAPAN

CYBER VIEW

Watch the Watchers

Purchase a top-of-the-line desktop computer today, and odds are that it will contain Intel's new Pentium III microprocessor. If so, then the first time you boot it, the machine may present you with a puzzling choice. In essence, the beast will say: *I have a name—a unique serial number—etched indelibly into my circuitry. By default, I will always keep this name a secret. However, if you check this box here, I will show my ID to programs that ask for it, and some of those programs may, with your permission, pass the number along to Web sites that you visit. Which option do you choose?*

Anonymity or a traceable name? Private Web surfing or myriad records scattered around the Internet noting what you—or rather whoever was using your machine—looked at and clicked on? The choice might seem like no choice at all. Even offering it, privacy pressure groups have argued, borders on the criminal. On-line anonymity is such an obvious and fundamental good, they imply, that there should be no way so convenient and reliable to reveal one's identity. In February watchdog groups launched a boycott of Intel's products to force the company to make computer chips that are once again indistinguishable.

The boycott will almost certainly fail to change Intel's chips, but the brouhaha surrounding it may well succeed in persuading most Pentium III owners to keep their machines unidentifiable. If so, the cause of secrecy and anonymity, so widely accepted on the Net as the best strategy to prevent the misuse of private information by corporations and governments, will advance another step.

But before reflexively retreating behind cloak and shadow, it is worth considering where those steps lead and whether there might be a less hazardous way for us to protect ourselves from information abuse. In his recent book, *The Transparent Society* (Addison-Wesley, 1998), David Brin points out that attempts to win freedom by evading the eyes of the powerful have usually failed, for two reasons.

First, the rich and mighty always have better surveillance technology and more of it. Most Web services already record the Internet addresses of all visitors; many others will tag your machine with a so-called cookie, unless you expressly forbid it, so that they can recognize you when you return. If companies want to share their cookie jars with one another—or if Microsoft decides to attach your Windows serial number to every Web page request your browser sends out—they have the right to try. By hook or by crook, some Web servers will soon be able to make a good guess at who you are even if you have never visited that site before.

Banning chip IDs will not delay this day for long, Brin asserts. "We are talking about an entire *class* of information—and one of the easiest to conceal," he says. "Identifiers are small, simple and can be embedded in myriad ways—in any piece of software that you buy, for instance. Programmers have for many years put [such undocumented] 'trap doors' in their code." A big secret can render a little one irrelevant.

Hence the second way in which blindness can backfire: easy anonymity raises temptation and provides cover for those who have power to abuse. The same mask that lets you skulk unrecognized through the red-light districts of cyberspace can be worn by some bandit as he uses a bogus storefront to snatch your credit-card number with impunity. If executives at the tobacco companies had communicated via encrypted messages sent through anonymizing mail servers instead of by signed memoranda, would their deceit ever have been exposed?

DAVID SUTER

Accountability and privacy are both relatively new inventions; villagers three centuries ago knew little of either. But of the two, accountability is much more precious, and it is hard to enforce when a large swath of public life is shrouded in secrecy.

Privacy laws and encryption, used sparingly, can help protect against violations that cause real harm. But they should not become an automatic response to vague threats. You don't don a balaclava before going to the mall, even though you are under constant video surveillance as you walk through the stores, and a nosy neighbor might spot you in Victoria's Secret fingering lingerie two sizes too small for your spouse. You do, however, show the clerk at the mall your driver's license when you pay by check, and the numeric name of your Pentium III could serve a similar purpose, adding to your password some assurance—not proof—that you are not an impostor. A chip ID for computers is no more foolproof and hardly more threatening than caller-ID is for telephones. Both identify devices, not people; both can be disabled easily. And both could be used to develop, with time and some difficulty, a directory linking people with their machines. Of course, the phone book was around long before caller-ID.

Instead of pressing for a ban on chip IDs, Brin argues, privacy advocates should urge Intel to disclose details of its design so that they can search for other, secret identifiers. "Another nice bit of reciprocal transparency would be to require that anyone who queries the identifier must give a receipt that includes their own identifier," he suggests. That way Victoria's Secret Online Shop could track down those who give it stolen credit-card numbers, just as you could nab a bandit who steals yours.

The World Wide Web Consortium has been working on a Platform for Privacy Preferences Project that, when complete, will provide a way for Web surfers to negotiate what information they are willing to share with Web sites. Once the platform is in place, Web services will be able to send new visitors a proposal: a request for particular personal data in exchange for access and certain binding promises—enforced by auditing firms—about how the data will be used. Swapping processor names could help seal such an exchange and move us one step closer to a society based on well-informed trust rather than blind suspicion.

—W. Wayt Gibbs in San Francisco

SPECIAL REPORT

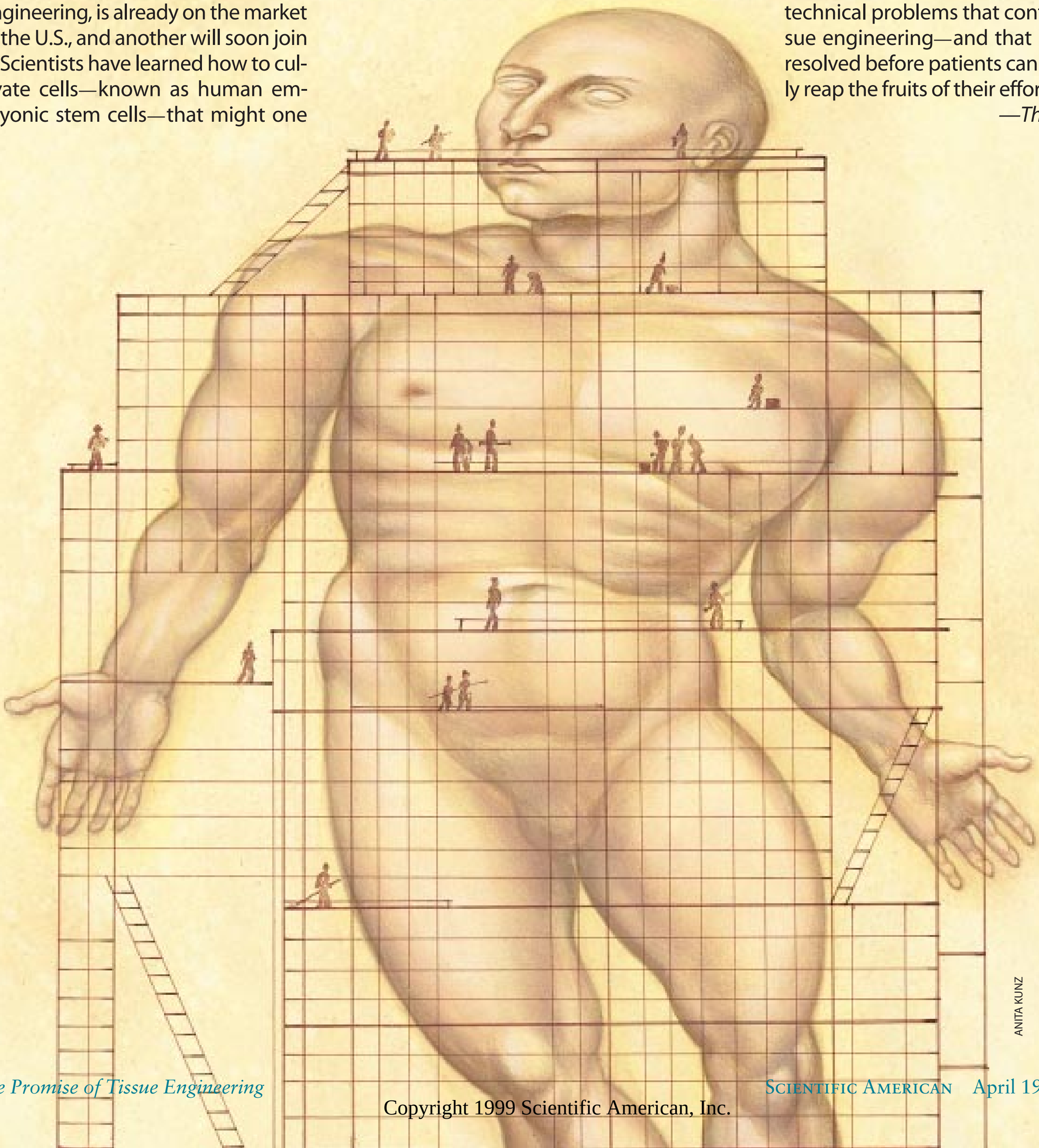
The Promise of TISSUE ENGINEERING

Imagine a day when people with liver failure can be cured with implanted "neo-organs" made of liver cells and plastic fibers; when insulin-dependent diabetics can forgo their frequent insulin injections because they have semisynthetic replacement pancreases; when kidney dialysis machines are obsolete because anyone with damaged kidneys can be outfitted with new ones grown from their very own cells. Sound like science fiction?

Not to scientists working in tissue engineering, a field of science that is barely a decade old. One form of man-made skin, the first commercial product of tissue engineering, is already on the market in the U.S., and another will soon join it. Scientists have learned how to cultivate cells—known as human embryonic stem cells—that might one day allow researchers to build custom-made organs on demand. Tiny tubes containing cells that secrete painkilling substances have been implanted into the spinal columns of people with chronic pain. And tissue-engineered cartilage is in clinical tests and is expected to be commercially available within the next few years.

In the following special report, some of the leading scientists in tissue engineering outline the current successes of their young research field and sketch a "brave new world" in which people need not die for lack of spare parts. They also take a hard look at some of the ethical and technical problems that confront tissue engineering—and that must be resolved before patients can routinely reap the fruits of their efforts.

—*The Editors*



ANITA KUNZ

GROWING NEW

Researchers have taken the first steps toward creating semisynthetic, living organs that can be used as human replacement parts

by David J. Mooney and Antonios G. Mikos

Every day thousands of people of all ages are admitted to hospitals because of the malfunction of some vital organ. Because of a dearth of transplantable organs, many of these people will die. In perhaps the most dramatic example, the American Heart Association reports only 2,300 of the 40,000 Americans who needed a new heart in 1997 got one. Lifesaving livers and kidneys likewise are scarce, as is skin for burn victims and others with wounds that fail to heal. It can sometimes be easier to repair a damaged automobile than the vehicle's driver because the former may be rebuilt using spare parts, a luxury that human beings simply have not enjoyed.

It is theoretically possible to engineer organs such as livers, kidneys, breasts and intestines.

An exciting new strategy, however, is poised to revolutionize the treatment of patients who need new vital structures: the creation of man-made tissues or organs, known as neo-organs. In one scenario, a tissue engineer injects or places a given molecule, such as a growth factor, into a wound or an organ that requires regeneration. These molecules cause the patient's own cells to migrate into the wound site, turn into the right type of cell and regenerate the tissue. In the second, and more ambitious, procedure, the patient receives cells—either his or her own or those of a donor—that have been harvested previously and incorporated into three-dimensional scaffolds of biodegradable polymers, such as those used to make dissolvable sutures. The entire structure of cells and scaffolding is transplanted into the wound site, where the cells replicate, reorganize and form new tissue. At the same time, the artificial polymers break down, leaving only a completely natural final product in the body—a neo-organ. The creation of neo-organs applies the basic knowledge gained in biology over the past few decades to the problems of tissue and organ reconstruction, just as advances in materials science make possible entirely new types of architectural design.

Science-fiction fans are often confronted with the concept of tissue engineering. Various television programs and movies have pictured individual organs or whole people (or aliens) growing from a few isolated cells in a vat of some powerful nutrient. Tissue engineering does not yet rival these fictional presentations, but a glimpse of the future has already arrived. The creation of tissue for medical use is already a fact, to a limited extent, in hospitals across the U.S. These groundbreaking applications involve fabricated skin, cartilage, bone, ligament and tendon and make musings of "off-the-shelf" whole organs seem less than far-fetched.

Indeed, evidence abounds that it is at least theoretically possible to engineer large, complex organs such as livers, kidneys, breasts, bladders and intestines, all of which include many different kinds of cells. The proof can be found in any expectant mother's womb, where a small group of undifferentiated cells finds the way to develop into a complex individual with multiple organs and tissues with vastly different properties and functions. Barring any unforeseen impediments, teasing out the details of the process by which a liver becomes a liver, or a lung a lung, will eventually allow researchers to replicate that process.

A Pinch of Protein

Cells behave in predictable ways when exposed to particular biochemical factors. In the simpler technique for growing new tissue, the engineer exposes a wound or damaged organ to factors that act as proponents of healing or regeneration. This concept is based on two key observations, in bones and in blood vessels.

In 1965 Marshall R. Urist of the University of California at Los Angeles demonstrated that new,

ORGANS

bony tissue would form in animals that received implants of powdered bone. His observation led to the isolation of the specific proteins (the bone morphogenetic proteins, or BMPs) responsible for this activity and the determination of the DNA sequences of the relevant genes. A number of companies subsequently began to produce large quantities of recombinant human BMPs; the genes coding for BMPs were inserted into mammalian cell lines that then produced the proteins.

Various clinical trials are under way to test the ability of these bone growth promoters to regenerate bony tissue. Applications of this approach that are currently being tested include healing acute bone fractures caused by accidents and boosting the regeneration of diseased periodontal tissues. Creative BioMolecules in Hopkinton, Mass., recently completed clinical trials showing that BMP-7 does indeed help heal severe bone fractures. This trial followed 122 patients with leg fractures in which the sections failed to rejoin after nine months. Patients whose healing was encouraged by BMP-7 did as well as those who received a surgical graft of bone harvested from another part of their body.

A critical challenge in engineering neo-organs is feeding every cell. Tissues more than a few millimeters thick require blood vessels to grow into them and supply nutrients. Fortunately, investigations by Judah Folkman have shown that cells already in the body can be coaxed into producing new blood vessels. Folkman, a cancer researcher at Harvard Medical School's Children's Hospital, recognized this possibility almost three decades ago in studies aimed, ironically, at the prevention of cellular growth in the form of cancerous tumors.

Folkman perceived that developing tumors need to grow their own blood vessels to supply themselves with nutrients. In 1972 he proposed that specific molecules could be used to inhibit such vessel growth, or angiogenesis, and perhaps starve tumors. (This avenue of attack against cancer became a major news story in 1998.) Realizing that other molecules would undoubtedly abet angiogenesis, he and others

GRANT JERDING

Human body may be more than a sum of parts, but replacing failing parts should extend and improve life.

have subsequently identified a number of factors in each category.

That work is now being exploited by tissue engineers. Many angiogenesis-stimulating molecules are commercially available in recombinant form, and animal studies have shown that such molecules promote the growth of new blood vessels that bypass blockages in, for example, the coronary artery. Small-scale trials are also under way to test this approach in the treatment of similar conditions in human subjects.

Scientists must surmount a few obstacles, however, before drugs that promote tissue and organ formation become commonplace. To date, only the factors responsible for bone and blood vessel growth have been characterized. To regenerate other organs, such as a liver, for example, the specific molecules for their development must be identified and produced reliably.

An additional, practical issue is how best to administer the substances that would shape organ regeneration. Researchers must answer these questions: What specific concentrations of the molecules are needed for the desired effect? How long should the cells be exposed? How long will the factors be active in the body? Certainly multiple factors will be needed for complex organs, but when exactly in the development of the organ does one factor need to replace another? Controlled drug-delivery technology such as transdermal patches developed by the pharmaceutical industry will surely aid efforts to resolve these concerns.

Synthetic polymer scaffold in the shape of a nose (*left*) is "seeded" with cells called chondrocytes that replace the polymer with cartilage over time (*right*) to make a suitable implant.

PRASAD SHASTRI AND IVAN MARTIN *Massachusetts Institute of Technology*

In particular, injectable polymers may facilitate the delivery of bioactive molecules where they are needed, with minimal surgical intervention. Michael J. Yaszemski of the Mayo Clinic, Alan W. Yasko of the M. D. Anderson Cancer Center in Houston and one of us (Mikos) are developing new injectable biodegradable polymers for orthopedic applications. The polymers are moldable, so they can fill irregularly shaped defects, and they harden in 10 to 15 minutes to provide the reconstructed skeletal region with mechanical properties similar to those of the bone they replace. These polymers subsequently degrade in a controlled fashion, over a period of weeks to months, and newly grown bone fills the site.

We have also been studying the potential of injectable, biodegradable hydrogels—gelatinlike, water-filled polymers—for treating dental defects, such as poor bonding between teeth and the underlying bone, through guided bone regeneration. The hydrogels incorporate molecules that both modulate cellular function and induce bone formation; they provide a scaffold on which new bone can grow, and they minimize the formation of scar tissue within the regenerated region.

An intriguing variation of more conventional drug delivery has been pioneered by Jeffrey F. Bonadio, Steven A. Goldstein and their co-workers at the University of Michigan. (Bonadio is now at Selective Genetics in San Diego.) Their approach combines the concepts of gene therapy and tissue engineering. Instead of administering growth factors directly, they insert genes that encode those molecules. The genes are part of a plasmid, a circular piece of DNA constructed for this purpose. The surrounding cells take up the DNA and treat it as their own. They turn into tiny factories, churning out the factors coded for by the plasmid. Because the inserted DNA is free-floating, rather than incorporated into the cells' own DNA, it eventually degrades and the product ceases to be synthesized. Plasmid inserts have successfully promoted bone regrowth in animals; the duration of their effects is still being investigated.

One of us (Mooney), along with Lonnie D. Shea and our other aforementioned Michigan colleagues, recently demonstrated with animals that three-dimensional biodegradable polymers spiked with plasmids will release that DNA over extended periods and simultaneously serve as a scaffold for new tissue formation. The DNA finds its way into adjacent cells as they migrate into the polymer scaffold. The cells then express the desired proteins. This technique makes it possible to control tissue formation more precisely; physicians might one day be able to manage the dose and time course of molecule production by the cells that take up the DNA and deliver multiple genes at various times to promote tissue formation in stages.

A Dash of Cells

Promoting tissue and organ development via growth factors is obviously a considerable step forward. But it pales in comparison to the ultimate goal of the tissue engineer: the creation from scratch of whole neo-organs. Science fiction's conception of prefabricated "spare parts" is slowly taking shape in the efforts to transplant cells directly to the body that will then develop into the proper bodily component. The best way to sprout organs and tissues is still to rely on the body's own biochemical wisdom; the appropriate cells are transferred, in a three-dimensional matrix, to the desired site, and growth unfolds within the person or organism rather than in an external, artificial environment. This approach, pioneered by Ioannis V. Yannas, Eugene Bell and Robert S. Langer of the Massachusetts Institute of Technology, Joseph P. Vacanti of Harvard Medical School and others in the 1970s and 1980s, is now actually in use in some patients, notably those with skin wounds or cartilage damage.

The usual procedure entails the multiplication of isolated cells in culture. These cells are then used to seed a matrix, typically one consisting of synthetic polymers or collagen, the protein that forms the natural support scaffolding of most tissues. In addition to merely delivering the cells, the matrix both creates and maintains a space for the formation of the tissue and guides its structural development. Once the developmental rules for a given organ or tissue are fully known, any of those entities could theoretically be grown from a small sample of starter cells. (A sufficient understanding of the developmental pathways should eventually allow the transfer of this procedure from the body to the laboratory, making true off-the-shelf organs possible. A surgeon could implant these immediately in an emergency situation—an appealing notion, because failing organs can quickly lead to death—instead of waiting weeks or months to grow a new organ in the laboratory or to use growth factors to induce the patient's own body to grow the tissues.)

Sufficient knowledge of how organs naturally develop should eventually make true "off-the-shelf" organs a reality.

In the case of skin, the future is here. The U.S. Food and Drug Administration has already approved a living skin product—and others are now in the regulatory pipeline. The need for skin is acute: every year 600,000 Americans suffer from diabetic ulcers, which are particularly difficult to heal; another 600,000 have skin removed to treat skin cancer; and between 10,000 and 15,000 undergo skin grafts to treat severe burns.

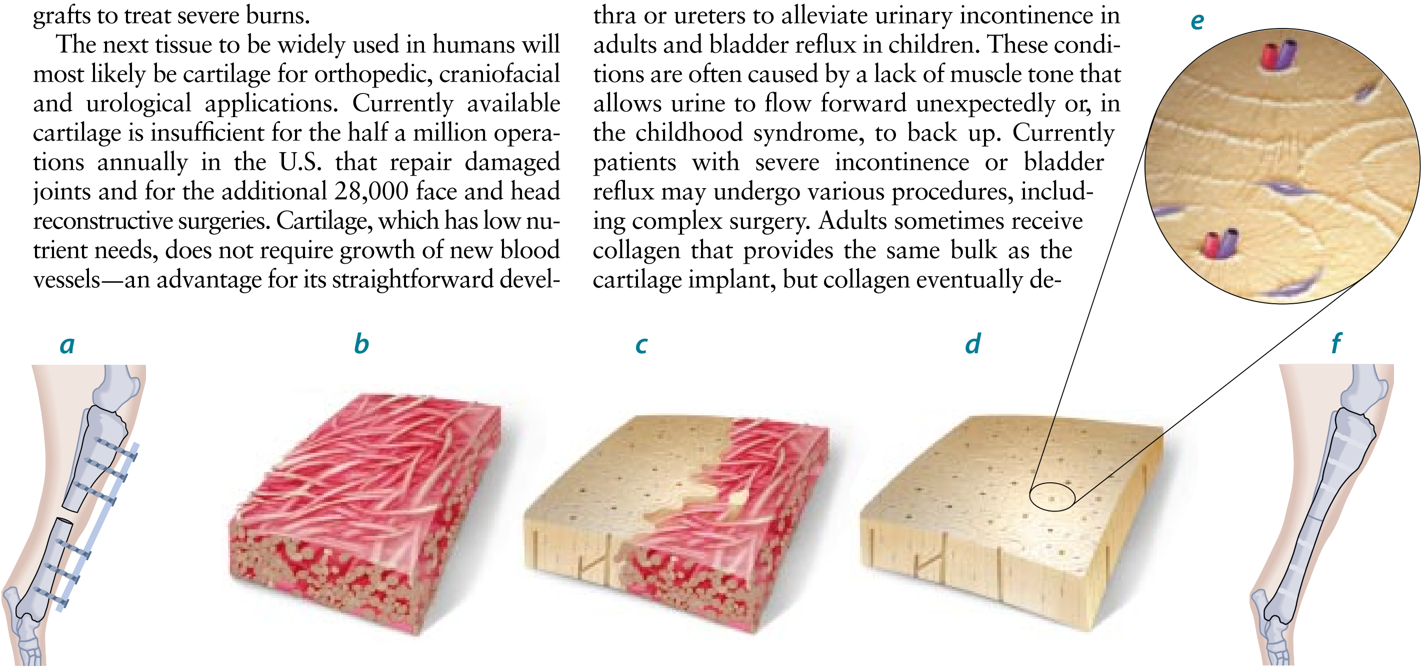
The next tissue to be widely used in humans will most likely be cartilage for orthopedic, craniofacial and urological applications. Currently available cartilage is insufficient for the half a million operations annually in the U.S. that repair damaged joints and for the additional 28,000 face and head reconstructive surgeries. Cartilage, which has low nutrient needs, does not require growth of new blood vessels—an advantage for its straightforward development as an engineered tissue.

Genzyme Tissue Repair in Cambridge, Mass., has received FDA approval to engineer tissues derived from a patient's own cells for the repair of traumatic knee-cartilage damage. Its procedure involves growing the patient's cells in the lab, harvested from the same knee under repair when possible, and then implanting those cells into the injury. Depending on the patient and the extent of the defect, full regeneration takes between 12 and 18 months. In animal studies, Charles A. Vacanti of the University of Massachusetts Medical School in Worcester, his brother, Joseph Vacanti, Langer and their colleagues have shown that new cartilage can be grown in the shapes of ears, noses and other recognizable forms.


ADVANCED TISSUE SCIENCES, INC.

Cartilaginous ear awaits a useful incarnation as a replacement body part. An ear-shaped polymer mold enabled researchers to produce the "bioartificial" structure.

The relative ease of growing cartilage has led Anthony J. Atala of Harvard Medical School's Children's Hospital to develop a novel approach for treating urological disorders such as incontinence. Reprogenesis in Cambridge, Mass., which supports Atala's research, is testing whether cartilage cells can be removed from patients, multiplied in the laboratory and used to add bulk to the urethra or ureters to alleviate urinary incontinence in adults and bladder reflux in children. These conditions are often caused by a lack of muscle tone that allows urine to flow forward unexpectedly or, in the childhood syndrome, to back up. Currently patients with severe incontinence or bladder reflux may undergo various procedures, including complex surgery. Adults sometimes receive collagen that provides the same bulk as the cartilage implant, but collagen eventually de-



LAURIE GRACE (*a* and *f*); KEITH KASNOT (*b–e*)

New bone grows to fill a space between two bone segments. A dog leg bone with a missing section is held in place with braces (*a*). A polymer scaffold primed with bone growth–promoting proteins (*b*) fills in the gap. The scaffold is slowly infiltrated by new bone (*c*) and ultimately gets completely replaced (*d*). The cells (*e*) have their own blood supply (*red and blue vessels*). The leg bone has healed (*f*).

grades. The new approach involves minimally invasive surgery to deliver the cells and grow the new tissue.

Walter D. Holder, Jr., and Craig R. Halberstadt of Carolinas Medical Center in Charlotte, N.C., and one of us (Mooney) have begun to apply such general tissue-engineering concepts to a major women's health issue. We are attempting to use tissue from the legs or buttocks to grow new breast tissue, to replace that removed in mastectomies or lumpectomies. We propose to take a biopsy of the patient's tissue, isolate cells from this biopsy and multiply these cells outside the body. The woman's own cells would then be returned to her in a biodegradable polymer matrix. Back in the body, cell growth and the deterioration of the matrix would lead to the formation of completely new, natural tissue. This process would create only a soft-tissue mass, not the complex system of numerous cell types that makes up a true breast. Nevertheless, it could provide an alternative to current breast prostheses or implants.

Skin, bone and cartilage are the first success stories. The holy grail of tissue engineering remains complete internal organs.

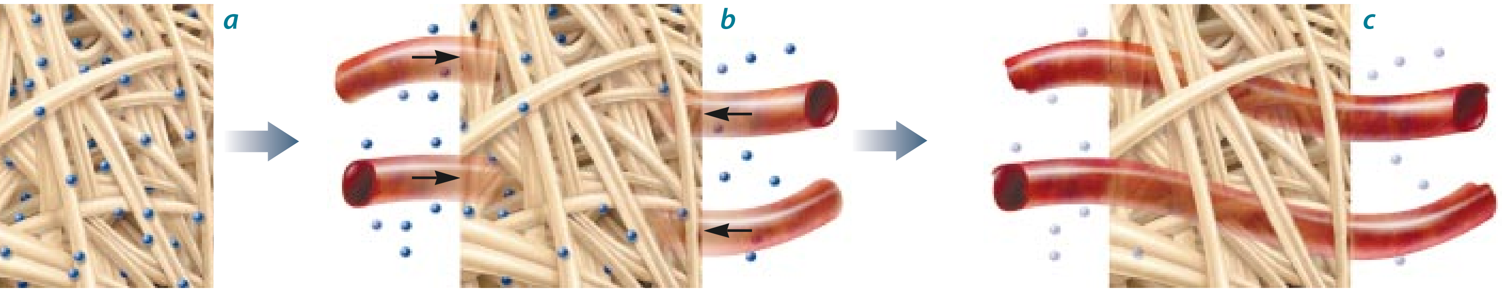
Optimism for the growth of large neo-organs of one or more cell types has been fueled by success in several animal models of human diseases. Mikos recently demonstrated that new bone tissue can be grown by transplanting cells taken from bone marrow and growing them on biodegradable polymers. Transplantation of cells to skeletal defects makes it possible for cells to produce factors locally, thus offering a new means of delivery for growth-promoting drugs.

Recipes for the Future

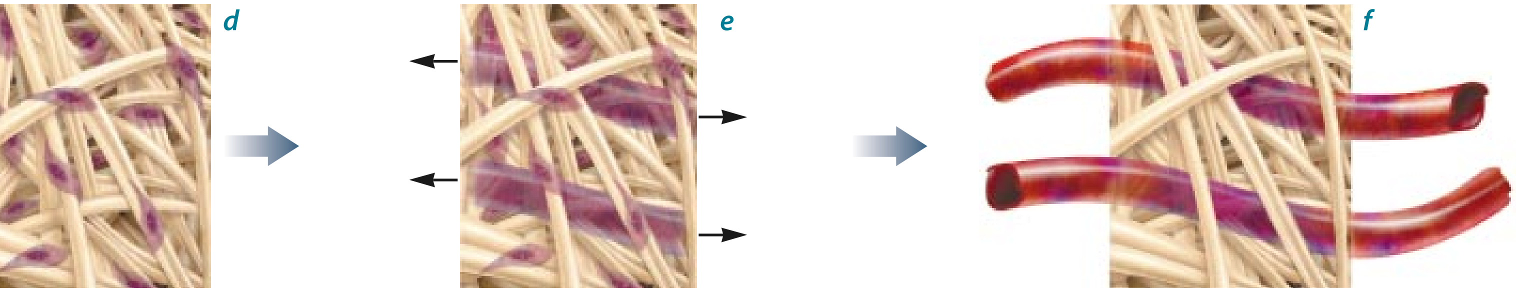
In any system, size imposes new demands. As previously noted, tissues of any substantial size need a blood supply. To address that requirement, engineers may need to transplant the right cell types together with drugs that spur angiogenesis. Molecules that promote blood vessel growth could be included in the polymers used as transplant scaffolds. Alternatively, we and others have proposed that it may be possible to create a blood vessel network within an engineered organ prior to transplantation by incorporating cells that will become blood vessels within the scaffold matrix. Such engineered blood vessels would then need only to connect to surrounding vessels for the engineered tissue to develop a blood supply.

In collaboration with Peter J. Polverini of Michigan, Mooney has shown that transplanted blood vessel cells will indeed form such connections and that the new vessels are a blend of both implanted and host cells. But this technique might not work when transplanting engineered tissue into a site where blood vessels have been damaged by cancer

VESSEL INGROWTH VIA GROWTH FACTORS



VESSEL OUTGROWTH VIA CELL IMPLANTS



KEITH KASNOT

Vascularization of new tissue can be accomplished in two ways. Vessels from the surrounding tissue can be induced to infiltrate the tissue. Such vessel growth is promoted by including growth factors (*blue dots*) in the polymer scaffold of the insert (*a*). These factors diffuse into the local environment, where they encourage existing blood vessels to grow into the polymer (*b*). Ultimately, cells growing in from both sides knit together to form a continuous vessel (*c*). Vessels may also grow from within a polymer scaffold if that scaffold is seeded (*d*) with endothelial cells (*purple*). The cells will proliferate within the polymer and grow outward toward the natural tissue (*e*). These new vessels combine with existing blood vessels (*red*) to create a continuous vessel (*f*).

therapy or trauma. In such situations, it may be necessary to propagate the tissue first at another site in the body where blood vessels can more readily grow into the new structure. Mikos collaborates with Michael J. Miller of the M. D. Anderson Cancer Center to fabricate vascularized bone for reconstructive surgery using this approach. A jawbone, for instance, could be grown connected to a well-vascularized hipbone for an oral cancer patient who has received radiation treatments around the mouth that damaged the blood supply to the jawbone.

On another front, engineered tissues typically use biomaterials, such as collagen, that are available from nature or that can be adapted from other biomedical uses. We and others, however, are developing new biodegradable, polymeric materials specific to this task. These materials may accurately determine the size and shape of an engineered tissue, precisely control the function of cells in contact with the material and degrade at rates that optimize tissue formation.

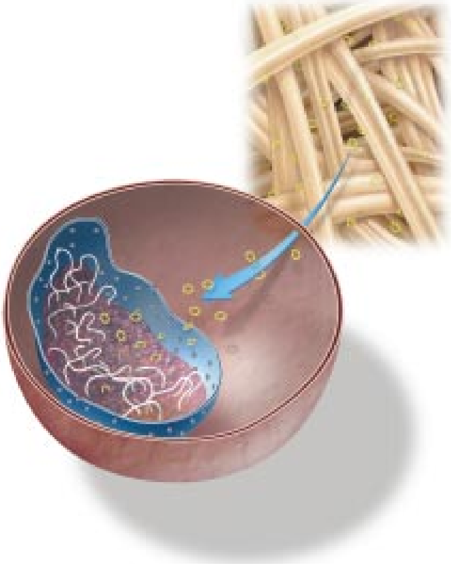
Structural tissues, such as skin, bone and cartilage, will most likely continue to dominate the first wave of success stories, thanks to their relative simplicity. The holy grail of tissue engineering, of course, remains complete internal organs. The liver, for example, performs many chemical reactions critical to life, and more than 30,000 people die every year because of liver failure. It has been recognized since at least the time of the ancient Greek legend of Prometheus that the liver has the unique potential to regenerate partially after injury, and tissue engineers are now trying to exploit this property of liver cells.

A number of investigators, including Joseph Vacanti and Achilles A. Demetriou of Cedars-Sinai Medical Center in Los Angeles, have demonstrated that new liverlike tissues can be created in animals from transplanted liver cells. We have developed new biomaterials for growing liverlike tissues and shown that delivering drugs to transplanted liver cells can increase their growth. The new tissues grown in all these studies can replace single chemical functions of the liver in animals, but the entire function of the organ has not yet been replicated.

H. David Humes of Michigan and Atala are using kidney cells to make neo-organs that possess the filtering capability of the kidney. In addition, recent animal studies by Joseph Vacanti's group have demonstrated that intestine can be grown—within the abdominal cavity—and then spliced into existing intestinal tissue. Human versions of these neointestines could be a boon to patients suffering from short-bowel syndrome, a condition caused by birth defects or trauma. This syndrome affects overall physical development because of digestion problems and subsequent insufficient nutrient intake. The only available treatment is an intestinal transplant, although few patients actually get one, again because of the extreme shortage of donated organs. Recently Atala has also demonstrated in animals that a complete bladder can be formed with this approach and used to replace the native bladder.

Even the heart is a target for regrowth. A group of scientists headed by Michael V. Sefton at the University of Toronto recently began an ambitious project to grow new hearts for the multitude of people who die from heart failure every year. It will very likely take scientists 10 to 20 years to learn how to grow an entire heart, but tissues such as heart valves and blood vessels may be available sooner. Indeed, several companies, including Advanced Tissue Sciences in La Jolla, Calif., and Organogenesis in Canton, Mass., are attempting to develop commercial processes for growing these tissues.

Prediction, especially in medicine, is fraught with peril. A safe way to prophesy the future of tissue engineering, however, may be to weigh how surprised workers in the field would be after being told of a particular hypothetical advance. Tell us that completely functional skin constructs will be available for most medical uses within five years, and we would consider that reasonable. Inform us that fully functional, implantable livers will be here in five years, and we would be quite incredulous. But tell us that this same liver will be here in, say, 30 years, and we might nod our heads in sanguine acceptance—it sounds possible. Ten millennia ago the development of agriculture freed humanity from a reliance on whatever sustenance nature was kind enough to provide. The development of tissue engineering should provide an analogous freedom from the limitations of the human body. SA


KEITH KASNOT

Plasmids, circlets of DNA (*yellow*), find their way from a polymer scaffold to a nearby cell in the body, where they serve as the blueprints for making desirable proteins. Adding the proteins themselves would be less effective because the proteins tend to degrade much faster than the plasmids do. Researchers attempting to use growth promoters in tissue engineering may thus find it more reliable to insert plasmids than the proteins they encode.

The Authors

DAVID J. MOONEY and ANTONIOS G. MIKOS have collaborated for eight years. Mooney has been on the faculty at the University of Michigan since 1994, where he is associate professor of biologic and materials sciences and of chemical engineering. He studies how cells respond to external biochemical and mechanical signals and designs and synthesizes polymer scaffolds used in tissue engineering. Mikos is associate professor of bioengineering and of chemical engineering at Rice University. Mikos's research focuses on the synthesis, processing and evaluation of new biomaterials for tissue engineering, including those useful for scaffolds, and on nonviral vectors for gene therapy.

Further Reading

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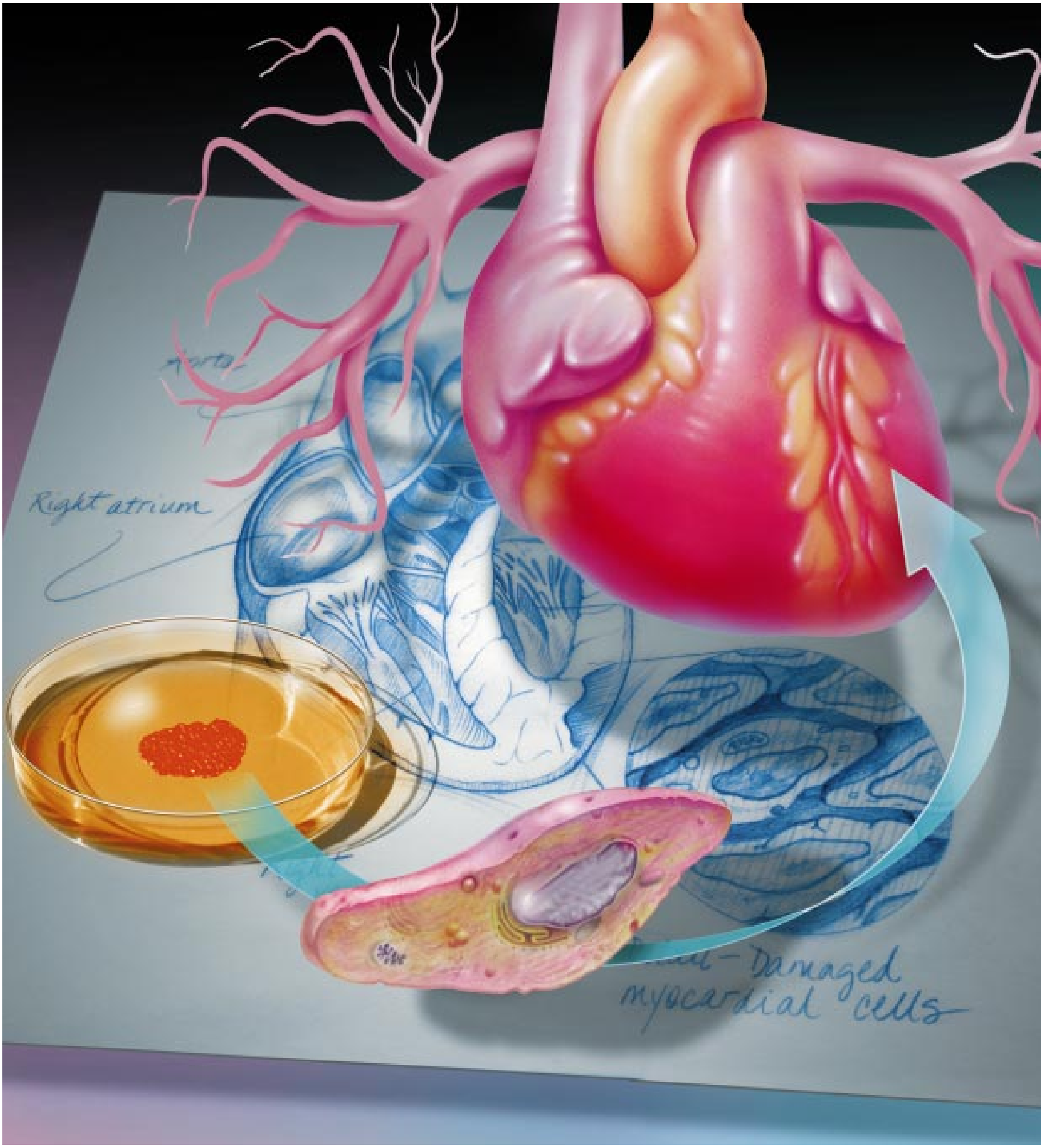
EMBRYONIC STEM

Cells able to generate virtually all other cell types have recently been isolated. One day they could help repair a wide variety of damaged tissues



Cultured cells derived from early human embryos may eventually be coaxed to develop into replacement tissue for damaged organs, such as the heart.

CYNTHIA TURNER

CELLS for MEDICINE

by Roger A. Pedersen

Your friend has suffered a serious heart attack while hiking in a remote region of a national park. By the time he reaches a hospital, only one third of his heart is still working, and he seems unlikely to return to his formerly active life. Always the adventurer, though, he volunteers for an experimental treatment. He provides a small sample of skin cells. Technicians remove the genetic material from the cells and inject it into donated human eggs from which the chromosomes have been removed. These altered eggs are grown for a week in a laboratory, where they develop into early-stage embryos. The embryos yield cells that can be cultured to produce what are called embryonic stem cells. Such cells are able to form heart muscle cells, as well as other cell types.

The medical team therefore establishes a culture of embryonic stem cells and grows them under conditions that induce them to begin developing into heart cells. Being a perfect genetic match for your friend, these cells can be transplanted into his heart without causing his immune system to reject them. They grow and replace cells lost during the heart attack, returning him to health and strength.

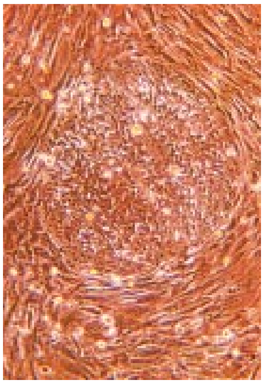
This scenario is for now hypothetical, but it is not far-fetched. Researchers already know of various types of stem cells. These are not themselves specialized to carry out the unique functions of particular organs, such as the heart, the liver or the brain. But when stem cells divide, some of the progeny "differentiate"—they undergo changes that commit them to mature into cells of specific types. Other progeny remain as stem cells. Thus, intestinal stem cells continually regenerate the lining of the gut, skin stem cells make skin, and hematopoietic stem cells give rise to the range of cells found in blood. Stem cells enable our bodies to repair everyday wear and tear.

Embryonic stem cells are even more extraordinary: they can give rise to essentially all cell types in the body. Human embryonic stem cells were first grown in culture just last year. In February 1998 James A. Thomson of the University of Wisconsin found the first candidates when he noted that certain human cells plucked from a group growing in culture resembled embryonic stem cells that he had earlier derived from rhesus monkey embryos. A thousand miles away in Baltimore, John D. Gearhart of Johns Hopkins University was isolating similar cells by culturing fragments of human fetal ovaries and testes. And in California, researchers at Geron Corporation in Menlo Park and in my laboratory at the University of California at San Francisco were carrying out related studies.

But Thomson was well served by his previous experience with embryonic stem cells of rhesus monkeys and marmosets, which—like humans—are primates. In the following months he pulled ahead of the rest of us in the difficult task of inducing the fragile human cells to grow in culture, and he confirmed that they were indeed embryonic stem cells.

Far-reaching Potential

In studies reported in the November 6, 1998, issue of *Science,* Thomson demonstrated that the human cells formed a wide variety of recognizable tissues when transplanted under the skin of mice. Discussing his results before an inquisitive subcommittee of the U.S. Senate, Thomson described how the cells gave rise to tissue like that lining the gut as well as to cartilage, bone, muscle and neural epithelium (precursor tissue of the nervous system), among other types. What is more, descendants of all three fundamental body layers of a mammalian embryo were represented. Some normally derive from the outermost layer (the ectoderm), others from the innermost or middle layers (the endoderm or mesoderm). This variety offered further evidence of the cells' developmental flexibility. Such results encourage hope that research on embryonic stem cells will ultimately lead to techniques for generating cells that can be employed in therapies, not just for heart attacks, but for many conditions in which tissue is damaged.


JAMES A. THOMSON *University of Wisconsin*

Human embryonic stem cells growing in culture (*central clump*) are maintained on a layer of mouse "feeder" cells (*background*).

If it were possible to control the differentiation of human embryonic stem cells in culture, the resulting cells could potentially help repair damage caused by congestive heart failure, Parkinson's disease, diabetes and other afflictions. They could prove especially valuable for treating conditions affecting the heart and the islets of the pancreas, which retain few or no stem cells in an adult and so cannot renew themselves naturally. One recent finding hints that researchers might eventually learn how to modify stem cells that have already partly differentiated so as to change the course of their development.

First, though, investigators will have to learn

YORGOS NIKAS *Hammersmith Hospital, London*

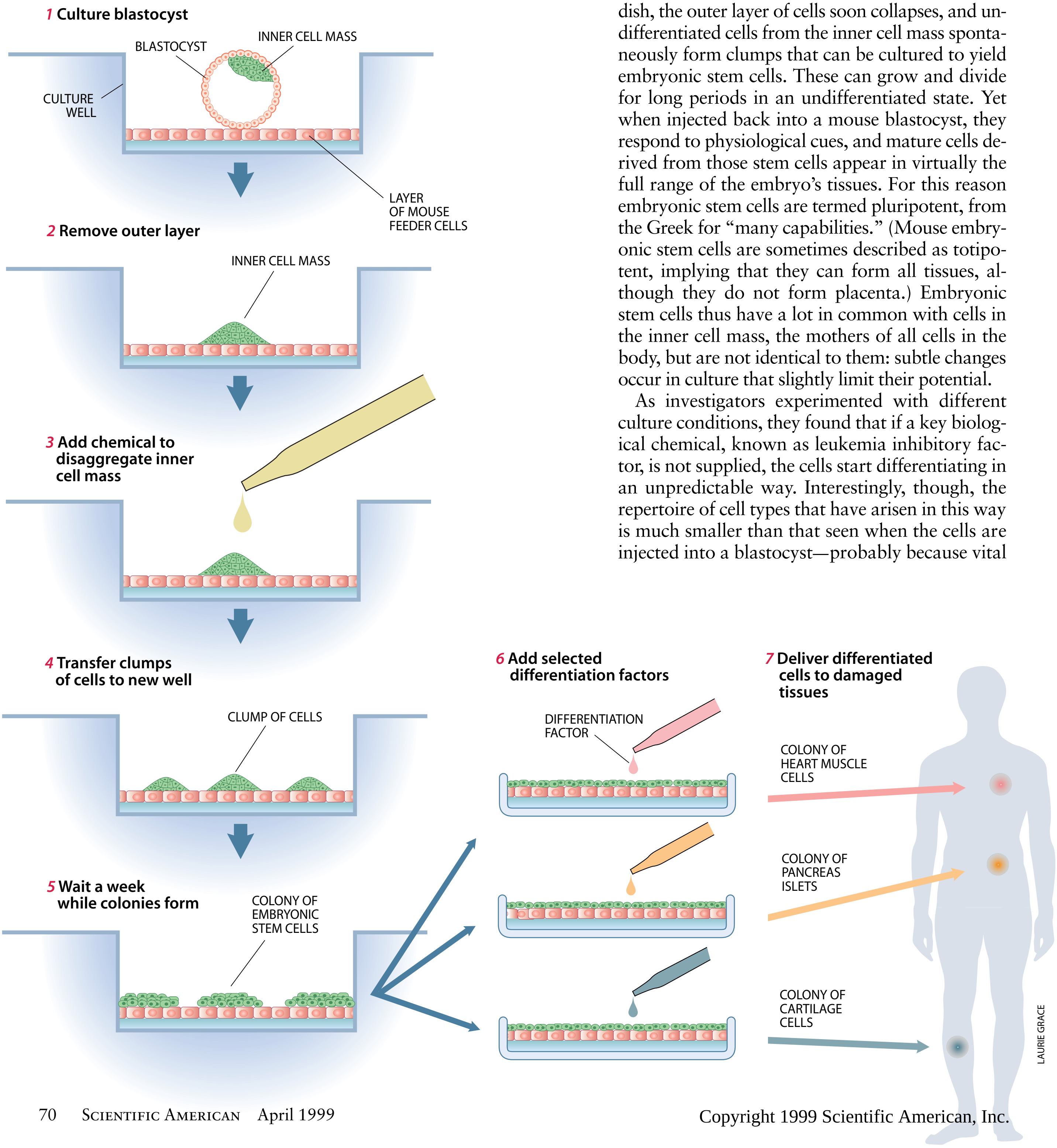
Procedure for generating human embryonic stem cells (*steps 1–5*) involves culturing an early embryo, or blastocyst. That shown in the micrograph at the left has been opened up to reveal the inner cell mass. Cells derived from embryonic stem cells might in the future be administered to patients (*6* and *7*).

much more about how to induce embryonic stem cells to mature into desired tissues. Much of what is known so far has been gleaned from studies of mouse embryonic stem cells, which were the first to be characterized.

Researchers derived them in 1981 from mouse embryos at the 100-cell stage. Such embryos consist of a hollow ball of cells known as a blastocyst. Hardly wider than an eyelash, a blastocyst has an internal thickening of its wall known as the inner cell mass. In a uterus, it would form the entire fetus and its membranes, such as the amnion.

When mouse blastocysts are cultured in a petri dish, the outer layer of cells soon collapses, and undifferentiated cells from the inner cell mass spontaneously form clumps that can be cultured to yield embryonic stem cells. These can grow and divide for long periods in an undifferentiated state. Yet when injected back into a mouse blastocyst, they respond to physiological cues, and mature cells derived from those stem cells appear in virtually the full range of the embryo's tissues. For this reason embryonic stem cells are termed pluripotent, from the Greek for "many capabilities." (Mouse embryonic stem cells are sometimes described as totipotent, implying that they can form all tissues, although they do not form placenta.) Embryonic stem cells thus have a lot in common with cells in the inner cell mass, the mothers of all cells in the body, but are not identical to them: subtle changes occur in culture that slightly limit their potential.

As investigators experimented with different culture conditions, they found that if a key biological chemical, known as leukemia inhibitory factor, is not supplied, the cells start differentiating in an unpredictable way. Interestingly, though, the repertoire of cell types that have arisen in this way is much smaller than that seen when the cells are injected into a blastocyst—probably because vital



LAURIE GRACE

biological chemicals present in the embryo are not in the culture medium. This contrast raised the question of whether artificial conditions could be found that would mimic those in the embryo.

Directing Development

Such manipulations are possible. Gerard Bain and David I. Gottlieb and their associates at the Washington University School of Medicine have shown that treating mouse embryonic stem cells with the vitamin A derivative retinoic acid can stimulate them to produce neurons (nerve cells). That simple chemical seems to achieve this dramatic effect on the cells by activating a set of genes used only by neurons while inhibiting genes expressed in cells differentiating along other pathways.

My colleague Meri Firpo and her former coworkers in Gordon Keller's laboratory at the National Jewish Medical and Research Center in Denver had comparable success deriving blood cells. They discovered that specific growth factors stimulated cells derived from embryonic stem cells to produce the complete range of cells found in blood.

Embryonic stem cells might even generate some useful tissues without special treatment. I never cease to be amazed, when looking through a microscope at cultures derived from embryonic stem cells, to see spontaneously differentiating clumps beating with the rhythm of a heart. Investigators could potentially allow such transformations to occur and then select out, and propagate, the cell types they need.

Loren J. Field and his associates at Indiana University School of Medicine have done just that. Employing a simple but elegant method, they enriched the yield of spontaneously differentiating heart muscle cells, or cardiomyocytes, to greater than 99 percent purity.

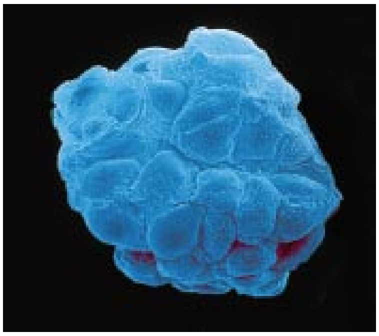
To achieve that goal, they first introduced into mouse embryonic stem cells an antibiotic-resistance gene that had been engineered to express itself only in cardiomyocytes. After allowing the cells to differentiate and exposing them to enough antibiotic to kill cells that lacked the resistance gene, Field's team was able to recover essentially pure cardiomyocytes. Remarkably, when the cells were transplanted into the hearts of adult mice, the cardiomyocytes engrafted and remained viable for as long as seven weeks, the longest period the researchers analyzed.

Likewise, Terrence Deacon of Harvard Medical School and his co-workers have transplanted embryonic stem cells into a particular region in the brains of adult mice. They observed that many of the engrafted cells assumed the typical shape of neurons. Some of those cells produced an enzyme that is needed to make the neurotransmitter dopamine and occurs in quantity in dopamine-secreting neurons. Others produced a chemical found in a different class of neurons. What is more, the nervelike cells in the grafts elaborated projections that resembled the long, signal-carrying neuronal branches known as axons; in the brain, some of

Ethics and Embryonic Cells

The full potential of recent discoveries on embryonic stem cells will be realized only if society deems this research worthy of support. Many people feel that human embryos growing in laboratory dishes, even at the earliest stages of development (between fertilization and the 100-cell blastocyst stage), warrant special moral consideration, because they can grow into human beings if returned to a uterus for gestation. In 1994 an expert panel of ethicists and researchers convened by the U.S. National Institutes of Health studied the issue. It recommended that some embryo research, including the derivation and analysis of human embryonic stem cells, was ethically justifiable and merited consideration for federal funding.

Even so, a congressional ban has ensured that no federal monies have yet been appropriated for research on human embryos. (The work of James A. Thomson and John D. Gearhart mentioned in this article, as well as my own work on related cells, was all supported by Geron Corporation in Menlo Park, Calif.) Some countries, notably the U.K., have concluded that research on human embryos does warrant governmental review and support, whereas a few, such as Germany, have decided otherwise.



Human embryo is shown five days after fertilization.

Together with most of my colleagues, I consider laboratory research on human embryos a legitimate scientific activity, because of the work's enormous medical promise. Of course, informed consent must be obtained from the donors of any human materials used for research. Embryos are now routinely created in clinics to treat infertility, and those not implanted in a uterus are destroyed if they are not donated for research.

The transfer of experimental embryos to a uterus, however, must meet a different standard of ethics and safety, because that act opens up their potential to develop into human beings. Any manipulations on an embryo that is to develop must be demonstrably safe and bring unambiguous benefits for the resulting person.

It is clear that cloning human beings would not meet this standard, and I seriously doubt whether it ever will. That is why I spearheaded a voluntary moratorium on reproductive cloning of humans, a policy that has been endorsed by essentially all U.S. scientists who could credibly consider such an activity.

Early this year, the NIH announced that it will support research on lines of embryonic stem cells that scientists establish using funds from other sources. It did so after considering the biological potential of these cells. Once they are derived, either from a natural embryo or possibly from one produced through somatic cell nuclear transfer (as described in the main text), embryonic stem cells are no longer equivalent to an embryo in their developmental power.

Specifically, to grow stem cells in the test tube, researchers must remove the outer layer of cells in the originating blastocyst. These excised cells are essential to the development of the placenta, which normally nourishes the product of conception and protects it from rejection by the mother's immune system. By stripping them away, a researcher eliminates any possibility that the remaining inner cells can develop in a uterus. Embryonic stem cells provide a source of medically useful differentiating tissues that lack the awesome potential of an intact embryo. *—R.A.P.*

these extended into the surrounding tissue. Whether such cells not only look normal but also function normally has not yet been assessed. Nor is it clear which (if any) growth factors in the mice stimulated the transplants to form neurons: surprisingly, nervelike cells also developed in grafts placed adjacent to the kidney.

The technique for establishing a culture of embryonic stem cells is more involved when primate embryos are the source, rather than mouse embryos. The outer cell layer of the primate blastocyst does not fall apart so readily in culture, so researchers must remove it, or the cells of the inner cell mass will die. But the results from the mouse studies suggest that as researchers gain experience with human embryonic stem cells, it will become possible to stimulate them to produce, at least, blood cells, heart muscle cells and neurons. Other medically valuable types might be achievable, such as pancreatic islet cells, for treatment of diabetes; skin fibroblasts, for treatment of burns or wounds; chondrocytes, for regenerating cartilage lost in arthritis; and endothelial (blood vessel–forming) cells, to repair blood vessels damaged by atherosclerosis.

Researchers should be able to make perfectly matched tissues for transplantation.

Unfortunately, embryonic stem cells also have a dark side. The jumble of cell types they form when injected into mature mice constitute a type of tumor, known as a teratoma. Researchers will have to be sure, before using cells therapeutically, that they have all differentiated enough to be incapable of spreading inappropriately or forming unwanted tissue. Rigorous purification of such cells will be required to safeguard the recipients.

The cells that Gearhart obtained from developing ovaries and testes also show medical promise. They are called embryonic germ cells, because they are derived from the ancestors of sperm and eggs, which are together referred to as germ cells. Gearhart has shown that his cells, too, are pluripotent: in the petri dish they can give rise to cells characteristic of each of the embryo's basic layers. As of this writing, however, Gearhart has not published details of what happens when embryonic germ cells are placed under the skin of mice, so information about their potential for tissue formation is still somewhat limited.

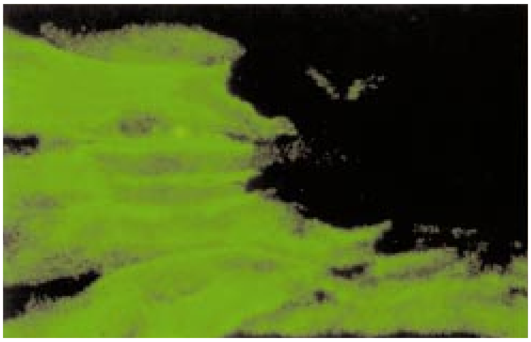
Challenges … and Opportunities

All the differentiated cells discussed so far would probably be useful in medicine as isolated cells, or as suspensions; they do not have to organize themselves into precisely structured, multicellular tissues to serve a valuable function in the body. That is good news, because organ formation is a complex, three-dimensional process. Organs generally result from interactions between embryonic tissues derived from two distinct sources. Lungs, for example, form when cells derived from the middle layer of the embryo interact with those of the embryonic foregut, which is derived from the inner layer. The process stimulates embryonic foregut cells to form branches that eventually become the lungs. For would-be tissue engineers, learning how to direct pluripotent stem cells through similar interactions with the goal of building entire organs will be hugely difficult. Nevertheless, some researchers are working on solutions to those very problems.

Another challenge is to create cells for transplantation that are not recognized as foreign by the recipient's immune system. This end could be achieved in principle by genetically altering human embryonic stem cells so they function as "universal donors" compatible with any recipient. Alternatively, embryonic stem cells genetically identical to the patient's cells could be created, as in the scenario of the heart attack victim described earlier.

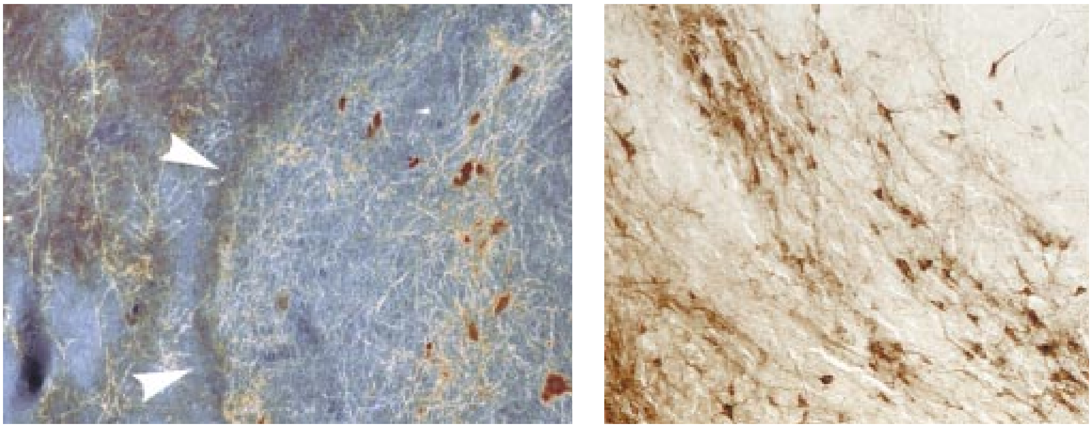
The first option, creating a universal donor cell type, would involve disrupting or altering a substantial number of genes in cells. The changes would prevent the cells from displaying proteins on their outer surface that label them as foreign for the immune system. Yet bringing about this alteration could be hard, because it would require growing embryonic stem cells under harsh conditions, in particular exposing them to multiple rounds of selection with different drugs.

The second option, making cells that are geneti-



PHOTOGRAPHS BY MICHAEL G. KLUG AND LOREN J. FIELD
Indiana University School of Medicine

Myosin, a protein found mainly in muscle, fluoresces red in cells derived from mouse embryonic stem cells (*above*). Transplanted into a mouse's heart, the cells become enmeshed with heart muscle (*right*). The donated cells can be distinguished by green fluorescence (*far right*).



TERRENCE DEACON *Harvard Medical School*

Cells resembling nerve cells (*brown and gold in left image*) form when mouse embryonic stem cells are placed in a mouse brain (*blue background*). Signs that the cells may indeed be nerve cells include the extension of projections into the surrounding tissue (*arrows*) and the production of an enzyme (*brown in right image*) made by certain nerve cells in the brain.

cally identical to the patient's tissues, involves combining embryonic stem cell technology and a fundamental step in cloning. Using a hollow glass needle one tenth of the diameter of a human hair, a researcher would transfer a somatic (nonreproductive) cell—or just its gene-containing nucleus—into an unfertilized egg whose chromosomes have been removed. The egg would then be activated by an electrical shock, launching it on its developmental journey with only the genetic information of the transferred, or donor, cell.

In several animal studies on nuclear transfer, cells from existing adult animals have been used as the gene donors, and the altered cells have been implanted into the uterus of a living animal. These experiments gave rise to Dolly the sheep and to some mice and cattle as well [see "Cloning for Medicine," by Ian Wilmut; SCIENTIFIC AMERICAN, December 1998]. To create cells for transplantation with this combination of approaches, an investigator would use a cell from the patient as a donor but would culture the resulting embryo only until it reached the blastocyst stage. Then the embryo would be used to produce embryonic stem cells that were genetically identical to a patient's own cells.

Human embryonic stem cells could have other applications, too. Because the cells could generate human cells in basically unlimited amounts, they should be extremely useful in research efforts designed for discovering rare human proteins. These programs need great quantities of cells in order to produce identifiable amounts of normally scarce proteins. And because embryonic stem cells resemble cells in early embryos, they could be employed to flag drugs that might interfere with development and cause birth defects.

Finally, such cells offer an approach to studying the earliest events in human development at the cellular and molecular levels in a way that is ethically acceptable. The moral issues associated with experiments on embryos should not arise because embryonic stem cells lack the ability to form an embryo by themselves [*see box on page 71*].

Research on the cells could provide insights into fundamental questions that have puzzled embryologists for decades, such as how embryonic cells become different from one another, and what causes them to organize into organs and tissues. The lessons learned from mice, frogs, fish and fruit flies on these subjects are highly germane to humans. Yet understanding these processes in our own species will ultimately provide us with the greatest benefits and the deepest satisfaction.

The Author

ROGER A. PEDERSEN is professor of obstetrics, gynecology and reproductive sciences at the University of California, San Francisco. He has spent three decades studying various aspects of mammalian embryology. His current interests include the role of DNA repair in early development, the formation and organization of early embryo cell types, and the differentiation of embryonic stem cells. Pedersen's moratorium on cloning of human beings can be read at http://www.faseb.org/opar/cloning.moratorium.html on the World Wide Web. For relaxation, Pedersen flies single-engine aircraft or plays his violin.

Further Reading

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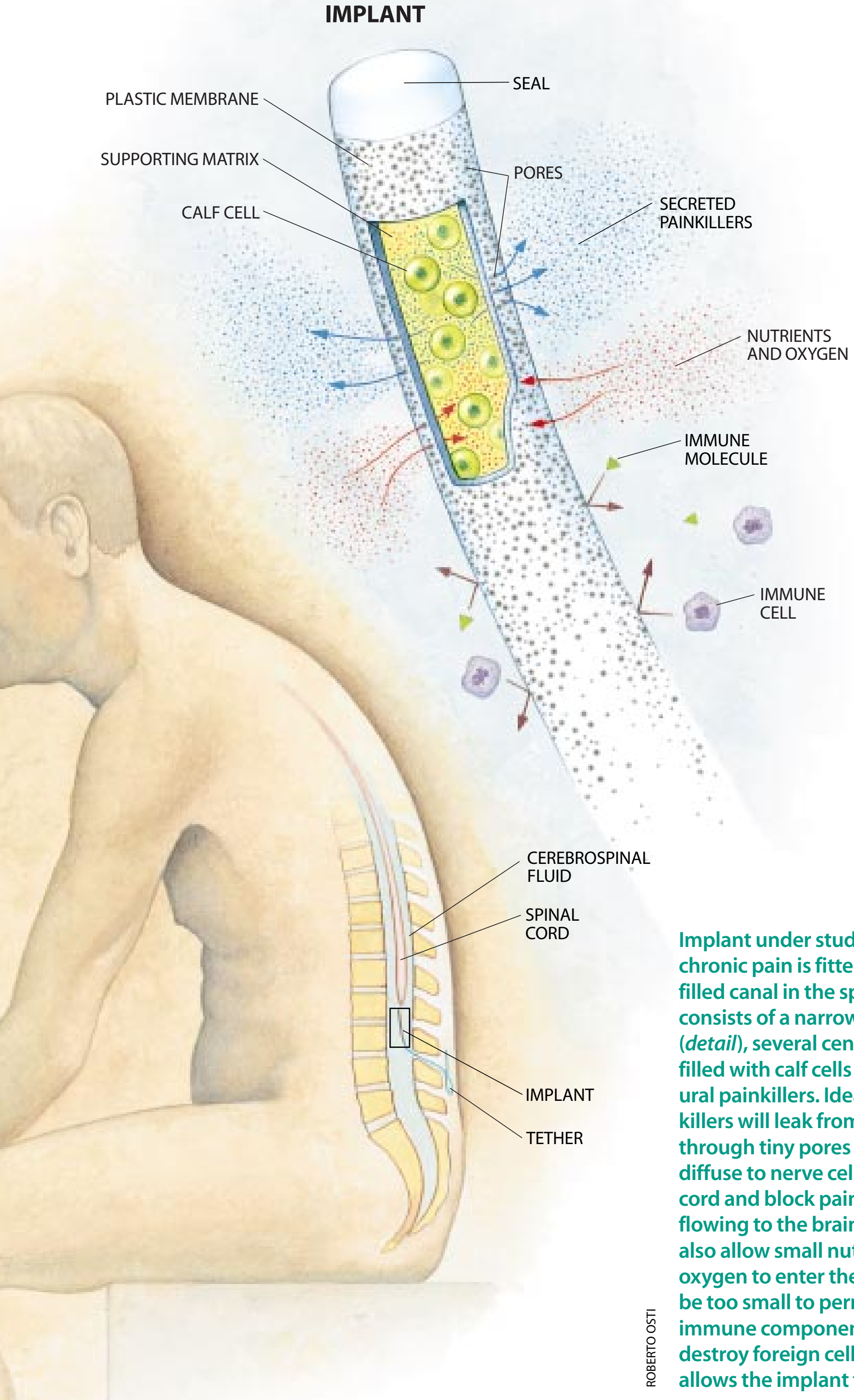
ENCAPSULATED

An emerging approach to treating disease combines living cells with plastic membranes that shield the cells from immune attack

by Michael J. Lysaght and Patrick Aebischer



Implant under study for relief of chronic pain is fitted into a fluid-filled canal in the spinal column. It consists of a narrow plastic tube (*detail*), several centimeters long, filled with calf cells that secrete natural painkillers. Ideally, the painkillers will leak from the implant through tiny pores in the plastic, diffuse to nerve cells in the spinal cord and block pain signals from flowing to the brain. The pores will also allow small nutrients and oxygen to enter the implant but will be too small to permit access by immune components that normally destroy foreign cells. The tether allows the implant to be removed.

ROBERTO OSTI

In 1994 a man suffering from relentless pain became one of the first volunteers to test an entirely new approach to treating human disorders. As he lay still, a surgeon threaded a small plastic tube into his spinal column. The sealed tube, five centimeters long and as thin as the wire in a standard paper clip, contained calf cells able to secrete a cocktail of painkillers.

If all went well, the secretions would seep out of the tube through minute pores and then diffuse into the spinal cord. Meanwhile, nutrients and oxygen from the surrounding cerebrospinal fluid would slip into the capsule to sustain the cells. At the same time, the tubing would bar entry by large substances. Specifically, it would prevent cells and antibody molecules of the immune system (both of which are relatively big) from contacting the bovine cells and destroying them as foreign invaders.

The ultimate aim of this particular procedure is to relieve discomfort, by interrupting the flow of pain signals through the spinal cord to detection centers in the brain. The 1994 study, however, was preliminary. It was designed to see whether the implanted cells could survive and release their analgesics for months. They did. Similar success in several patients later justified a major trial, now under way, to assess pain control directly.

But the results also had broader implications. They fueled growing optimism, based on extensive animal experiments, that combining living cells with protective synthetic membranes could help correct a range of human disorders.

Five years later excitement over that strategy—variously known as encapsulated-cell, immunoisolation or biohybrid therapy—seems entirely justified. Like the pain implant, a biohybrid liver-support system has progressed to a controlled human trial involving scores of

CELLS as THERAPY

patients and multiple centers. And immunoisolation therapies for various other conditions are being evaluated in smaller human tests or in studies of large animals. Among those conditions are devastating neurodegenerative disorders (such as Parkinson's and Huntington's diseases), hemophilia, anemia and growth retardation. Treatment of macular degeneration, a common cause of blindness, and other eye diseases are starting to be assessed as well, in rodents.

Most proposed applications involve implanting encapsulated cells in a selected site in the body. Some, though, such as the liver treatment, would incorporate cells and membranes into a bedside device resembling a kidney dialysis machine.

Immunoisolation therapy appeals to us and other researchers because it overcomes important disadvantages of implanting free cells. Like free cells, those encased in membranes can potentially replace critical functions of ones that have been damaged or lost. They can also supply such "extras" as painkillers. They can even provide gene therapy, secreting proteins encoded by genes that molecular biologists have introduced into cells.

Free cells, however, are likely to be ambushed by the immune system unless they come from the recipients themselves or their twins. For that reason, patients usually require immune-suppressing drugs. By mechanically blocking immune attacks, plastic membranes around grafted cells should obviate the need for such medicines, which can predispose people to infection, certain cancers (lymphomas) and kidney failure.

The immune protection afforded by plastic membranes should also allow cells derived from animals to be transplanted into people. Unencapsulated animal cells are not a viable option, because existing immune-suppressing drugs do not fully protect against the rejection of cross-species implants (xenografts). Use of animal cells would help compensate for the well-known shortage of human donor tissue. Finally, cells implanted within a plastic casing can be retrieved readily if need be. Free cells, in contrast, often cannot be recovered.

An Inspired Proposal

Current efforts to encapsulate cells for therapy owe a great debt to ideas put forward by William L. Chick in the mid-1970s, when he was at the Joslin Research Laboratory in Boston. Like legions of scientists then and now, he had his sights set on curing insulin-dependent (type I) diabetes, which usually strikes youngsters. This disorder arises when the pancreas stops making insulin, a hormone it normally releases in amounts tuned to control the concentrations of glucose (a sugar) in the blood. Daily insulin injections save lives, but they do not mimic the natural pattern of insulin release from the pancreas. In consequence, tissues may at times become exposed to too much glucose. Over years, this excess can lead to such diabetic complications as blindness and kidney failure.

Chick thought implantation of encapsulated pancreatic islets—the clusters of cells that contain the insulin-secreting components—might restore the proper pattern of insulin release without requiring the administration of immunosuppressants. Use of islets from pigs (then the main source of injected insulin) would, moreover, guarantee a rich pipeline of cells.

Studies in rodents in the mid-1970s and thereafter suggested his logic was sound. Unfortunately, certain technical obstacles have so far kept immunoisolation therapy from fulfilling its promise in diabetes. Chick died last year, without seeing his vision fulfilled. His pioneering ideas have, nonetheless, sparked impressive progress on other fronts, including device design.

Creative Configurations

Encapsulation systems now come in a multitude of configurations. All, however, include the same basic ingredients: cells (typically ones able to secrete useful products), a matrix that cushions the cells and otherwise supports their survival and function, and a somewhat porous membrane. Biomedical engineers now know that cells in an implant will work poorly or die if they are farther than 500 microns (millionths of a meter) from blood vessels or other sources of nourishment—a distance roughly equivalent to the diameter of the graphite in a mechanical pencil.

Vascular, or flow-through, designs were the first to be tested (for correcting diabetes in rodents). These devices divert a patient's circulating blood into a plastic tube and then back to the circulatory system. Secretory cells are placed in a closed chamber that surrounds a slightly porous segment of the tubing, the way a doughnut surrounds its hole. As blood flows through this part of the circuit, it can absorb substances secreted by the therapeutic cells and can provide oxygen and nutrients to the cells. If islets are in the chamber, they will match the insulin released to the concentration of glucose in the blood. For other applications, cells that emit a product at a constant rate can be chosen.

Flow-through devices can be produced in im-

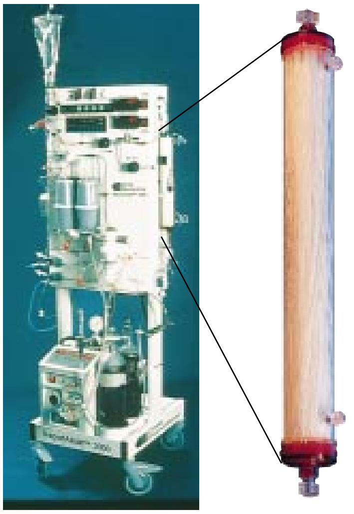
CYTOTHERAPEUTICS

Enlarged, cutaway view of an empty tubular implant reveals the membrane's foamlike structure.

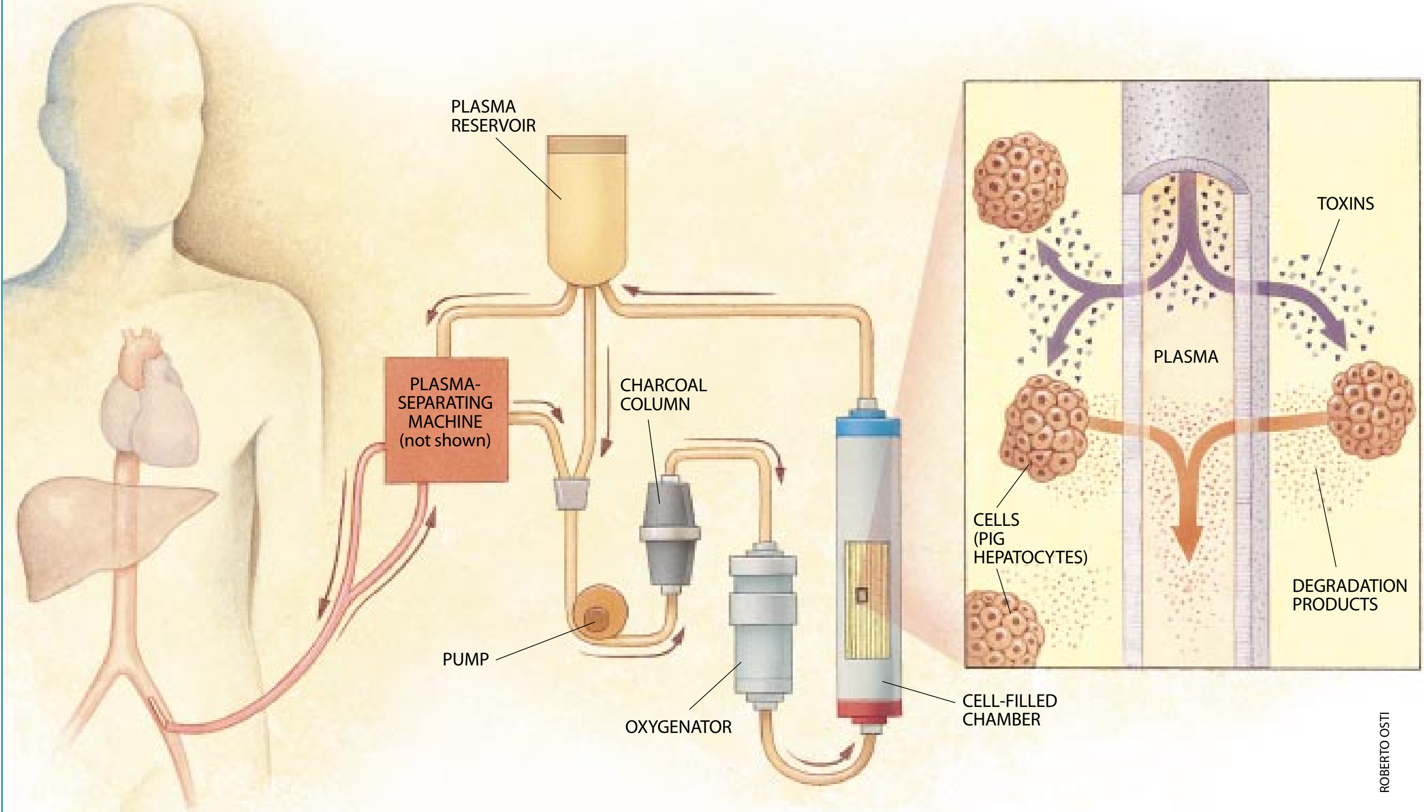
A Promising Liver-Support Approach

Not all encapsulation systems are implants. Liver-support systems currently being studied operate outside the body. They aim to sustain liver-failure patients until a compatible organ becomes available for transplantation. The particular device shown at the right and illustrated below was developed by teams led by Claudy J. P. Mullon of Circe Biomedical in Lexington, Mass., and Achilles A. Demetriou of Cedars-Sinai Medical Center in Los Angeles.

This machine draws blood from a patient and pumps the fluid component (plasma) through a charcoal column (meant to remove some toxins) and an oxygen-replenishing unit before delivering it to a chamber containing healthy liver cells—hepatocytes—from pigs. In the chamber (*detail*), the plasma courses through slightly porous tubes, which are surrounded by the hepatocytes. Toxins from the plasma diffuse into the cells, which are intended to convert the poisons into innocuous substances. After the purified plasma leaves the chamber, it recombines with blood cells and is returned to the patient. —*M.J.L. and P.A.*



CIRCE BIOMEDICAL (*machine*); SAM OGDEN (*detail*)



ROBERTO OSTI

plantable forms. But they will probably find most application in bedside equipment, because implants require invasive, vascular surgery and long-term administration of blood thinners (to prevent blood clots from forming in the tubing). In addition, if an implanted tube breaks, internal bleeding will result.

Searching for a less invasive method, researchers introduced "microencapsulation" in the late 1970s. To make microcapsules, workers put a single pancreatic islet or a few thousand individual cells into a drop of aqueous solution containing slightly charged polymers. Then they bathe the drop in a solution of oppositely charged polymers. The polymers react to form a coating around a cell-and-fluid-filled droplet measuring about 500 microns in diameter.

Microcapsules are easy to produce and thus are valuable for quick experiments but have notable drawbacks for human therapy. They are quite fragile. Once placed, they may be difficult to find and remove—a distinct problem if they have unwanted effects. What is more, the volume needed to correct a disorder may be too great to fit conveniently in a desired implant site.

The most practical format for human therapy appears to be preformed macrocapsules, initially empty units that are loaded with a matrix and all the cells needed for treatment. Some macrocapsules are disks about the size of a dime or a quarter. Others are roughly the size and shape of the stay in a shirt collar. Usually, however, macrocapsules intended for humans take the form of a sealed tube, or capillary, that is several centimeters long and between 500 and 1,000 microns in diameter.

Macrocapsules are far more durable and rugged than microcapsule droplets, contain internal reinforcements, can be tested for seal integrity before implantation and can be designed to be refillable in the body. They can also be retrieved simply. Their main limitation is the number of cells they can accommodate: up to about five million for a tube and up to 50 or 100 million for a disk or flat sheet. Those figures are adequate for many applications, but not all. Enlarging the capsules can render them prone to bending, which promotes breakage. In addition, the edges of bent regions encourage fibrosis, an ingrowth of local tissue. Fibrosis can choke off transport to and from encapsulated cells.

Immunoisolation technology suddenly offered a new way to provide gene therapy.

Fabricators of shunts, microcapsules and macrocapsules aim for a membrane pore size that will allow diffusion of molecules measuring up to 50,000 daltons, or units of molecular weight. Holes that size generally are small enough to block invasion by immune cells and most immune molecules but are large enough to allow the inflow of nutrients and oxygen and the outflow of proteins secreted by implanted cells. Actual membranes end up containing a range of pore sizes, however, and so some large immune system molecules will inevitably pass through the membranes into an implant. Fortunately, this phenomenon does not undermine most implants.

New Focus on Designer Cells

Until the late 1980s, most biohybrid devices relied on primary cells: those taken directly from donor tissue. Primary cells are convenient for small studies in small animals, but obtaining the large quantities needed for big animals (including humans) or for numerous recipients can be problematic. And because every donor has its own history, guaranteeing the safety of primary cells can be a formidable undertaking. In the early 1990s, therefore, some teams began turning to cell lines.

These lines consist of immortal, or endlessly dividing, cells that multiply readily in culture without losing their ability to perform specialized functions, such as secreting helpful substances. Many primary cells replicate poorly in culture or have other disadvantages. Hence, to make a cell line, investigators often have to alter the original versions. Once established, though, cell lines can provide an ongoing supply of uniform cells for transplantation.

The potential utility of cell lines for encapsulation therapy became abundantly clear in animal tests that we and our colleagues performed starting in 1991. The well-established PC-12 line, derived from a rodent adrenal tumor (a pheochromocytoma), was known to secrete high levels of dopamine, a signaling molecule depleted in the brains of patients with Parkinson's disease. To see whether implants containing these cells might be worth studying as a therapy for Parkinson's, we put small tubes of the cells into the brain of diverse animals whose dopamine-producing cells had been chemically damaged to produce Parkinson-like symptoms. In many subjects, including nonhuman primates, the procedure dramatically reversed the symptoms.

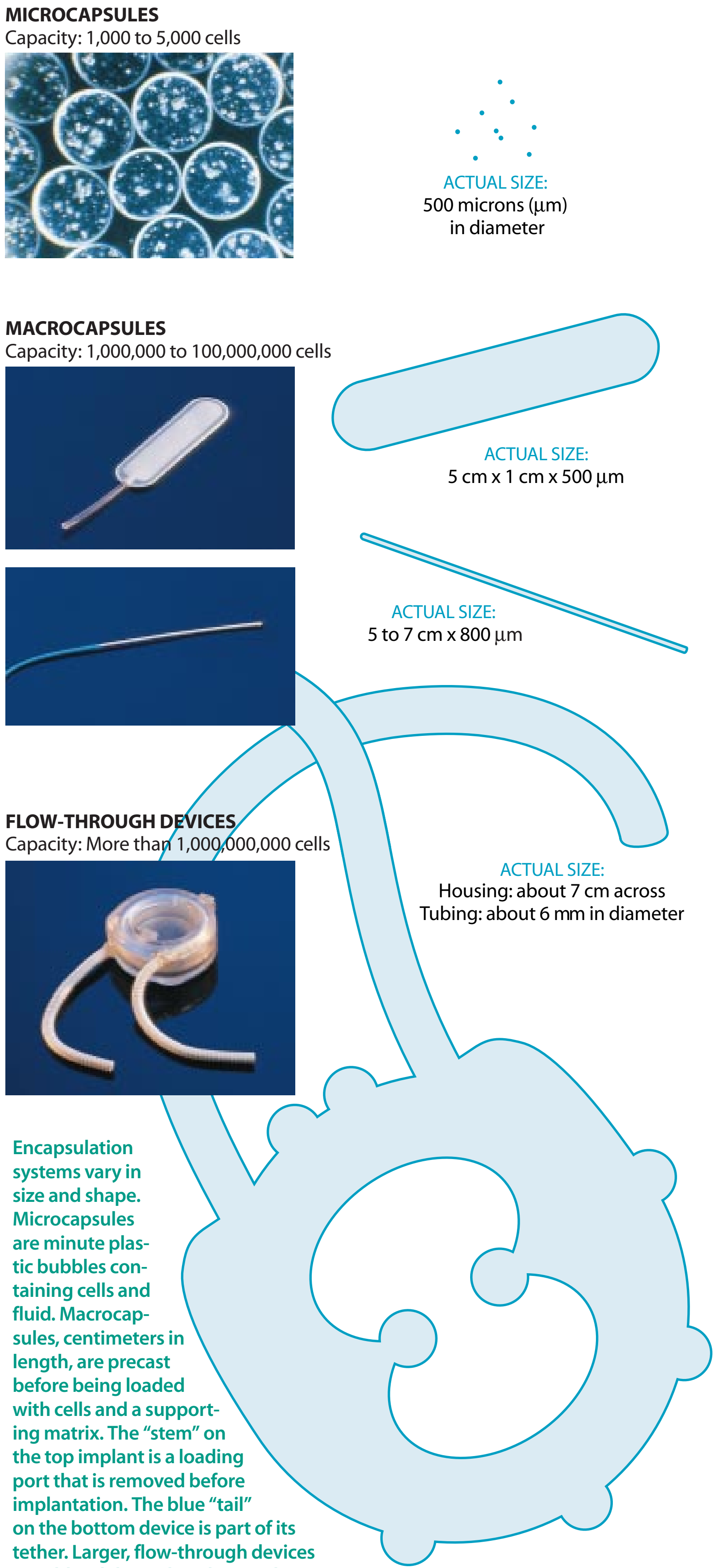
Significantly, the cells did not proliferate uncontrollably and puncture the capsules. They replaced cells that had died but did not allow the population to exceed the carrying capacity of the implant. The studies also eased fears that if immortalized cells escaped, they would inevitably spawn cancerous tumors. Immortalization is one step on a cell's road to cancer. To be truly malignant, though, cells must acquire the ability to invade neighboring tissue, grow their own blood supply and spread to distant sites. Tumor formation is a potential concern in same-species transplants of immortalized cells, but cross-species transplants turn out to be less worrisome: unencapsulated rat PC-12 cells in primate brains did not generate tumors. In fact, they did not even survive; the recipients' immune system destroyed them quickly.

The PC-12 work was never followed up in Parkinson's patients, perhaps because other promising treatments took precedence. Still, the studies did demonstrate the feasibility of deploying cell lines in immunoisolation therapies.

Success with cell lines also opened the door to use of genetically modified cells, because dividing cells are most amenable to taking up introduced genes and producing the encoded proteins. In other words, immunoisolation technology suddenly offered a new way to provide gene therapy. Molecular biologists would insert genes for medically useful proteins into cell lines able to manufacture the proteins, and the cells would then be incorporated into plastic-covered implants.

Gene therapy protocols frequently remove cells from patients, insert selected genes, allow the altered cells to multiply and then return the resulting collection to the body in the hope that the encoded proteins will be made in the needed quantities. The output of capsules filled with genetically altered cells, in contrast, can be measured before the implants are delivered to patients. Later, the capsules can be removed easily if need be.

An unresolved issue is whether cell lines enlisted for encapsulation therapies should be derived from animals or humans. Primary cells, taken directly from donors, almost certainly need to come from animals, because human donor tissue is in such short supply. Some researchers prefer animal-derived lines because renegade cells that broke free from an implant, being highly foreign to the recipient, would meet the promptest immune destruction.



MICROCAPSULES
Capacity: 1,000 to 5,000 cells

ACTUAL SIZE:
500 microns (µm)
in diameter

MACROCAPSULES
Capacity: 1,000,000 to 100,000,000 cells

ACTUAL SIZE:
5 cm x 1 cm x 500 µm

ACTUAL SIZE:
5 to 7 cm x 800 µm

FLOW-THROUGH DEVICES
Capacity: More than 1,000,000,000 cells

ACTUAL SIZE:
Housing: about 7 cm across
Tubing: about 6 mm in diameter

Encapsulation systems vary in size and shape. Microcapsules are minute plastic bubbles containing cells and fluid. Macrocapsules, centimeters in length, are precast before being loaded with cells and a supporting matrix. The "stem" on the top implant is a loading port that is removed before implantation. The blue "tail" on the bottom device is part of its tether. Larger, flow-through devices pass blood through a plastic tube, a segment of which is surrounded by a cell-filled chamber (*ring*). The one shown is implantable. Silhouettes at the right depict actual sizes.

SAM OGDEN (*photographs*); LAURIE GRACE (*silhouettes*); DEVICES COURTESY OF PATRICK AEBISCHER (*microcapsules*); THERACYTE (*top macrocapsule*); CYTOTHERAPEUTICS (*bottom macrocapsule*); CIRCE BIOMEDICAL (*flow-through device*)

To provide human therapeutic proteins to a recipient, cell designers could readily equip the animal cells with human genes for those proteins. Other workers favor human-derived lines, in part because human cells tend to fare better within capsules. They also skirt the risk that animal pathogens will be transferred to humans. For extra safety, human cells could be engineered to elicit swift immune recognition should they escape.

Readers may notice that encapsulated cells, genetically altered or not, often essentially serve as delivery vehicles for therapeutic proteins. Yet proteins can be delivered by injection. Why, then, would cell implantation be needed at all?

Encapsulated-cell therapy can be very helpful when injections cannot provide enough of a protein where it is needed most, such as in a tumor or behind the blood-brain barrier—a natural filter that blocks many blood-borne substances from reaching cells of the brain and spinal cord. Encapsulated cells would likewise be valuable when a therapeutic protein is too unstable to be formulated as a drug or when reproducing a natural pattern of protein delivery is important (as with diabetes).

Human Studies

Genetically manipulated cell lines are likely to predominate in biohybrid devices of the future. Yet applications involving primary cells, having been studied the longest, have progressed to the most definitive clinical tests. One example, developed by the two of us and a large contingent of associates, is the treatment for chronic pain described at the start of this article. We obtain the cells for the pain implant from the adrenal glands of calves raised under highly controlled conditions. Certain adrenal components—the chromaffin cells—naturally release a suite of analgesics. After carefully purifying about three million of these cells, we fit them into a hollow fiber that is sealed at both ends, linked to a tether (for retrieval) and implanted, through a minimally invasive procedure, into the spinal column.

When our surgical collaborators showed in the mid-1990s that such implants could function for months in patients, they noted possible signs of pain control. Several patients reported significant reductions in discomfort and in morphine use. But these experiments did not include a comparison group receiving a placebo (say, an empty capsule), so we could not be sure whether our treatment was truly responsible. The large clinical trial now in progress involves more than 100 patients and is designed specifically to address the extent of pain relief. It is headed by Moses B. Goddard of CytoTherapeutics in Lincoln, R.I.

Regardless of the outcome, the data already in hand demonstrate that immunoisolated cells of animal origin can live for months in the central nervous system of subjects who are taking no immune-suppressing drugs. In contrast, no organ transplanted from animals to humans has survived without encapsulation even when supported by the aggressive delivery of immunosuppressants.

A second well-developed application of immunoisolation therapy—the liver-assist device—also relies on cells harvested directly from animals. Within a healthy liver, cells known as hepatocytes take up toxins and break them into innocuous forms. When the liver fails, such toxins can accumulate to lethal levels. Liver transplants can save patients, but many die waiting for a donor organ matched to their tissue type. The biohybrid liver systems under study aim to keep patients alive until a donor is found.

We expect to see glucose-responsive, insulin-secreting cell lines tested in large animals five years from now, possibly much sooner.

This "bridge to transplant" therapy employs a bedside, vascular apparatus. In essence, blood from the patient is pumped to a closed chamber in which a semiporous segment of the blood-carrying tube is surrounded by a suspension of pig hepatocytes. The hepatocytes take up the toxins from the flowing blood and degrade them, so that healthier blood returns to the body as it completes its circuit [*see box on page 78*]. In contrast to the pain implant, which delivers a few milligrams of cells and is expected to function continuously for months or years, a liver device can accommodate between 20 and 200 grams of purified hepatocytes (about the weight of the meat in a Big Mac) and would be needed for just six to 24 hours at a time.

In an initial study involving close to 40 patients with terminal liver failure, the equipment tested functioned exactly as hoped. That finding, reported in 1998, paved the way for a large, controlled trial now starting in the U.S. and Europe. Expectations of success are high, and researchers have reason to believe that under special circumstances, such as acute liver failure caused by excessive intake of acetaminophen, the liver might regenerate and that no transplantation would be required. Yet optimism has to be tempered by past experience. The path to liver-support systems is littered with interventions that worked beautifully in initial tests but faded in large trials.

For both the pain and liver applications, scientists must address concerns that genes from unknown animal viruses might be hiding in the harvested cells and that those genes might give rise to viruses and to dangerous infections in transplant recipients. (Rigorous screening methods ensure that no already known pathogen is transferred.) Fortunately, plastic membranes should provide a formidable barrier to the transmission of animal viruses, and to date, no patient has acquired even a benign infection from donor cells. Even so, investigators are neither cavalier nor complacent about the issue and continue to attend to it closely.

Although less advanced, human trials of gene therapy applications have begun as well. Two small studies target disorders of the central nervous system. The first clinical trial of genetically altered encapsulated cells took aim at amyotrophic lateral sclerosis (ALS), the neurodegenerative condition marked by decay of spinal nerves that control the muscles. ALS killed baseball legend Lou Gehrig. In 1996 six patients received implants containing a cell line—derived from baby hamster kidney cells—that had been given the gene for a protein called ciliary-derived neurotrophic factor (CNTF). This gene was chosen because other studies in animals and people had suggested the factor might retard the deterioration of neurons that usually die in ALS patients. The protocol was much like that used for chronic pain: a small tube filled with cells was implanted in the spinal column.

The study examined whether the cells survived and released potentially therapeutic amounts of CNTF throughout the three-month experiment. The cells functioned well. The treatment did not appear to retard disease progression, however, although the test had too few subjects and was too short to be particularly informative on that score. Nevertheless, this trial suggested that if the right gene or mix of genes for treating ALS were found, encapsulated cells would serve as a good means of delivering them to the central nervous system.

Implants containing the same cell line are now being evaluated in patients with Huntington's disease, which progressively kills certain brain cells. This time, however, the capsules have been placed into fluid-filled spaces in the brain called ventricles. This gene therapy protocol is being conducted in Paris and has just started. A number of animal experiments evaluating immunoisolation for the delivery of gene therapy have begun as well. Several are listed in the table on the next page.


PATRICK AEBISCHER

Fine tube harboring hamster cells was removed from the spinal column of a human subject after 17 weeks. At excision, the cells were still secreting a therapeutic protein, and the encapsulation device was free of surface damage. The results support hopes that implants containing cells from nonhuman species can function for long periods.

The Special Challenge of Diabetes

If immunoisolation research is progressing well in many areas, why has no one managed, after more than 20 years of trying, to perfect an islet-cell encapsulation procedure to correct diabetes?

After 1977, when Chick and his colleagues reversed diabetes in rodents, at least a dozen laboratories around the world replicated that feat, with a wide range of implant designs in various rodent models of diabetes. But immunoisolation therapy based on islets has not fared well in larger species, such as dogs, monkeys and humans. The most positive results come from single cases. Moreover, on close examination, many of those reported successes have been achieved only with the help of immunosuppressants or some amount of injected insulin.

Much of the difficulty stems from the sheer number of islets required by large animals and humans: 700,000 or so, sheltering approximately two billion insulin-producing, "beta" cells. That amount is

Gene Therapy Applications under Study

Target Disease	Gene Product	Status
Amyotrophic lateral sclerosis (ALS)	Ciliary-derived neurotrophic factor (CNTF), a protein that protects neurons (nerve cells) from death	Implant in fluid-filled channel in the spine has passed phase I human trials (which examine safety in a small number of subjects)
Huntington's disease	CNTF	Implant in brain ventricle, or cavity, is in phase I human trials
Parkinson's disease	Glial-derived neurotrophic factor (GDNF), a protein that protects dopamine-secreting neurons	Implant in brain ventricle is under study in nonhuman primates
Anemia	Erythropoietin (EPO), a protein that stimulates production of red blood cells	Subcutaneous implant (under the skin) is under study in nonhuman primates and rodents
Hemophilia	Factor VIII or factor IX, proteins important to blood clotting	Subcutaneous implants are under study in dogs and rodents
Dwarfism	Human growth hormone (HGH), a protein that stimulates body growth	Subcutaneous implant is under study in pigs and rodents
Type II (noninsulin-dependent) diabetes	Glucagonlike peptide-1 (GLP-1), a protein that stimulates insulin release	Subcutaneous implant is under study in rodents
Macular degeneration	CNTF	Eye implant is under study in rodents

RICHARD HUNT

Disorders listed above are among those that might be addressed with implants of genetically altered encapsulated cells. Implanted cells equipped with a gene encoding a therapeutic protein can potentially deliver the medicinal protein indefinitely, often at the biological site where it is needed most.

nearly 1,000 times greater than the cell volume encapsulated successfully in clinical implants to date. Diabetes in mice can be reversed with only about 500 islets, which technicians generally extract from donor pancreases by hand. But hand-picking 700,000 islets is out of the question, and semiautomated techniques have not been able to isolate the required quantities of healthy islets consistently. Further, in the native pancreas, each islet enjoys its own blood supply. Islets suffer in the spartan environment within implanted capsules. For these reasons and others, we agree with those who have concluded that an implanted semiartificial pancreas based on encapsulated islets is most likely to remain an unfulfilled goal for the foreseeable future.

A new proposal, though, just might break the impasse. Employing a variety of approaches, at least three groups are developing cell lines that release insulin in response to the same complex signals that trigger insulin secretion from the healthy pancreas. The plan is to create cells that produce more insulin than natural beta cells (so that fewer cells would be required) and that are equipped to survive in the nutrient-poor, oxygen-depleted environment of an implant. Five years ago creation of such cells might have been regarded as impossible, but recent progress in cell and molecular biology has been overwhelming.

We expect to see glucose-responsive, insulin-secreting cell lines tested in large animals five years from now, possibly much sooner. And we are hopeful that those lines will progress rapidly to the clinic after that. Some experts believe this prediction is too conservative; others counsel that the goal will take longer to achieve. But everyone agrees that an artificial pancreas or a biohybrid version must continue to rank as a top priority for 21st-century medicine. As that work continues, new applications for immunoisolation therapy should arise as well. Indeed, we anticipate that over the next 20 years, encapsulated-cell therapy will emerge from its investigative stages to play a key role in treating some of the most refractory and debilitating diseases of humankind. SA

The Authors

MICHAEL J. LYSAGHT and PATRICK AEBISCHER have long collaborated on the development of biohybrid organs. Lysaght, a biomedical engineer who has made many contributions to the medical applications of synthetic membranes, is associate professor of artificial organs at Brown University and president of the Rhode Island Center for Cellular Medicine. He joined the university in 1995, after 25 years as a researcher and executive in the medical device industry. Aebischer, who was trained as a physician and neuroscientist, now concentrates on developing therapeutic applications of molecular medicine. Formerly at Brown, he is today chief of the division of surgical research and director of the Gene Therapy Center at Lausanne University Medical School in Switzerland; he is also on the faculty of the Federal Swiss Polytechnical Institute in Lausanne.

Further Reading

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SKIN: THE FIRST TISSUE-ENGINEERED PRODUCTS

Last year the first living, tissue-engineered skin product became commercially available—and a second is expected to be on the market within a few months. Top researchers from each of the two companies involved tell how their products came to be

The Organogenesis Story

by Nancy Parenteau

At Organogenesis, we have created a skin construct, Apligraf, that is unique in that it is made up of the two layers that constitute human skin, the dermis (inner layer) and the epidermis (outer layer). In May 1998 Apligraf was approved as a biomedical device by the U.S. Food and Drug Administration. It became the first device containing living human cells to win such approval.

During the development of Apligraf, we at Organogenesis had to decide whether to attempt to win regulatory approval for products that were, in effect, precursors to Apligraf—either dermis or epidermis by itself—or to trust that we could develop our product before other companies beat us to it. We bet on two-layered skin because it was closer to true skin, and grafts of true skin clearly worked. In addition, the dermal substrate would enhance the epidermal layer's survival. Our gamble paid off.

The idea for Apligraf dates back almost two decades. While at the Massachusetts Institute of Technology, Eugene Bell noted that fibroblasts, the cells that form the dermis, could infiltrate a collagen gel and turn it into a fibrous, living matrix. Collagen is a fundamental part of the extracellular matrix, the biological "glue" that holds cells in place. In 1981 he found that keratinocytes, the cells of the epidermal layer, would grow on that dermal substrate, forming a primitive skin equivalent. He also determined that the construct could be grafted onto rats. Organogenesis was founded in 1985 to commercialize Bell's technology. I brought my background in keratinocyte biology to the company in 1986.

We were confident that artificial, bilayered skin would have clinical benefits. A temporary skin substitute made of collagen and another extracellular matrix constituent was created by John F. Burke, then at Shriners' Hospital in Boston, and Ioannis V. Yannas of M.I.T. It had helped burn patients in clinical trials by preventing water loss and promoting dermal healing. In addition, Howard Green of Harvard Medical School had devised a method for growing sheets of epidermal cells for burn patients.

An initial obstacle to developing Apligraf was obtaining a supply of collagen to support the growth of the cells. Suppliers could not guarantee us a sufficiently pure form of collagen with the correct properties. To overcome this, Paul Kemp of our company and his colleagues developed a way to derive collagen from bovine tendons. They also came up with a cold chemical sterilization technique that destroyed any contaminants without disrupting the collagen.

My colleagues and I then set out to find the culture conditions that would provide the optimum number of living human keratinocytes. At the time, however, all known methods for culturing keratinocytes were covered by patents held by other companies, and some aspects of those techniques were undesirable for our purposes. Accordingly, we set out to develop our own, unique keratinocyte culture systems. In doing so, we gained a deeper understanding of keratinocyte growth that helped us develop our subsequent production procedures.

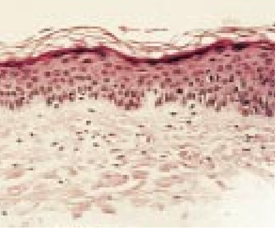
We looked to newborn human foreskins collected from circumcisions as a source for fibroblasts and


ORGANOGENESIS, INC.

Apligraf assumes the shape of the dish in which it is grown. Clinical trials have shown that it can help heal the wounds of patients with venous ulcers, which are caused by poor blood flow in the legs.

keratinocytes because of those cells' tremendous proliferative potential and their ready supply. We had learned how to grow a dermal layer and to seed the top with the epidermal cells, but a great challenge was maintaining that two-sidedness. Real skin migrates to cover wounds, and, unchecked, an epidermal layer will simply continue to grow around anything, forming a cyst.

We found a solution to this problem serendipitously. One day Kemp cast a collagen lattice into a transwell, a small cup on a plate of many such cups that is used to grow cell cultures. The bottoms of transwell cups are porous, and the sides usually carry slight electrical charges, which impels cells to stick to them. But the plate Kemp used was old and had lost its charge, so the collagen stuck only to the porous bottom. It pulled down and away from the sides of the cup, forming an almost level top rather than the usual curved shape. This particular conformation turned out to be perfect for supporting the growth of a controlled layer of epidermis on top of the collagen-fed dermal layer.



ORGANOGENESIS, INC.

Two-layered structure—with epidermis on top and dermis on the bottom—is the hallmark of Apligraf.

At this point, we could have developed either layer separately and attempted to win FDA approval. But we decided to risk the wait and go for bilayered skin. From 1990 to 1992 we marketed a version of our product that was used as an alternative to animals in toxicological and pharmacological studies. At that point, Michael Sabolinski of our company set out to determine the most appropriate first clinical application of our technology so we could design a clinical trial that stood the best chance of passing muster with the FDA. Apligraf is a device, but because it is alive it also has biologic activity. We therefore worked with FDA officials to determine the standards of approval, safety testing and manufacturing by which we would be judged.

We chose venous ulcers, skin lesions resulting from leaky veins caused by faulty valves in the leg, as Apligraf's test wound. In our trial, Apligraf revealed multiple mechanisms of action: it worked as a simple graft in some cases; in others, it directly stimulated wound repair through its own natural contingent of growth factors and other proteins. The most difficult ulcers, those that had existed for at least a year, showed the most striking healing. After 24 weeks, 47 percent of the hardest-to-heal wounds were completely closed with Apligraf, compared with only 19 percent with conventional therapy, which consists basically of applying pressure and keeping the wound moist. These results convinced the FDA to approve Apligraf for this use.

Apligraf is now commercially available in the U.S. and Canada, marketed by Novartis Pharmaceuticals. It is delivered "fresh" and has a five-day shelf life at room temperature. Studies in patients with burns or diabetic ulcers and in those undergoing dermatological surgery are either completed, near complete or under way.

NANCY PARENTEAU is chief scientific officer and senior vice president of research and development at Organogenesis, Inc., in Canton, Mass.

The Advanced

by Gail Naughton

We have created two skin products at Advanced Tissue Sciences: a nonliving wound covering called TransCyte, and Dermagraft, which consists of living cells. In March 1997 TransCyte became the first human, tissue-engineered product to receive regulatory approval when the FDA okayed its use for the treatment of full-thickness (third-degree) burns. The FDA granted approval for an additional use, the treatment of partial-thickness (second-degree) burns, in October 1997.

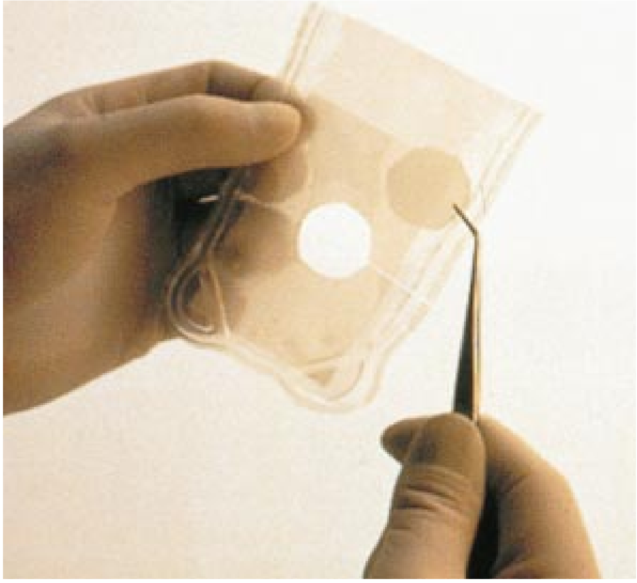
We produce TransCyte from fibroblasts isolated from newborn human foreskins, which have a large capacity for replication. Our manufacturing processes use a closed, sterile system containing polymers that act as a scaffold on which the cells grow. The environment mimics physiological conditions within the body; over a two-week growth period, the cells divide and produce growth factors, collagens and other proteins to form a functional human dermis. TransCyte is alive until frozen for shipment and off-the-shelf use.

We have embarked on an additional trial of Dermagraft and expect FDA approval at its successful conclusion.

We learned a great deal while producing TransCyte. That knowledge was crucial in our development of the even more ambitious Dermagraft. The key difference between the two products is that Dermagraft remains a living tissue, so it can be used in instances in which new skin must be induced to grow, such as diabetic foot ulcers or bedsores. These wounds require the kinds of growth factors and other proteins that living tissue produces in order to heal. (Burns, on the other hand, are rife with enzymatic activity; the nonmetabolic TransCyte helps to quiet the raging chemistry common in those wounds.) Dermagraft is currently in clinical trials in the U.S. and is being marketed internationally by our partner Smith & Nephew for use against diabetic foot ulcers.

Techniques similar to those developed to produce TransCyte generate Dermagraft. The living

Tissue Sciences Story



ADVANCED TISSUE SCIENCES, INC.

Dermagraft is frozen and then thawed for use as necessary. One foreskin, which provides starter cells, can produce enough skin to cover six football fields.

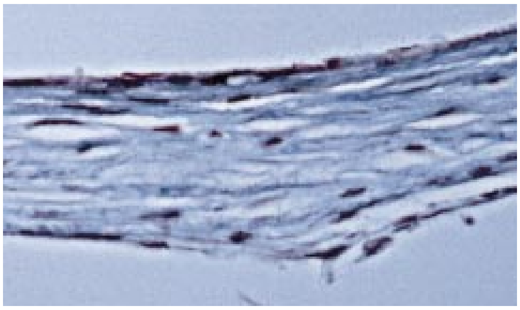
product is also frozen, for easy shipment and storage, but in a manner that leaves the cells alive. Following cryopreservation, the product is shipped and stored at –70 degrees Celsius (–94 degrees Fahrenheit); it is thawed before use and cut to the exact shape and size of the wound.

Dermagraft's odyssey through the regulatory process thus far has been both instructive and, at times, frustrating. At the start, no cookbook for tissue manufacturing existed, and little was known about cryopreservation. We developed production procedures and learned much about the effects of freezing on tissue function. During our pivotal trial for the treatment of hard-to-heal diabetic foot ulcers, we learned that 50 percent of the cells in Dermagraft need to survive freezing for the product to function optimally. Fifteen percent of diabetics develop these ulcers, as their prematurely aging cells fail to produce normal collagens and matrix proteins.

Those who received Dermagraft with at least 50 percent living cells improved greatly; 50.8 percent healed in 12 weeks. In contrast, the ulcers of only 31.7 percent of patients treated using conventional methods healed during the same time frame. Patients who received low-activity Dermagraft, with too few live cells, did no better than controls.

A supplemental, uncontrolled trial of the active version of Dermagraft again showed excellent healing, confirming the importance of a specific number of live cells in the implant. Based on these data, a panel of outside experts convened by the FDA recommended in January 1998 that Dermagraft be approved for the treatment of diabetic foot ulcers, contingent on an additional clinical trial after the product was released. The FDA ordinarily agrees with such panel recommendations. In this case, however, the FDA asked that the additional trial take place before approval.

We have since embarked on a fully controlled 30-center trial of the metabolically active version of Dermagraft and expect FDA approval at its successful conclusion. The new world of tissue-engineered products presents the FDA with unique challenges. In parts of Europe, our products are considered pharmaceuticals. In the U.S., they are devices. Regulations that cover all circumstances simply have not yet been fully defined for devices that have pharmacological activity, such as Dermagraft. We thus understand the FDA's conservatism in this area. In the meantime, the agency has recognized Dermagraft's value by granting it an Investigational Device Exemption, or IDE. This exemption basically allows Dermagraft to be available while it is still wending its way through the regulatory process.



ADVANCED TISSUE SCIENCES, INC.

Dermagraft consists of a single layer of dermis. Clinical trials suggest it is effective for treating diabetic foot ulcers.

Following approval for diabetic foot ulcers, Dermagraft should find roles in the treatment of venous ulcers, pressure ulcers (bedsores) and other chronic wounds. Knowledge gained from this enterprise has helped us create a "recipe" for frozen tissues with long shelf lives. That knowledge is being incorporated into other products in development, such as cartilage and blood vessels.

GAIL NAUGHTON is president and chief operating officer of Advanced Tissue Sciences, Inc., in La Jolla, Calif.

TISSUE ENGINEERING:

The obstacles to building new organs from cells and synthetic polymers are daunting but surmountable

As the other articles in this special report indicate, tissue engineering has emerged as a thriving new field of medical science. Just a few years ago most scientists believed that human tissue could be replaced only with direct transplants from donors or with fully artificial parts made of plastic, metal and computer chips. Many thought that whole bioartificial organs—hybrids created from a combination of living cells and natural or artificial polymers—could never be built and that the shortage of human organs for transplantation could only be met by somehow using organs from animals.

Now, however, innovative and imaginative work in laboratories around the world is demonstrating that creation of biohybrid organs is entirely feasible. Biotechnology companies that develop tissue-engineered products have a market worth of nearly $4 billion, and they are spending 22.5 percent more every year. But before this investment will begin to pay off in terms of reliably relieving human suffering caused by defects in a wide range of tissues, tissue engineering must surmount some important hurdles.

Someday equipping patients with tissue-engineered organs and tissues may be as routine as coronary bypasses are today.

Off-the-Shelf Cells

Establishing a reliable source of cells is a paramount priority for tissue engineers. Animal cells are a possibility, but ensuring that they are safe remains a concern, as does the high likelihood of their rejection by the immune system. For those reasons, human cells are favored.

The recent identification of human embryonic stem cells—cells that can give rise to a wide array of tissues that make up a person—offers one approach to the problem [see "Embryonic Stem Cells for Medicine," by Roger A. Pedersen, on page 68]. But researchers are a long way from being able to manipulate embryonic stem cells in culture to produce fully differentiated cells that can be used to create or repair specific organs.

A more immediate goal would be to isolate so-called progenitor cells from tissues. Such progenitors have taken some of the steps toward becoming specialized, but because they are not yet fully differentiated they stay flexible enough to replenish several different cell types. Arnold I. Caplan of the Cleveland Clinic and his colleagues, for instance, have isolated progenitor cells from human bone marrow that can be prompted in the laboratory to form either the osteoblasts that make bone or the chondrocytes that compose cartilage. Similarly, Lola Reid of the University of North Carolina at Chapel Hill has identified small, oval-shaped progenitor cells in adult human livers that can be manipulated in culture to form either mature hepatocytes—cells that produce bile and break down toxins—or the epithelial cells that line bile ducts.

Generating "universal donor" cell lines would be another approach. To make such cells, scientists would remove, or use other molecules to mask, proteins on the surfaces of cells that normally identify the donor cells as "nonself." This strategy is now being used by Diacrin in Charlestown, Mass., to make some types of pig cells acceptable for transplantation in humans. Diacrin also plans to use the "masking" technology to allow cell transplants between unmatched human donors. It has received regulatory approval in the U.S. to begin human trials of masked human liver cells for some cases of liver failure.

In principle, such universal donor cells would not be expected to be rejected by the recipient; they could be generated for various types of cells from many different tissues and kept growing in culture until needed. But it is not yet clear how universal donor cells will perform in large-scale clinical trials.

Parts Factories

Finding the best ways to produce cells and tissues has been far from straightforward. Scientists have identified only a handful of the biochemical signals that dictate the differentiation of embryonic stem cells and progenitor cells into specialized cell types, and we cannot yet isolate cultures of stem cells and progenitor cells from bone marrow without having connective tissue cells such as fibroblasts mixed in. (Fibroblasts are undesirable because they divide quickly and can overgrow cultures of stem cells.)

In addition, scientists need to develop more advanced procedures for growing cells in large quanti-

THE CHALLENGES AHEAD

by Robert S. Langer and Joseph P. Vacanti

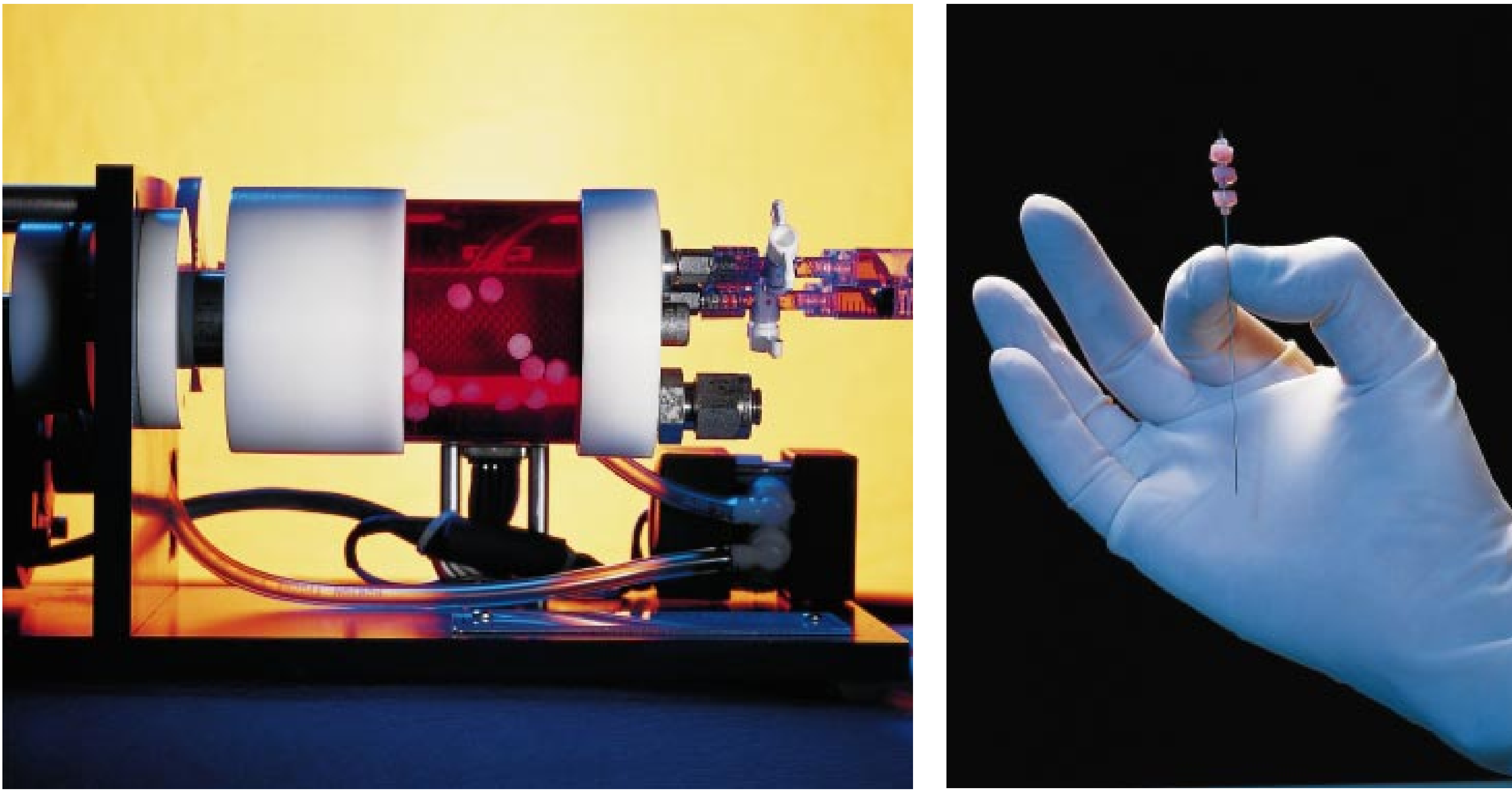
ties in so-called bioreactors, growth chambers equipped with stirrers and sensors that regulate the appropriate amounts of nutrients, gases such as oxygen and carbon dioxide, and waste products. Existing methods often yield too few cells or sheets of tissue that are thinner than desired.

New solutions are beginning to appear, however. For several years, researchers struggled to grow segments of cartilage that were thick enough for medical uses such as replacing worn-out cartilage in the knee. But once the cartilage grew beyond a certain thickness, the chondrocytes in the center were too far away from the growth medium to take up nutrients and gases, respond to growth-regulating chemical and physical signals, or expel wastes. Gordana Vunjak-Novakovic and Lisa Freed of the Massachusetts Institute of Technology solved the problem by culturing chondrocytes on a three-dimensional polymer scaffold in a bioreactor [*see photograph below*]. The relatively loose weave of the scaffold and the stirring action of the bioreactor ensured that all the cells became attached uniformly throughout the scaffold material and were bathed in culture medium.

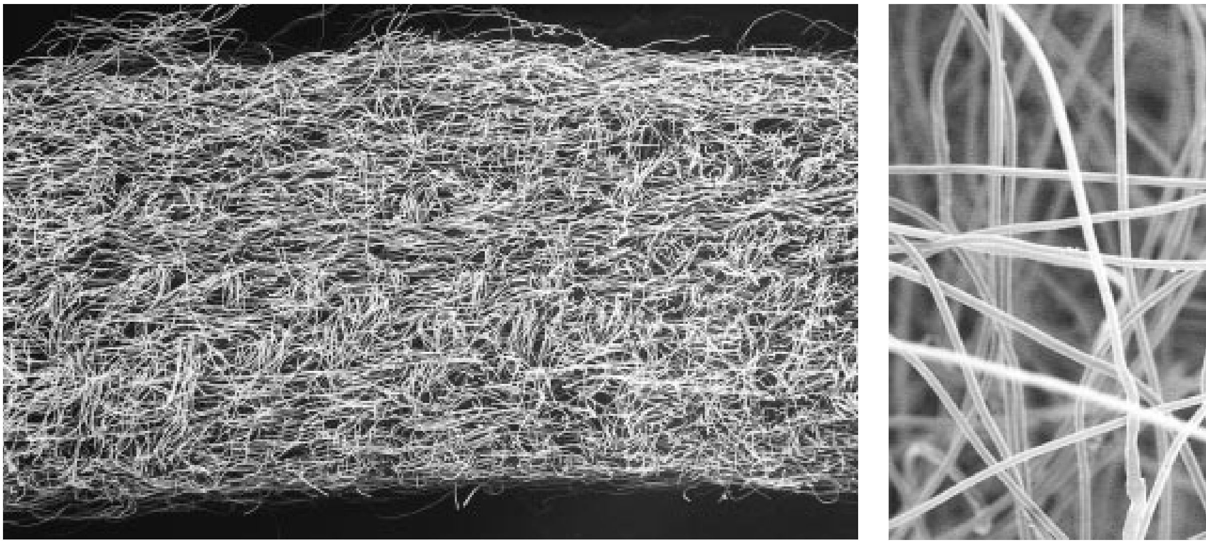
Maximizing the mechanical properties of tissues as they grow in bioreactors will be crucial because many tissues remodel, or change their overall organization, in response to being stretched, pulled or compressed. Tissue-engineered cartilage, for example, becomes larger and contains more collagen and other proteins that form a suitable extracellular matrix if it is cultured in rotating vessels that expose the developing tissue to variations in fluid forces. (Extracellular matrix is a weblike network that serves as a support for cells to grow on and organize into tissues.) Cartilage cultured in this way contains extracellular matrix proteins that make it stiffer, more durable and more responsive physiologically to external forces.

Likewise, John A. Frangos of the University of California at San Diego has shown that osteoblasts

PHOTOGRAPHS BY SAM OGDEN



Bioreactors are already churning out bioartificial human body parts made of polymer scaffolds and cells. The bioreactor below is growing plugs of human cartilage (*below right*) for use in joint repair. As the drum turns, all cells in the cartilage become bathed equally with growth medium.



PHOTOGRAPHS BY GORDANA VUNJAK-NOVAKOVIC AND LISA FREED *M.I.T.*

cultured on a base of collagen beads being stirred in a bioreactor make more bone minerals than they do when they are grown in a flat, stationary dish. And Laura E. Niklason, who is now at Duke University, has demonstrated that tissue-engineered small arteries made of endothelial cells (blood vessel lining) and smooth muscle cells shaped into tubes develop mechanical properties more akin to natural blood vessels if they have growth medium pulsed through them to imitate the blood pressure generated by a beating heart. Several other teams—including ours—are developing ways to grow skeletal and cardiac muscle, tissues that become stronger as they respond to physical stress.

Desirable Properties

Learning how to regulate cell behavior represents another important challenge. Living systems are incredibly complex: The human liver, for example, contains six different types of cells that are organized into microscopic arrays called lobules. Each cell can perform hundreds of different biochemical reactions. What is more, the biochemical activity of each cell often depends on its interaction with other cells and with the network of extracellular matrix that wends through every tissue. David J. Mooney of the University of Michigan, for instance, has shown that hepatocytes produce varying levels of a given protein according to the stickiness of the material they are growing on. To develop organs such as an implantable, bioartificial liver—one major goal of tissue engineering—researchers must better understand how to grow hepatocytes and other cells of the liver under conditions that maximize their abilities to perform their normal physiological roles.

Bioartificial heart valve made of biodegradable plastic is being "seeded" with cells from the linings of sheep blood vessels. Once implanted into a recipient sheep, the plastic breaks down gradually and is replaced by natural proteins made by the recipient's own cells in a poorly understood process called remodeling.

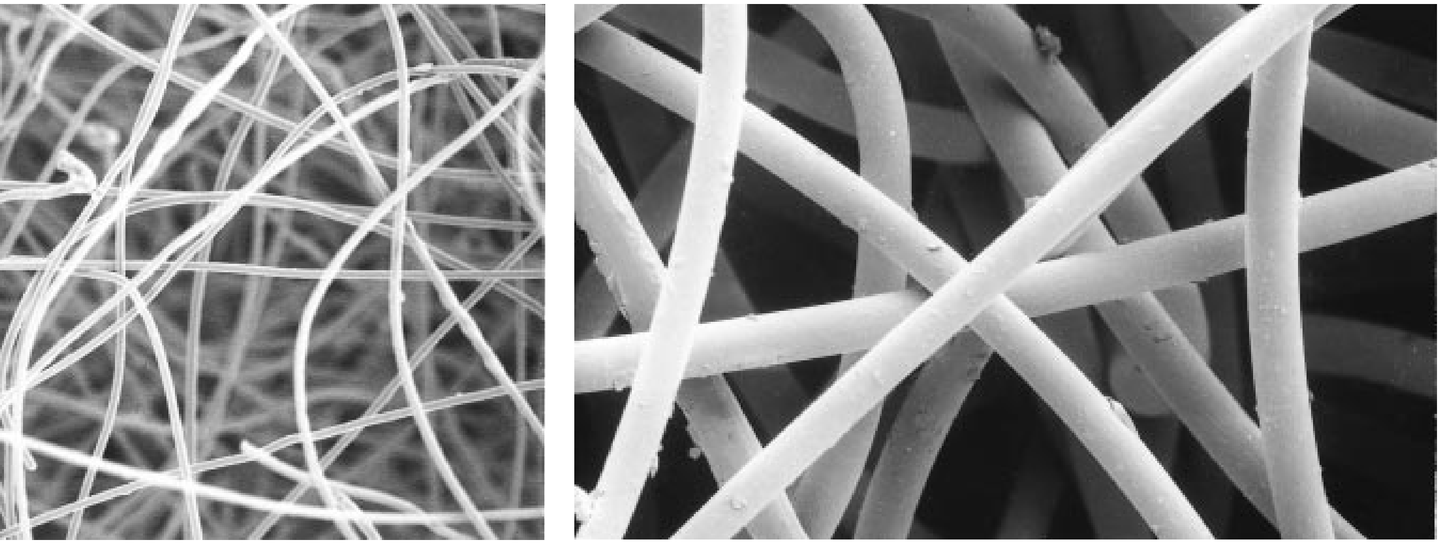
ULRICH A. STOCK *Harvard Medical School*

Understanding "remodeling" will be essential for crafting bioartificial organs and tissues that become a permanent part of the recipient. In the most successful laboratory tests of tissue-engineered products, the transplant has stimulated the growth of the recipient's own cells and tissues, which have eventually replaced the artificial polymers and transplanted cells of the graft. In collaboration with Toshiharu Shinoka and John E. Mayer of Children's Hospital in Boston, for instance, we have shown that a heart valve leaflet made of artificial polymers and lamb epithelial cells and myofibroblasts (a type of cell that helps to close wounds) became stronger, more elastic and thinner once transplanted into sheep. Moreover, the leaflet no longer consisted of artificial polymers after 11 weeks: it had been remodeled to contain only sheep extracellular matrix. Still, the precise biochemical signals and growth factors that dictate such remodeling processes remain essentially unknown.

Creating new materials that are biodegradable and do not induce the formation of scar tissue is an emerging area of tissue engineering that offers many challenges. Most of the materials now used as scaffolds for tissue engineering fall into one of two categories: synthetic materials such as biodegradable suture material or natural materials such as collagen or alginate (a gel-like substance derived from algae). The advantage of synthetic materials is that their strength, speed of degradation, microstructure and permeability can be controlled during production; natural materials, however, are usually easier for cells to stick to.

Researchers are now trying to combine the best of both worlds to design new generations of materials with particularly desirable properties. Some, for instance, are constructing biodegradable polymers that contain regions with biological activities that mimic the natural extracellular matrix of a particular tissue. One such polymer contains RGD, part of the extracellular matrix protein fibronectin. RGD is named for the single-letter abbreviation for the amino acids it is made of: arginine (*R*), glycine (*G*) and asparagine (*D*). Many types of cells normally stick to fibronectin by binding to RGD, so RGD-containing polymers might provide a more natural environment for growing cells.

Other scientists are attempting to make polymers that conduct electricity, which might be useful in growing tissue-engineered nerves, or polymers that



Biodegradable polymer scaffold shown at progressively higher magnification (*left to right*) is commonly used as the basis for tissue-engineered organs and tissues. Scientists are seeking to create even better scaffold materials that can help shape the biological and physical properties of the products they are developing.

gel rapidly. Such fast-setting polymers could be useful in injectable bioartificial products, including those that might be used to fill in a broken bone.

Inducing the growth of blood vessels, a process known as angiogenesis, will be key to sustaining many tissue-engineered organs—particularly pancreases, livers and kidneys, which require a large blood supply. Researchers have already successfully stimulated angiogenesis in bioartificial tissues growing in the laboratory by coating the polymer scaffolding supporting the tissues with growth factors that trigger blood vessel formation [see "Growing New Organs," by David J. Mooney and Antonios G. Mikos, on page 60]. Future studies will need to examine the best ways for releasing the growth factors and controlling their activity so that blood vessels form only when and where they are needed.

To the Patient

Developing new methods of tissue preservation is important to ensure that tissue-engineered products survive the trip from the factory to the operating room in good working order and do not die during transplantation. Technologies adapted from the field of donor-organ transplantation might be useful in this situation. For example, surgeons now know that much of the injury to a transplanted organ occurs during reperfusion, when the organ is connected to a blood supply in the recipient. Reperfusion induces the formation of oxygen free radicals, which literally poke holes in cell membranes and kill cells. To avoid reperfusion injury, surgeons currently add to the preservation solution chemicals that sop up such free radicals. Finding better molecules to protect tissue-engineered products from reperfusion injury and ischemic injury, which results when blood flow is insufficient, will be necessary. Cryopreservation techniques also need to be perfected so that bioartificial organs and tissues can be kept frozen until needed; methods currently used for cells will need to be developed further to work for larger tissues.

Determining the federal regulatory process for tissue-engineered products still presents a thorny issue. Bioartificial tissues and organs cut across nearly all the areas regulated by the U.S. Food and Drug Administration: they are essentially medical devices, but because they contain living cells they also produce biological substances that act like drugs. Accordingly, the FDA has treated the first tissue-engineered products to seek regulatory approval—two versions of bioartificial skin—as combination products. The agency is making tissue-engineering a priority area and is working to develop clear-cut policies to deal with bioartificial products.

We are confident that scientists and government regulators will clear all the hurdles described in this article to bring a variety of tissue-engineered products to the market in the coming years. Much challenging work remains, but someday—perhaps many years from now—equipping patients with tissue-engineered organs and tissues may be as routine as coronary bypasses are today.

The Authors

ROBERT S. LANGER and JOSEPH P. VACANTI not only pioneered many of the techniques used in tissue engineering but also trained other scientists who currently work in the field. Langer is Kenneth J. Germeshausen Professor of Chemical and Biomedical Engineering at the Massachusetts Institute of Technology. Vacanti is John Homans Professor of Surgery at Harvard Medical School and the director of the Laboratory for Tissue Engineering and Organ Fabrication at Massachusetts General Hospital. Langer and Vacanti have served as scientific advisers to several companies involved in tissue engineering.

Further Reading

TISSUE ENGINEERING. Robert Langer and Joseph P. Vacanti in *Science*, Vol. 260, pages 920–926; May 14, 1993.

ARTIFICIAL ORGANS. Robert Langer and Joseph P. Vacanti in *Scientific American*, Vol. 273, No. 3, pages 130–133; September 1995.

AN ECONOMIC SURVEY OF THE EMERGING TISSUE ENGINEERING INDUSTRY. M. J. Lysaght, N. A. P. Nguy and K. Sullivan in *Tissue Engineering*, Vol. 4, No. 3, pages 231–238; Fall 1998.

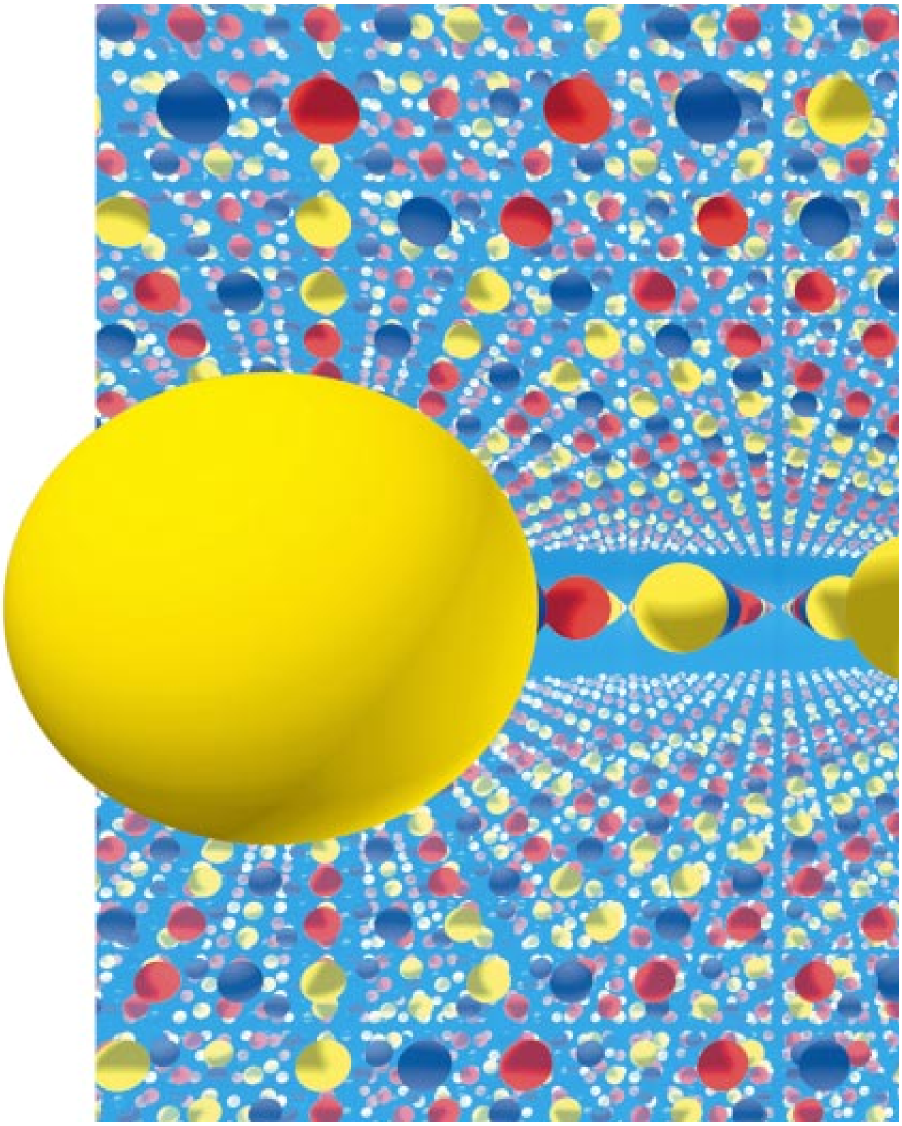
Is Space Finite?

Conventional wisdom says the universe is infinite. But it could be finite, merely giving the illusion of infinity. Upcoming measurements may finally answer this ancient question

by Jean-Pierre Luminet,
Glenn D. Starkman
and Jeffrey R. Weeks

Looking up at the sky on a clear night, we feel we can see forever. There seems to be no end to the stars and galaxies; even the darkness in between them is filled with light if only we stare through a sensitive enough telescope. In truth, of course, the volume of space we can observe is limited by the age of the universe and the speed of light. But given enough time, could we not peer ever farther, always encountering new galaxies and phenomena?

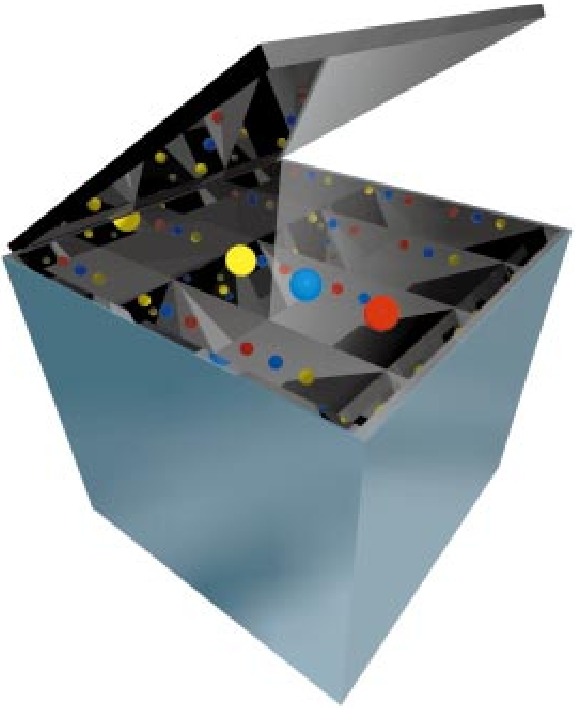
Maybe not. Like a hall of mirrors, the apparently endless universe might be deluding us. The cosmos could, in fact, be finite. The illusion of infinity would come about as light

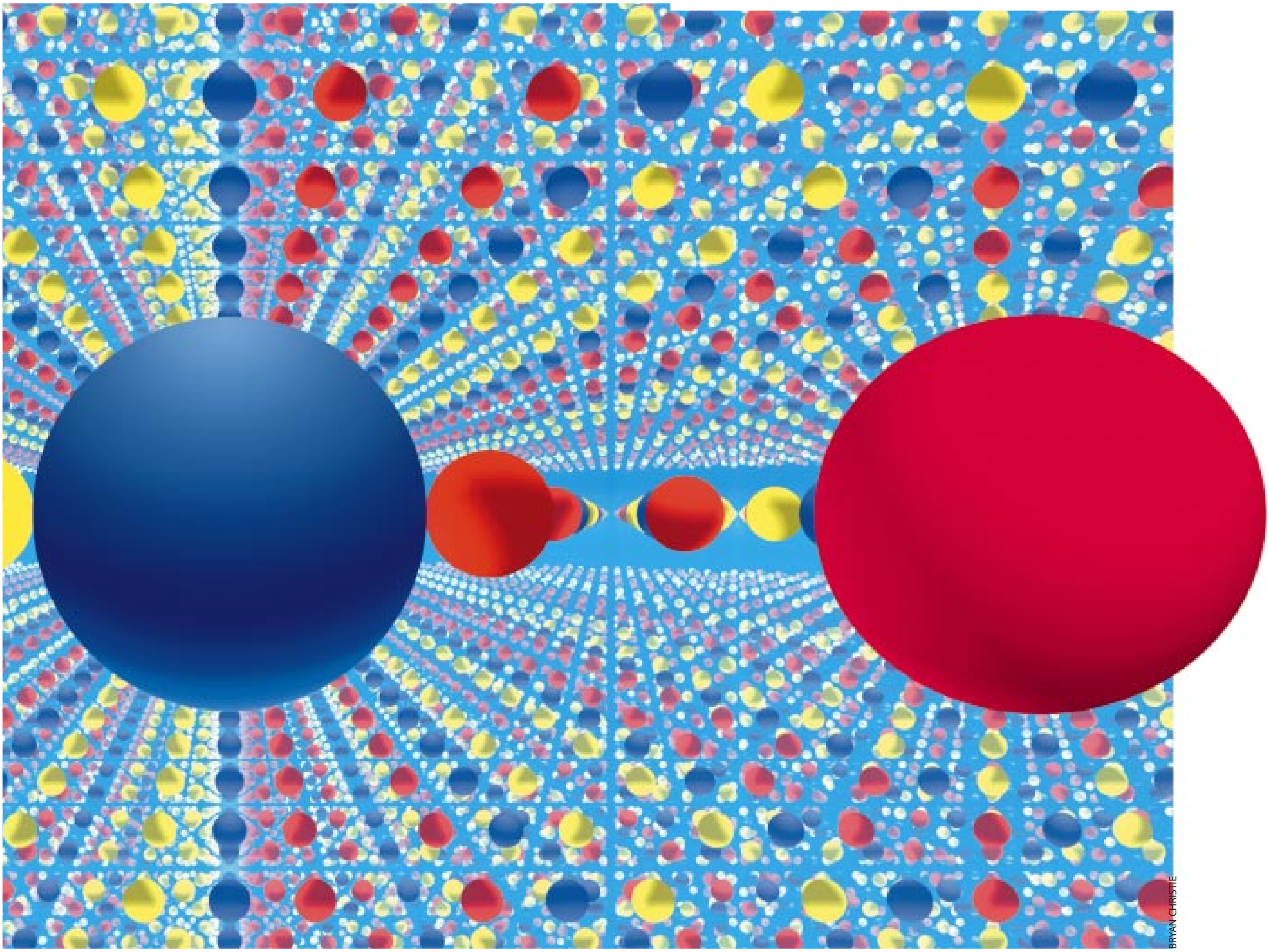


"INFINITY BOX" evokes a finite cosmos that looks endless. The box contains only three balls, yet the mirrors that line its walls produce an infinite number of images. Of course, in the real universe there is no boundary from which light can reflect. Instead a multiplicity of images could arise as light rays wrap around the universe over and over again. From the pattern of repeated images, one could deduce the universe's true size and shape.

wrapped all the way around space, perhaps more than once—creating multiple images of each galaxy. Our own Milky Way galaxy would be no exception; bizarrely, the skies might even contain facsimiles of the earth at some earlier era. As time marched on, astronomers could watch the galaxies develop and look for new mirages. But eventually no new space would enter into their view. They would have seen it all.

The question of a finite or infinite universe is one of the oldest in philosophy. A common misconception is that it has already been settled in favor of the latter. The reasoning, often repeated in textbooks, draws an unwarranted conclusion from Einstein's general theory of relativity. According to relativity, space is a dynamic medium that can curve in one of three ways, depending on the distribution of matter and energy within it. Because we are embedded in space, we cannot see the flexure directly but rather perceive it as gravitational attraction and geometric distortion of images. To determine which of the three geometries our universe has, astronomers have been measuring the density of matter and energy in the cosmos. It now appears to be too low to force space to arch back on itself—a "spherical" geometry. Therefore, space must have either the fa-



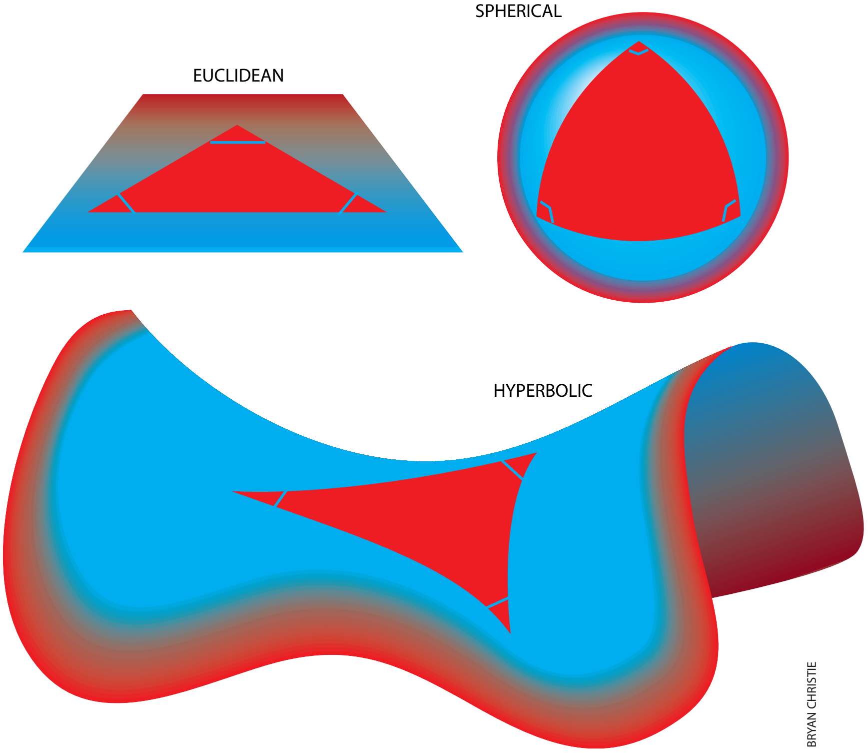


BRYAN CHRISTIE

miliar Euclidean geometry, like that of a plane, or a "hyperbolic" geometry, like that of a saddle [*see illustration at right*]. At first glance, such a universe stretches on forever.

One problem with this conclusion is that the universe could be spherical yet so large that the observable part seems Euclidean, just as a small patch of the earth's surface looks flat. A broader issue, however, is that relativity is a purely local theory. It predicts the curvature of each small volume of space—its geometry—based on the matter and energy it contains. Neither relativity nor standard cosmological observations say anything about how those volumes fit together to give the universe its overall shape—its topology. The three plausible cosmic geometries are consistent with many different topologies. For example, relativity would describe both a torus (a doughnutlike shape) and a plane with the same equations, even though the torus is finite and the plane is infinite. Determining the topology requires some physical understanding beyond relativity.

The usual assumption is that the universe is, like a plane, "simply connected," which means there is only one direct path for light to travel from a source to an observer. A simply connected Euclidean or hyperbolic universe would indeed be infinite. But the universe might instead be "multiply connected," like a torus, in which case there are many different such paths. An observer would see multiple images of each galaxy and could easily misinterpret them as distinct galaxies in an endless space, much as a visitor to a mirrored room has the illusion of seeing a huge crowd.



BRYAN CHRISTIE

LOCAL GEOMETRY of space can be Euclidean, spherical or hyperbolic—the only possibilities consistent with the observed symmetry of the cosmos on large scales. On the Euclidean plane, the angles of a triangle add to exactly 180 degrees; on the spherical surface, they add to over 180 degrees; and on the hyperbolic surface (or saddle), to less than 180 degrees. Local geometry determines how objects move. But it does not describe how individual volumes connect to give the universe its global shape.

A multiply connected space is no mere mathematical whimsy; it is even preferred by some schemes for unifying the fundamental forces of nature, and it does not contradict any available evidence. Over the past few years, research into cosmic topology has blossomed. New observations may soon reach a definitive answer.

Comfort in the Finite

Many cosmologists expect the universe to be finite. Part of the reason may be simple comfort: the human mind encompasses the finite more readily than the infinite. But there are also two scientific lines of argument that favor finitude. The first involves a thought experiment devised by Isaac Newton and revisited by George Berkeley and Ernst Mach. Grappling with the causes of inertia, Newton imagined two buckets partially filled with water. The first bucket is left still, and the surface of the water is flat. The second bucket is spun rapidly, and the surface of the water is concave. Why?

The naive answer is centrifugal force. But how does the second bucket know it is spinning? In particular, what defines the inertial reference frame relative to which the second bucket spins and the first does not? Berkeley and Mach's answer was that all the matter in the universe collectively provides the reference frame. The first bucket is at rest relative to distant galaxies, so its surface remains flat. The second bucket spins relative to those galaxies, so its surface is concave. If there were no distant galaxies, there would be no reason to prefer one reference frame over the other. The surface in both buckets would have to remain flat, and therefore the water would require no centripetal force to keep it rotating. In short, it would have no inertia. Mach inferred that the amount of inertia a body experiences is proportional to the total amount of matter in the universe. An infinite universe would cause infinite inertia. Nothing could ever move.

In addition to Mach's argument, there is preliminary work in quantum cosmology, which attempts to describe how the universe emerged spontaneously from the void. Some such theories predict that a low-volume universe is more probable than a high-volume one. An infinite universe would have zero probability of coming into existence [see "Quantum Cosmology and the Creation of the Universe," by Jonathan J. Halliwell; SCIENTIFIC AMERICAN, December 1991]. Loosely speaking, its energy would be infinite, and no quantum fluctuation could muster such a sum.

Historically, the idea of a finite universe ran into its own obstacle: the apparent need for an edge. Aristotle argued that the universe is finite on the grounds that a boundary was necessary to fix an absolute reference frame, which was important to his worldview. But his critics wondered what happened at the edge. Every edge has another side. So why not redefine the "universe" to include that other side? German mathematician Georg F. B. Riemann solved the riddle in the mid-19th century. As a model for the cosmos, he proposed the hypersphere—the three-dimensional surface of a four-dimensional ball, just as an ordinary sphere is the two-dimensional surface of a three-dimensional ball. It was the first example of a space that is finite yet has no problematic boundary.

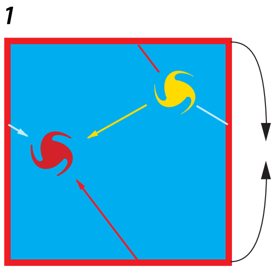
One might still ask what is outside the universe. But this question supposes that the ultimate physical reality must be a Euclidean space of some dimension. That is, it presumes that if space is a hypersphere, then that hypersphere must sit in a four-dimensional Euclidean space, allowing us to view it from the outside. Nature, however, need not cling to this notion. It would be perfectly acceptable for the universe to be a hypersphere and not be embedded in any higher-dimensional space. Such an object may be difficult to visualize, because we are used to viewing shapes from the outside. But there need not be an "outside."

By the end of the 19th century, mathematicians had discovered a variety of finite spaces without boundaries. German astronomer Karl Schwarzschild brought this work to the attention of his colleagues in 1900. In a postscript to an article in *Vierteljahrschrift der Astronomischen Gesellschaft,* he challenged his readers:

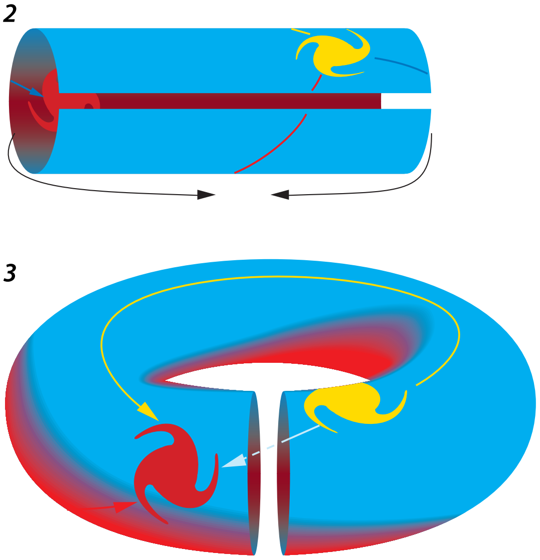
> Imagine that as a result of enormously extended astronomical experience, the entire universe consists of countless identical copies of our Milky Way, that the infinite space can be partitioned into cubes each containing an exactly identical copy of our Milky Way. Would we really cling on to the assumption of infinitely many identical repetitions of the same world? . . . We would be much happier with the view that these repetitions are illusory, that in reality space has peculiar connection properties so that if we leave any one cube through a side, then we immediately reenter it through the opposite side.

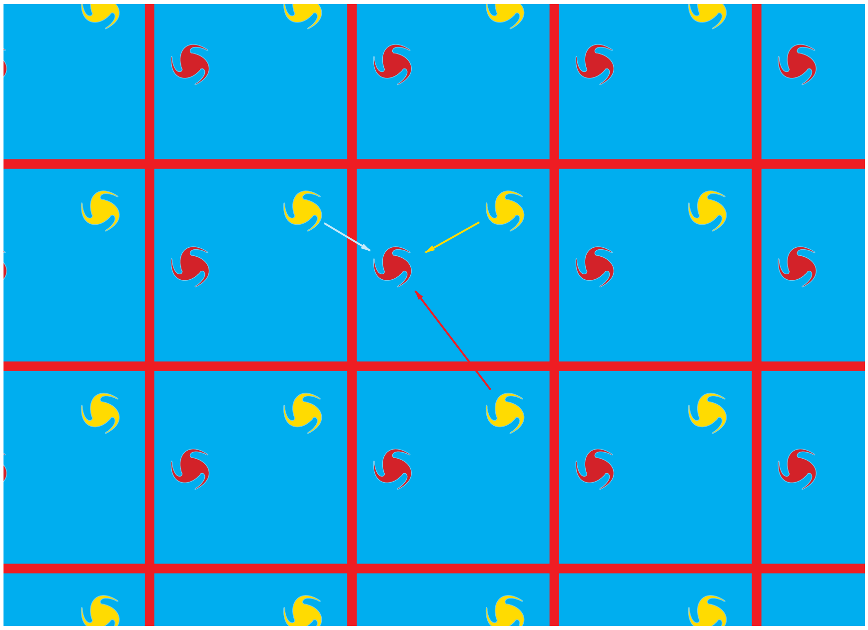
Schwarzschild's example illustrates how one can mentally construct a torus from Euclidean space. In two dimensions, begin with a square and identify opposite sides as the same—as is done in many video games, such as the venerable Asteroids, in which a spaceship going off the right side of the screen reappears on the left side. Apart from the interconnections between sides, the space is as it was before. Triangles span 180 degrees, parallel laser beams never meet and so on—all the familiar rules of Euclidean geometry hold. At first glance, the space looks infinite to those who live within it, because there is no limit to how far they can see. Without traveling around the universe and reencountering the same objects, the ship could not tell that it is in a torus [*see illustration below*]. In three dimensions, one begins with a cubical block of space and glues together opposite faces to produce a 3-torus.

The Euclidean 2-torus, apart from some sugar glazing, is topologically equivalent to the surface of a doughnut. Unfortunately, the Euclidean torus is food only for the mind. It cannot sit in our three-dimensional Euclidean space. Doughnuts may do so because they have been bent into a spherical geometry around the outside and a hyperbolic geometry around the hole.



DOUGHNUT SPACE, more properly known as the Euclidean 2-torus, is a flat square whose opposite sides are connected (*1*). Anything crossing one edge reenters from the opposite edge. Although this surface cannot exist within our three-dimensional space, a distorted version can be built by taping together top and bottom (*2*) and scrunching the resulting cylinder into a ring (*3*). For observers in the pictured red galaxy, space seems infinite because their line of sight never ends (*below*). Light from the yellow galaxy can reach them along several different paths, so they see more than one image of it. A Euclidean 3-torus is built from a cube rather than a square.





BRYAN CHRISTIE

Without this curvature, doughnuts could not be viewed from the outside.

When Albert Einstein published the first relativistic model of the universe in 1917, he chose Riemann's hypersphere as the overall shape. At that time, the topology of space was an active topic of discussion. Russian mathematician Aleksander Friedmann soon generalized Einstein's model to permit an expanding universe and a hyperbolic space. His equations are still routinely used by cosmologists. He emphasized that the equations of his hyperbolic model applied to finite universes as well as to the standard infinite one—an observation all the more remarkable because, at the time, no examples of finite hyperbolic spaces were known.

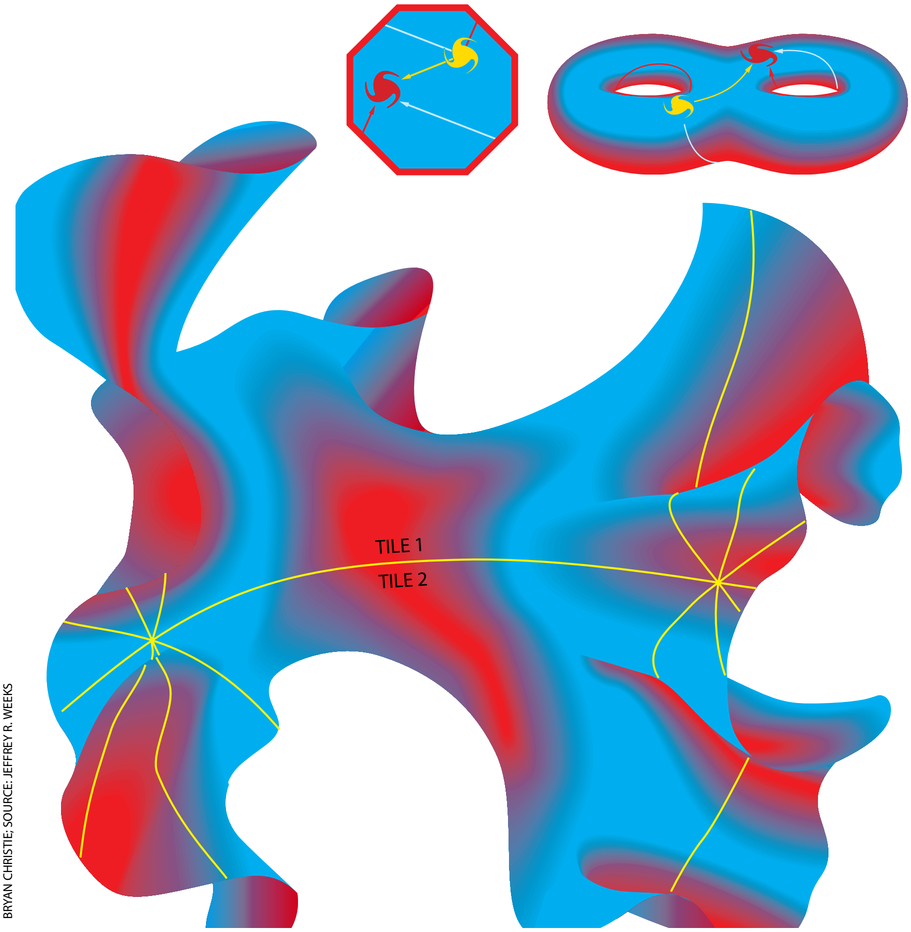
Eightfold

Of all the issues in cosmic topology, perhaps the most difficult to grasp is how a hyperbolic space can be finite. For simplicity, first consider a two-dimensional universe. Mimic the construction of a 2-torus but begin with a hyperbolic surface instead. Cut out a regular octagon and identify opposite pairs of edges, so that anything leaving the octagon across one edge returns at the opposite edge. Alternatively, one could devise an octagonal Asteroids screen [*see illustration at right*]. This is a multiply connected universe, topologically equivalent to a two-holed pretzel. An observer at the center of the octagon sees the nearest images of himself or herself in eight different directions. The illusion is that of an infinite hyperbolic space, even though this universe is really finite. Similar constructions are possible in three dimensions, although they are harder to visualize. One cuts a solid polyhedron out of a hyperbolic three-dimensional space and glues pairs of faces so that any object leaving from one face returns at the corresponding point on the matching face.

The angles of the octagon merit careful consideration. On a flat surface, a polygon's angles do not depend on its size. A large regular octagon and a small regular octagon both have inside angles of 135 degrees. On a curved surface, however, the angles do vary with size. On a sphere the angles increase as the polygon grows, whereas on a hyperbolic surface the angles decrease. The above construction requires an octagon that is just the right size to have 45-degree angles, so that when the opposite sides are identified, the eight corners will meet at a single point and the total angle will be 360 degrees. This subtlety explains why the construction would not work with a flat octagon; in Euclidean geometry, eight 135-degree corners cannot meet at a single point. The two-dimensional universe obtained by identifying opposite sides of an octagon must be hyperbolic. The topology dictates the geometry.

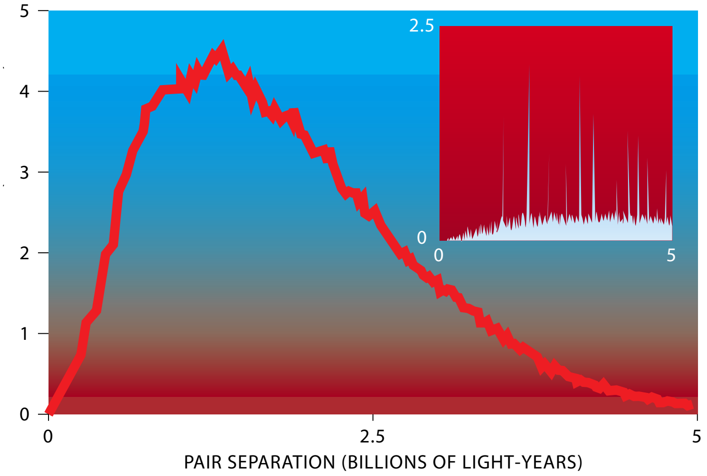
The size of the polygon or polyhedron is measured relative to the only geometrically meaningful length scale for a space: the radius of curvature. A sphere, for example, can have any physical size (in meters, say), but its surface area will always be exactly 4π times the square of its radius—that is, 4π square radians. The same principle applies to the size of a hyperbolic topology, for which a radius of curvature can also be defined. The most compact hyperbolic topology, discovered by one of us (Weeks) in 1985, may be constructed by identifying pairs of faces of an 18-sided polyhedron. It has a volume of approximately 0.94 cubic radian. Other topologies are built from larger polyhedra.

The universe, too, can be measured in units of radians. Diverse astronomical observations agree that the density of matter in the cosmos is only a third of that needed for space to be Euclidean. Either a cosmological constant makes up the difference [see "Cosmological Antigravity," by Lawrence M. Krauss; Scientific American, January], or the universe has a hyperbolic geometry with a radius of curvature of 18 billion light-years. In the latter case, the observable universe has a volume of 180 cubic radians—enough room for nearly



BRYAN CHRISTIE; SOURCE: JEFFREY R. WEEKS

FINITE HYPERBOLIC SPACE is formed by an octagon whose opposite sides are connected, so that anything crossing one edge reenters from the opposite edge (*top left*). Topologically, the octagonal space is equivalent to a two-holed pretzel (*top right*). Observers who lived on the surface would see an infinite octagonal grid of galaxies. Such a grid can be drawn only on a hyperbolic manifold—a strange floppy surface where every point has the geometry of a saddle (*bottom*).



BRYAN CHRISTIE; SOURCE: JEAN-PIERRE LUMINET

DISTANCES BETWEEN GALAXY CLUSTERS do not show the pattern expected for a finite, interconnected universe—namely, sharp peaks at distances related to the true size of the cosmos (*inset*). But the authors only studied clusters within roughly two billion light-years of the earth. The universe could still be interconnected on larger scales.

200 of the Weeks polyhedra. In other words, if the universe has the Weeks topology, its volume is only 0.5 percent of what it appears to be. As space expands uniformly, its proportions do not change, so the topology remains constant.

In fact, almost all topologies require hyperbolic geometries. In two dimensions, a finite Euclidean space must have the topology of either a 2-torus or a Klein bottle; in three dimensions, there are only 10 Euclidean possibilities—namely, the 3-torus and nine simple variations on it, such as gluing together opposite faces with a quarter turn or with a reflection, instead of straight across. By comparison, there are infinitely many possible topologies for a finite hyperbolic three-dimensional universe. Their rich structure is still the subject of intense research [see "The Mathematics of Three-Dimensional Manifolds," by William P. Thurston and Jeffrey R. Weeks; SCIENTIFIC AMERICAN, July 1984].

Cosmic Crystals

Despite the plethora of possibilities, the cosmologists of the 1920s had no way to measure the topology of the universe directly, and so they eventually lost interest in the issue. The decades from 1930 to 1990 were the dark ages of the subject. Most astronomy textbooks, quoting one another for support, stated that the universe must be either a hypersphere, an infinite Euclidean space or an infinite hyperbolic space. Other topologies were largely forgotten. But the 1990s have seen the rebirth of the subject. Roughly as many papers have been published on cosmic topology in the past three years as in the preceding 80. Most exciting of all, cosmologists are finally poised to determine the topology observationally.

The simplest test of topology is to look at the arrangement of galaxies. If they lie in a rectangular lattice, with images of the same galaxy repeating at equivalent lattice points, the universe is a 3-torus. Other patterns reveal more complicated topologies. Unfortunately, looking for such patterns is difficult, because the images of a galaxy would depict different points in its history. Astronomers would need to recognize the same galaxy despite changes in appearance or shifts in position relative to neighboring galaxies. Over the past 25 years researchers such as Dmitri Sokoloff of Moscow State University, Viktor Shvartsman of the Soviet Academy of Sciences, J. Richard Gott III of Princeton University and Helio V. Fagundes of the Institute for Theoretical Physics in São Paulo have looked for and found no repeating images among galaxies within one billion light-years of the earth.

Others—such as Boudewijn F. Roukema of the Inter-University Center for Astronomy and Astrophysics in Pune, India—have sought patterns among quasars. Because these objects, thought to be powered by black holes at the cores of galaxies, are bright, any patterns among them can be seen from large distances. The observers identified all groupings of four or more quasars. By examining the spatial relations within each group, they checked whether any pair of groups could in fact be the same group seen from two different directions. Roukema identified two possibilities, but they may not be statistically significant.

Roland Lehoucq and Marc Lachièze-Rey of the Center for Astrophysical Studies in Saclay, France, together with one of us (Luminet), have tried to circumvent the problems of galaxy recognition in another way. We have developed the method of cosmic crystallography, which in a Euclidean universe can make out a pattern statistically without needing to recognize specific galaxies as images of one another. If galaxy images repeat periodically, a histogram of all galaxy-to-galaxy distances should show peaks at certain distances, which represent the true size of the universe. So far we have seen no patterns [*see illustration above*], but this may be because of the paucity of data on galaxies farther away than two billion light-years. The Sloan Digital Sky Survey—an ongoing American-Japanese collaboration to prepare a three-dimensional map of much of the universe—will produce a larger data set for these studies.

Finally, several other research groups plan to ascertain the topology of the universe using the cosmic microwave background, the faint glow remaining from the time when the primordial plasma of the big bang condensed to hydrogen and helium gas. The radiation is remarkably homogeneous: its temperature and intensity are the same in all parts of the sky to nearly one part in 100,000. But there are slight undulations discovered in 1991 by the Cosmic Background Explorer (COBE) satellite. Roughly speaking, the microwave background depicts density variations in the early universe, which ultimately seeded the growth of stars and galaxies [see "The Evolution of the Universe," by P. James E. Peebles, David N. Schramm, Edwin L. Turner and Richard G. Kron; SCIENTIFIC AMERICAN, October 1994].

Circular Reasoning

These fluctuations are the key to resolving a variety of cosmological issues, and topology is one of them. Microwave photons arriving at any given moment began their journeys at approximately the same time and distance from the earth. So their starting points form a sphere, called the last scattering surface, with the earth at the center. Just as a sufficiently large paper disk overlaps itself when wrapped around a broom handle, the last scattering surface will intersect itself if it is big enough to wrap all the way around the universe. The intersection of a sphere with itself is simply a circle of points in space.

Looking at this circle from the earth, astronomers would see two circles in the sky that share the same pattern of temperature variations. Those two circles are really the same circle in space seen from two perspectives [*see illustration below*]. They are analogous to the multiple images of a candle in a mirrored room, each of which shows the candle from a different angle.

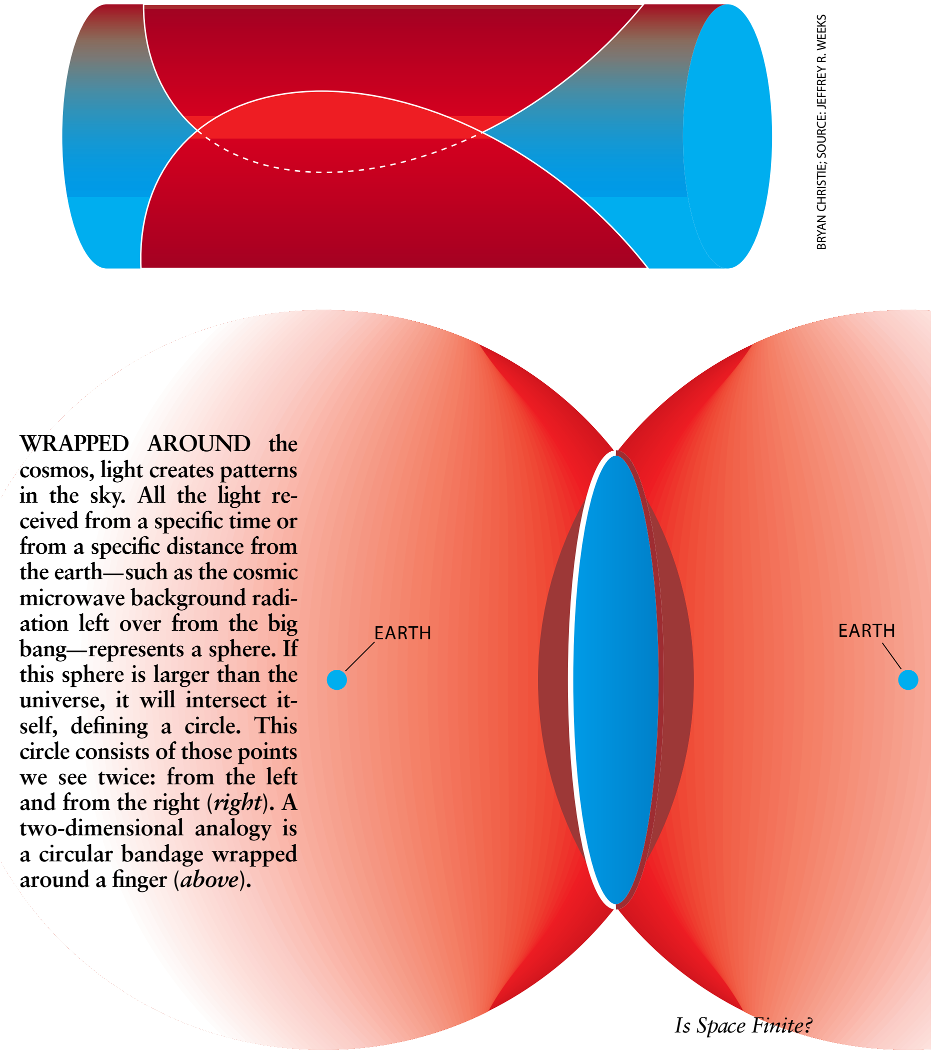
Two of us (Starkman and Weeks), working with David N. Spergel and Neil J. Cornish of Princeton, hope to detect such circle pairs. The beauty of this method is that it is unaffected by the uncertainties of contemporary cosmology—it relies on the observation that space has constant curvature but makes no assumptions about the density of matter, the geometry of space or the presence of a cosmological constant. The main problem is to identify the circles despite the forces that tend to distort their images. For example, as galaxies coalesce, they exert a varying gravitational pull on the radiation as it travels toward the earth, shifting its energy.

Unfortunately, COBE was incapable of resolving structures on an angular scale of less than 10 degrees. Moreover, it did not identify individual hot or cold spots; all one could say for sure is that statistically some of the fluctuations were real features rather than instrumental artifacts. Higher-resolution and lower-noise instruments have since been developed. Some are already making observations from ground-based or balloon-borne observatories, but they do not cover the whole sky. The crucial observations will be made by the National Aeronautics and Space Administration's Microwave Anisotropy Probe (MAP), due for launch late next year, and the European Space Agency's Planck satellite, scheduled for 2007.

The relative positions of the matching circles, if any, will reveal the specific topology of the universe. If the last scattering surface is just barely big enough to wrap around the universe, it will intersect only its nearest ghost images. If it is larger, it will reach farther and intersect the next nearest images. If the last scattering surface is large enough, we expect hundreds or even thousands of circle pairs [*see illustration on opposite page*]. The data will be highly redundant. The largest circles will completely determine the topology of space as well as the position and orientation of all smaller circle pairs. Thus, the internal consistency of the patterns will verify not only the correctness of the topological findings but also the correctness of the microwave background data.

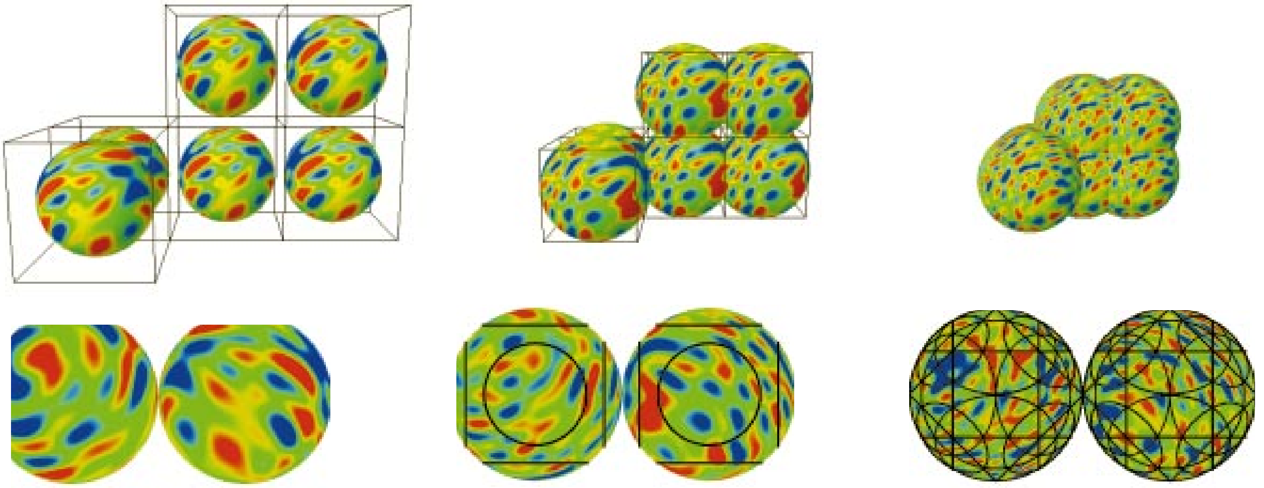
Other teams have different plans for the data. John D. Barrow and Janna J. Levin of the University of Sussex, Emory F. Bunn of Bates College, and Evan Scannapieco and Joseph I. Silk of the University of California at Berkeley intend to examine the pattern of hot and cold spots directly. The group has already constructed sample maps simulating the microwave background for particular topologies. They have multiplied the temperature in each direction by the temperature in every other direction, generating a huge four-dimensional map of what is usually called the two-point correlation function. The maps provide a quantitative way of comparing topologies. J. Richard Bond, Dmitry Pogosyan and Tarun Souradeep of the Canadian Institute for Theoretical Astrophysics are applying related new techniques to the existing COBE data, which could prove sufficiently accurate to identify the smallest hyperbolic spaces.

Beyond the immediate intellectual satisfaction, discovering the topology of space would have profound implications for physics. Although relativity says nothing about the universe's topology, newer and more comprehensive theories that are under development should predict the topology or at least assign probabilities to the various possibilities. These theories are needed to explain gravity in the earliest moments of the big bang, when quantum-mechanical effects were important [see "Quantum Gravity," by Bryce S. DeWitt; SCIENTIFIC AMERICAN, December 1983]. The theories of every-



WRAPPED AROUND the cosmos, light creates patterns in the sky. All the light received from a specific time or from a specific distance from the earth—such as the cosmic microwave background radiation left over from the big bang—represents a sphere. If this sphere is larger than the universe, it will intersect itself, defining a circle. This circle consists of those points we see twice: from the left and from the right (*right*). A two-dimensional analogy is a circular bandage wrapped around a finger (*above*).

BRYAN CHRISTIE; SOURCE: JEFFREY R. WEEKS



JEFFREY R. WEEKS

THREE POSSIBLE UNIVERSES, large, medium and small (*top row*), would produce distinctive patterns in the cosmic microwave background radiation, as simulated here (*bottom row*). Each of these universes has the topology of a 3-torus and is shown repeated six times to evoke the regular grid that an observer would see. In the large universe, the sphere of background radiation does not overlap itself, so no patterns emerge. In the medium universe, the sphere intersects itself once in each direction. One may verify that tracing clockwise around the central circle in the left hemisphere reveals the same sequence of colors as tracing counterclockwise in the right. Finally, in the small universe, the sphere intersects itself many times, resulting in a more complex pattern.

thing, such as string theory, are in their infancy and do not yet have testable consequences. But eventually the candidate theories will make predictions about the topology of the universe on large scales.

The tentative steps toward the unification of physics have already spawned the subfield of quantum cosmology. There are three basic hypotheses for the birth of the universe, which are advocated, respectively, by Andrei Linde of Stanford University, Alexander Vilenkin of Tufts University and Stephen W. Hawking of the University of Cambridge. One salient point of difference is whether the expected volume of a newborn universe is very large (Linde's and Vilenkin's proposals) or very small (Hawking's). Topological data may be able to distinguish among these models.

If observations do find the universe to be finite, it might help to resolve a major puzzle in cosmology: the universe's large-scale homogeneity. The need to explain this uniformity led to the theory of inflation, but inflation has run into difficulty of late, because in its standard form it would have made the cosmic geometry Euclidean—in apparent contradiction with the observed matter density. This conundrum has driven theorists to postulate hidden forms of energy and modifications to inflation [see "Inflation in a Low-Density Universe," by Martin A. Bucher and David N. Spergel; Scientific American, January]. An alternative is that the universe is smaller than it looks. If so, inflation could have stopped prematurely—before imparting a Euclidean geometry—and still have made the universe homogeneous. Igor Y. Sokolov of the University of Toronto and others have used COBE data to rule out this explanation if space is a 3-torus. But it remains viable if space is hyperbolic.

Since ancient times, cultures around the world have asked how the universe began and whether it is finite or infinite. Through a combination of mathematical insight and careful observation, science in this century has partially answered the first question. It might begin the next century with an answer to the second as well.

The Authors

JEAN-PIERRE LUMINET, GLENN D. STARKMAN and JEFFREY R. WEEKS say they relish participating in the boom years of cosmic topology, as researchers come together across disciplinary boundaries and no question is considered stupid. Luminet, who studies black holes at Paris Observatory, has written several books of science and of poetry and collaborated with composer Gérard Grisey on the musical performance *Le Noir de l'Etoile.* Starkman was institutionalized for six years—at the Institute for Advanced Study in Princeton, N.J., and then at the Canadian Institute for Theoretical Astrophysics in Toronto. He has been released into the custody of Case Western Reserve University in Cleveland. Weeks, the mathematician of the trio, resigned his position at Ithaca College to care for his newborn son and now receives funding from the National Science Foundation to develop research software.

Further Reading

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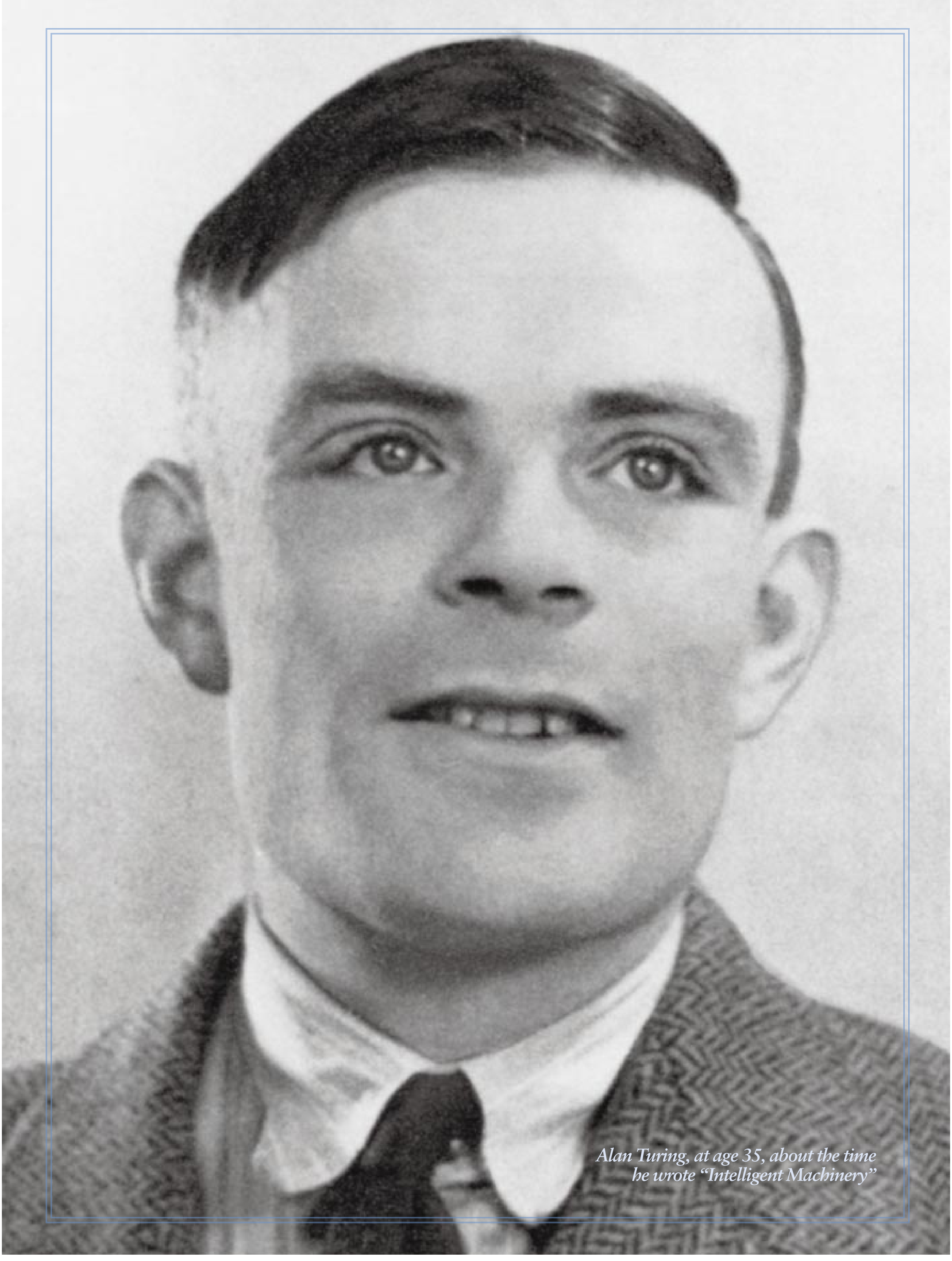


Alan Turing, at age 35, about the time he wrote "Intelligent Machinery"

Alan Turing's Forgotten Ideas in Computer Science

Well known for the machine, test and thesis that bear his name, the British genius also anticipated neural-network computers and "hypercomputation"

by B. Jack Copeland and Diane Proudfoot

W. HEFFER AND SONS LTD., CAMBRIDGE, ENGLAND

Alan Mathison Turing conceived of the modern computer in 1935. Today all digital computers are, in essence, "Turing machines." The British mathematician also pioneered the field of artificial intelligence, or AI, proposing the famous and widely debated Turing test as a way of determining whether a suitably programmed computer can think. During World War II, Turing was instrumental in breaking the German Enigma code in part of a top-secret British operation that historians say shortened the war in Europe by two years. When he died at the age of 41, Turing was doing the earliest work on what would now be called artificial life, simulating the chemistry of biological growth.

Throughout his remarkable career, Turing had no great interest in publicizing his ideas. Consequently, important aspects of his work have been neglected or forgotten over the years. In particular, few people—even those knowledgeable about computer science—are familiar with Turing's fascinating anticipation of connectionism, or neuronlike computing. Also neglected are his groundbreaking theoretical concepts in the exciting area of "hypercomputation." According to some experts, hypercomputers might one day solve problems heretofore deemed intractable.

The Turing Connection

Digital computers are superb number crunchers. Ask them to predict a rocket's trajectory or calculate the financial figures for a large multinational corporation, and they can churn out the answers in seconds. But seemingly simple actions that people routinely perform, such as recognizing a face or reading handwriting, have been devilishly tricky to program. Perhaps the networks of neurons that make up the brain have a natural facility for such tasks that standard computers lack. Scientists have thus been investigating computers modeled more closely on the human brain.

Connectionism is the emerging science of computing with networks of artificial neurons. Currently researchers usually simulate the neurons and their interconnections within an ordinary digital computer (just as engineers create virtual models of aircraft wings and skyscrapers). A training algorithm that runs on the computer adjusts the connections between the neurons, honing the network into a special-purpose machine dedicated to some particular function, such as forecasting international currency markets.

Modern connectionists look back to Frank Rosenblatt, who published the first of many papers on the topic in 1957, as the founder of their approach. Few realize that Turing had already investigated connectionist networks as early as 1948, in a little-known paper entitled "Intelligent Machinery."

Written while Turing was working for the National Physical Laboratory in London, the manuscript did not meet with his employer's approval. Sir Charles Darwin, the rather headmasterly director of the laboratory and grandson of the great English naturalist, dismissed it as a "schoolboy essay." In reality, this farsighted paper was the first manifesto of the field of artificial intelligence. In the work—which remained unpublished until 1968, 14 years after Turing's death—the British mathematician not only set out the fundamentals of connectionism but also brilliantly introduced many of the concepts that were later to become central to AI, in some cases after reinvention by others.

In the paper, Turing invented a kind of neural network that he called a "B-type unorganized machine," which consists of artificial neurons and devices that modify the connections between them. B-type machines may contain any number of neurons connected in any pattern but are always subject to the restriction that each neuron-to-neuron connection must pass through a modifier device.

Few realize that Turing had already investigated connectionist networks as early as 1948.

All connection modifiers have two training fibers. Applying a pulse to one of them sets the modifier to "pass mode," in which an input—either 0 or 1—passes through unchanged and becomes the output. A pulse on the other fiber places the modifier in "interrupt mode," in which the output is always 1, no matter what the input is. In this state the modifier destroys all information attempting to pass along the connection to which it is attached.

Once set, a modifier will maintain its function (either "pass" or "interrupt") unless it receives a pulse on the other training fiber. The presence of these ingenious connection modifiers enables the training of a B-type unorganized machine by means of what Turing called "appropriate interference, mimicking education." Actually, Turing theorized that "the cortex of an infant is an unorganized machine, which can be organized by suitable interfering training."

Each of Turing's model neurons has two input fibers, and the output of a neuron is a simple logical function of its two inputs. Every neuron in the network executes the same logical operation of "not and" (or NAND): the output is 1 if either of the inputs is 0. If both inputs are 1, then the output is 0.

Turing selected NAND because every other logical (or Boolean) operation can be accomplished by groups of NAND neurons. Furthermore, he showed that even the connection modifiers themselves can be built out of NAND neurons. Thus, Turing specified a network made up of nothing more than NAND neurons and their connecting fibers—about the simplest possible model of the cortex.

In 1958 Rosenblatt defined the theoretical basis of connectionism in one succinct statement: "Stored information takes the form of new connections, or transmission channels in the nervous system (or the creation of conditions which are functionally equivalent to new connections)." Because the destruction of existing connections can be functionally equivalent to the creation of new ones, researchers can build a network for accomplishing a specific task by taking one with an excess of connections and selectively destroying some of them. Both actions—destruction and creation—are employed in the training of Turing's B-types.

At the outset, B-types contain random interneural connections whose modifiers have been set by chance to either pass or interrupt. During training, unwanted connections are destroyed by switching their attached modifiers to interrupt mode. Conversely, changing a modifier from interrupt to pass in effect creates a connection. This selective culling and enlivening of connections hones the initially random network into one organized for a given job.

Turing wished to investigate other kinds of unorganized machines, and he longed to simulate a neural network and its training regimen using an ordinary digital computer. He would, he said, "allow the whole system to run for an appreciable period, and then break in as a kind of 'inspector of schools' and see what progress had been made." But his own work on neural networks was carried out shortly before the first general-purpose electronic computers became available. (It was not until 1954, the year of Turing's death, that Belmont G. Farley and Wesley A. Clark succeeded at the Massachusetts Institute of Technology in running the first computer simulation of a small neural network.)

Paper and pencil were enough, though, for Turing to show that a sufficiently large B-type neural network can be configured (via its connection modifiers) in such a way that it becomes a general-purpose computer. This discovery illuminates one of the most fundamental problems concerning human cognition.

From a top-down perspective, cognition includes complex sequential processes, often involving language or other forms of symbolic representation, as in mathematical calculation. Yet from a bottom-up view, cognition is nothing but the simple firings of neurons. Cognitive scientists face the problem of how to reconcile these very different perspectives.

Turing's discovery offers a possible solution: the cortex, by virtue of being a neural network acting as a general-purpose computer, is able to carry out the sequential, symbol-rich processing discerned in the view from the top. In 1948 this hypothesis was well ahead of its time, and today it remains among the best guesses concerning one of cognitive science's hardest problems.

Computing the Uncomputable

In 1935 Turing thought up the abstract device that has since become known as the "universal Turing machine." It consists of a limitless memory

Turing's Anticipation of Connectionism

In a paper that went unpublished until 14 years after his death (*top*), Alan Turing described a network of artificial neurons connected in a random manner. In this "B-type unorganized machine" (*bottom left*), each connection passes through a modifier that is set either to allow data to pass unchanged (*green fiber*) or to destroy the transmitted information (*red fiber*). Switching the modifiers from one mode to the other enables the network to be trained. Note that each neuron has two inputs (*bottom left, inset*) and executes the simple logical operation of "not and," or NAND: if both inputs are 1, then the output is 0; otherwise the output is 1.

In Turing's network the neurons interconnect freely. In contrast, modern networks (*bottom center*) restrict the flow of information from layer to layer of neurons. Connectionists aim to simulate the neural networks of the brain (*bottom right*).

that stores both program and data and a scanner that moves back and forth through the memory, symbol by symbol, reading the information and writing additional symbols. Each of the machine's basic actions is very simple—such as "identify the symbol on which the scanner is positioned," "write '1' " and "move one position to the left." Complexity is achieved by chaining together large numbers of these basic actions. Despite its simplicity, a universal Turing machine can execute any task that can be done by the most powerful of today's computers. In fact, all modern digital computers are in essence universal Turing machines [see "Turing Machines," by John E. Hopcroft; SCIENTIFIC AMERICAN, May 1984].

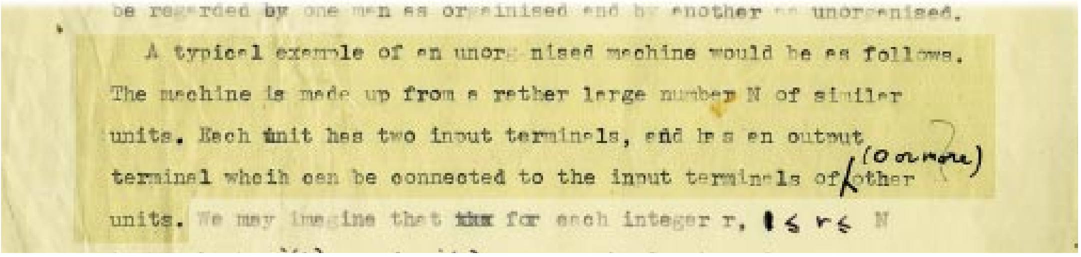
Turing's aim in 1935 was to devise a machine—one as simple as possible—capable of any calculation that a human mathematician working in accordance with some algorithmic method could perform, given unlimited time, energy, paper and pencils, and perfect concentration. Calling a machine "universal" merely signifies that it is capable of all such calculations. As Turing himself wrote, "Electronic computers are intended to carry out any definite rule-of-thumb process which could have been done by a human operator working in a disciplined but unintelligent manner."

Such powerful computing devices notwithstanding, an intriguing question arises: Can machines be devised that are capable of accomplishing even more? The answer is that these "hypermachines" can be described on paper, but no one as yet knows whether it will be possible to build one. The field of hypercomputation is currently attracting a growing number of scientists. Some speculate that the human brain itself—the most complex information processor known—is actually a naturally occurring example of a hypercomputer.

Before the recent surge of interest in hypercomputation, any information-processing job that was known to be too difficult for universal Turing machines was written off as "uncomputable." In this sense, a hypermachine computes the uncomputable.

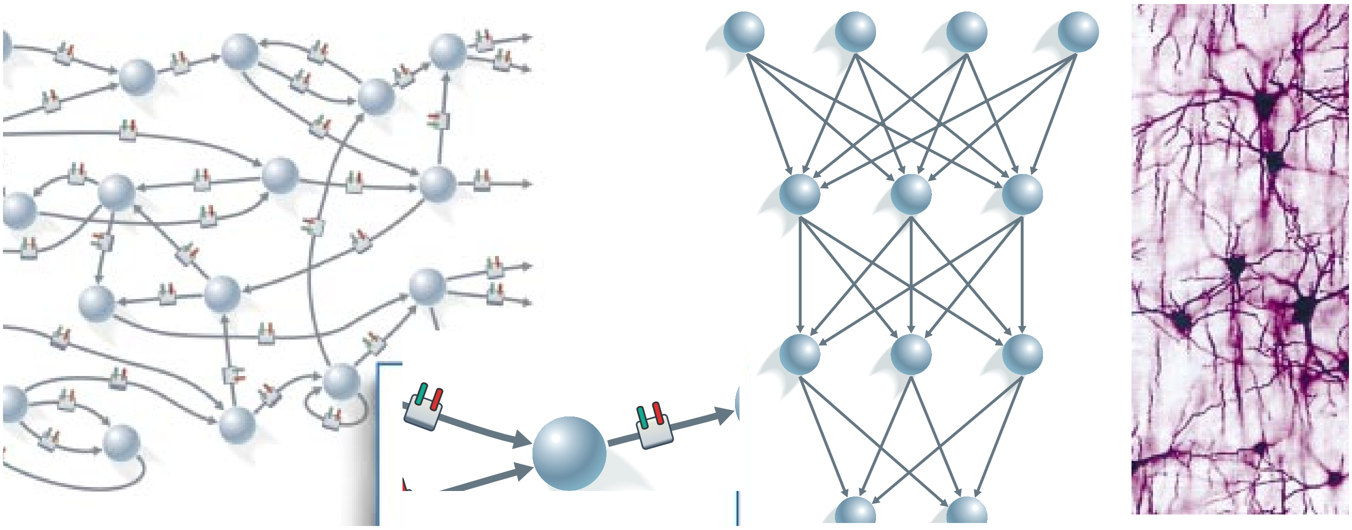
Examples of such tasks can be found in even the most straightforward areas of mathematics. For instance, given arithmetical statements picked at random, a universal Turing machine may not always be able to tell which are theorems (such as "7 + 5 = 12") and which are nontheorems (such as "every number is the sum of two even numbers"). Another type of uncomputable problem comes from geometry. A set of tiles—variously sized squares with different colored edges—"tiles the plane" if the Euclidean plane can be covered by copies of the tiles with no gaps or overlaps and with adjacent edges always the same color. Logicians William Hanf and Dale Myers of the University of Hawaii have discovered a tile set that tiles the plane only in patterns too complicated for a universal Turing machine to calculate. In the field of computer science, a universal Turing machine cannot always predict whether a given program will terminate or continue running forever. This is sometimes expressed by saying that no general-purpose programming language (Pascal, BASIC, Prolog, C and so on) can have a foolproof crash debugger: a tool that detects all bugs that could lead to crashes, including errors that result in infinite processing loops.

Turing himself was the first to investigate the idea of machines that can perform mathematical tasks too difficult



be regarded by one man as organised and by another as unorganised.

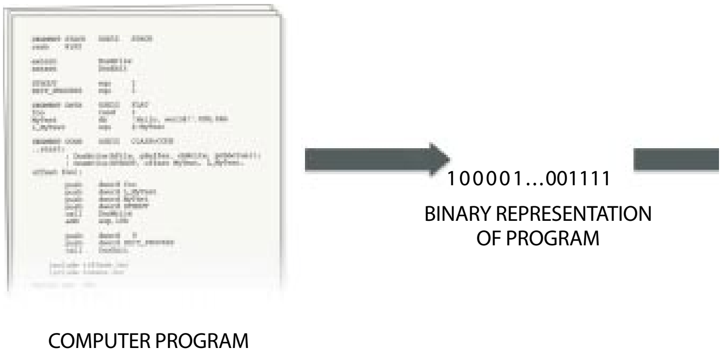
A typical example of an unorganised machine would be as follows. The machine is made up from a rather large number N of similar units. Each unit has two input terminals, and has an output terminal whcih can be connected to the input terminals of (0 or more) other units. We may imagine that ~~this~~ for each integer r, $1 \leq r \leq N$



TOM MOORE (*illustrations*); KING'S COLLEGE MODERN ARCHIVES, CAMBRIDGE UNIVERSITY LIBRARY (*top*); PETER ARNOLD, INC. (*bottom right*)

Using an Oracle to Compute the Uncomputable

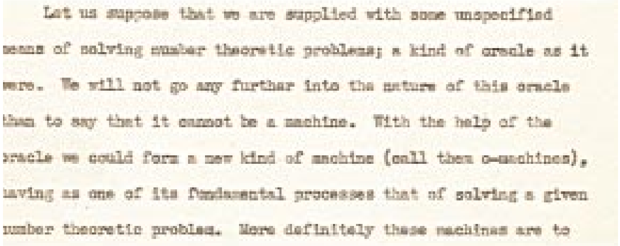
Alan Turing proved that his universal machine—and by extension, even today's most powerful computers—could never solve certain problems. For instance, a universal Turing machine cannot always determine whether a given software program will terminate or continue running forever. In some cases, the best the universal machine can do is execute the program and wait—maybe eternally—for it to finish. But in his doctoral thesis (*below*), Turing did imagine that a machine equipped with a special "oracle" could perform this and other "uncomputable" tasks. Here is one example of how, in principle, an oracle might work.



Consider a hypothetical machine for solving the formidable "terminating program" problem (*above*). A computer program can be represented as a finite string of 1s and 0s. This sequence of digits can also be thought of as the binary representation of an integer, just as 1011011 is the equivalent of 91. The oracle's job can then be restated as, "Given an integer that represents a program (for any computer that can be simulated by a universal Turing machine), output a '1' if the program will terminate or a '0' otherwise."

The oracle consists of a perfect measuring device and a store, or memory, that contains a precise value—call it τ for Turing—of some physical quantity. (The memory might, for example, resemble a capacitor storing an exact amount of

EXCERPT FROM TURING'S THESIS



Let us suppose that we are supplied with some unspecified means of solving number theoretic problems; a kind of oracle as it were. We will not go any further into the nature of this oracle than to say that it cannot be a machine. With the help of the oracle we could form a new kind of machine (call them o-machines), having as one of its fundamental processes that of solving a given number theoretic problem. More definitely these machines are to

PRINCETON ARCHIVES

for universal Turing machines. In his 1938 doctoral thesis at Princeton University, he described "a new kind of machine," the "O-machine."

An O-machine is the result of augmenting a universal Turing machine with a black box, or "oracle," that is a mechanism for carrying out uncomputable tasks. In other respects, O-machines are similar to ordinary computers. A digitally encoded program is fed in, and the machine produces digital output from the input using a step-by-step procedure of repeated applications of the machine's basic operations, one of which is to pass data to the oracle and register its response.

> *Even among experts, Turing's pioneering theoretical concept of a hypermachine has largely been forgotten.*

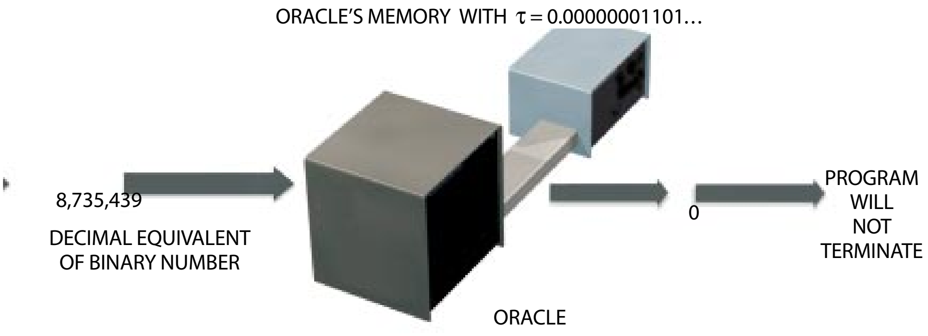
Turing gave no indication of how an oracle might work. (Neither did he explain in his earlier research how the basic actions of a universal Turing machine—for example, "identify the symbol in the scanner"—might take place.) But notional mechanisms that fulfill the specifications of an O-machine's black box are not difficult to imagine [*see box above*]. In principle, even a suitable B-type network can compute the uncomputable, provided the activity of the neurons is desynchronized. (When a central clock keeps the neurons in step with one another, the functioning of the network can be exactly simulated by a universal Turing machine.)

In the exotic mathematical theory of hypercomputation, tasks such as that of distinguishing theorems from nontheorems in arithmetic are no longer uncomputable. Even a debugger that can tell whether any program written in C, for example, will enter an infinite loop is theoretically possible.

If hypercomputers can be built—and that is a big if—the potential for cracking logical and mathematical problems hitherto deemed intractable will be enormous. Indeed, computer science may be approaching one of its most significant advances since researchers wired together the first electronic embodiment of a universal Turing machine decades ago. On the other hand, work on hypercomputers may simply fizzle out for want of some way of realizing an oracle.

The search for suitable physical, chemical or biological phenomena is getting under way. Perhaps the answer will be complex molecules or other structures that link together in patterns as complicated as those discovered by Hanf and Myers. Or, as suggested by Jon Doyle of M.I.T., there may be naturally occurring equilibrating systems with discrete spectra that can be seen as carrying out, in principle, an uncomputable task, producing appropriate output (1 or 0, for example) after being bombarded with input.

Outside the confines of mathematical logic, Turing's O-machines have largely been forgotten, and instead a myth has taken hold. According to this apocryphal account, Turing demonstrated in the mid-1930s that hypermachines are impossible. He and Alonzo Church, the logician who was Turing's doctoral adviser at Princeton, are mistakenly credited with having enunciated a principle to the effect that a universal Turing machine can exactly simulate the behavior



electricity.) The value of τ is an irrational number; its written representation would be an infinite string of binary digits, such as 0.00000001101…

The crucial property of τ is that its individual digits happen to represent accurately which programs terminate and which do not. So, for instance, if the integer representing a program were 8,735,439, then the oracle could by measurement obtain the 8,735,439th digit of τ (counting from left to right after the decimal point). If that digit were 0, the oracle would conclude that the program will process forever.

Obviously, without τ the oracle would be useless, and finding some physical variable in nature that takes this exact value might very well be impossible. So the search is on for some practicable way of implementing an oracle. If such a means were found, the impact on the field of computer science could be enormous. *—B.J.C. and D.P.*

TOM MOORE

of any other information-processing machine. This proposition, widely but incorrectly known as the Church-Turing thesis, implies that no machine can carry out an information-processing task that lies beyond the scope of a universal Turing machine. In truth, Church and Turing claimed only that a universal Turing machine can match the behavior of any human mathematician working with paper and pencil in accordance with an algorithmic method—a considerably weaker claim that certainly does not rule out the possibility of hypermachines.

Even among those who are pursuing the goal of building hypercomputers, Turing's pioneering theoretical contributions have been overlooked. Experts routinely talk of carrying out information processing "beyond the Turing limit" and describe themselves as attempting to "break the Turing barrier." A recent review in *New Scientist* of this emerging field states that the new machines "fall outside Turing's conception" and are "computers of a type never envisioned by Turing," as if the British genius had not conceived of such devices more than half a century ago. Sadly, it appears that what has already occurred with respect to Turing's ideas on connectionism is starting to happen all over again.

The Final Years

In the early 1950s, during the last years of his life, Turing pioneered the field of artificial life. He was trying to simulate a chemical mechanism by which the genes of a fertilized egg cell may determine the anatomical structure of the resulting animal or plant. He described this research as "not altogether unconnected" to his study of neural networks, because "brain structure has to be … achieved by the genetical embryological mechanism, and this theory that I am now working on may make clearer what restrictions this really implies." During this period, Turing achieved the distinction of being the first to engage in the computer-assisted exploration of nonlinear dynamical systems. His theory used nonlinear differential equations to express the chemistry of growth.

But in the middle of this groundbreaking investigation, Turing died from cyanide poisoning, possibly by his own hand. On June 8, 1954, shortly before what would have been his 42nd birthday, he was found dead in his bedroom. He had left a large pile of handwritten notes and some computer programs. Decades later this fascinating material is still not fully understood.

The Authors

B. JACK COPELAND and DIANE PROUDFOOT are the directors of the Turing Project at the University of Canterbury, New Zealand, which aims to develop and apply Turing's ideas using modern techniques. The authors are professors in the philosophy department at Canterbury, and Copeland is visiting professor of computer science at the University of Portsmouth in England. They have written numerous articles on Turing. Copeland's *Turing's Machines* and *The Essential Turing* are forthcoming from Oxford University Press, and his *Artificial Intelligence* was published by Blackwell in 1993. In addition to the logical study of hypermachines and the simulation of B-type neural networks, the authors are investigating the computer models of biological growth that Turing was working on at the time of his death. They are organizing a conference in London in May 2000 to celebrate the 50th anniversary of the pilot model of the Automatic Computing Engine, an electronic computer designed primarily by Turing.

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A New Eye Opens

ON THE HIGHEST MOUNTAIN IN THE PACIFIC BASIN, A 10-YEAR ODYSSEY WILL CULMINATE IN THE CAPTURE OF FIRST LIGHT FOR A TELESCOPE THAT MAY SURPASS SPACE-BASED OBSERVATORIES

by Gary Stix, *staff writer*

Photographs by Andy Ryan

STAR CATCHER, an 8.1-meter mirror in its protective casing, makes its way toward its home in the silvery open dome (*below*) of the Gemini North observatory on the summit of Mauna Kea.

on the Cosmos

From the vantage of a hillock of reddish cinder overlooking the precipitous, winding track, onlookers witnessed the convoy laboring upward at an almost imperceptible rate. The procession had taken three days to ascend the scant 100 kilometers (65 miles) from the seaport over rolling ranch land, through the ink-black lava fields, past the astronomers' enclave at 2,800 meters and up a narrow road chiseled into the alarmingly steep and unstable flanks of the long-dormant volcano. A fast walker could have outpaced this honor guard of four-wheel drives serving as an escort to the enormous flatbed. Two 450-horsepower tractor rigs, connected to each other by a 10-centimeter-thick rope, bore an octagonal steel case that contained a 22-metric-ton piece of glass too weak to support its own weight. Despite layers of high-tech cushioning, the mirror inside could have been damaged by a shock of several g's (the force imposed by a fall from a height of about half a meter). If it were blemished, the construction of this giant telescope, a decade in the planning and fabrication, would be set back years and millions of dollars.

Putting It Together

In recent months the Gemini team set about assembling the major pieces of the telescope. In late June powerful tractor trailers hauled the mirror from the port in Kawaihae Bay (*1*) over mountain roads (*2*) to the Gemini dome (*3*) on the summit of Mauna Kea. On December 11 the mirror left the problem-plagued coating chamber (*4*). A crane then lifted the reflector and set it into the mirror cell (*5*).

The 120 computer-controlled "actuators" in the cell apply pressure to the 20-centimeter-thick glass to nudge it into shape. These corrections compensate for slight deformations caused by changes in wind, temperature or the position of the telescope. The adjustments rid the mirror surface of the types of anomalies in shape that caused problems on the Hubble telescope. When the actuators are adjusted, the entire mirror surface becomes uniform to an accuracy of 100 to 200 nanometers.

After the mirror was moved into the cell, optomechanical engineer Eric Hansen proceeded to install a sensor inside the mirror cell (*6*). A few days later the mirror slipped into the telescope frame on a pneumatic hovercraftlike lift (*7*). The telescope frame (*8*) maintains the same temperature as the outer air, in part because of 10-meter-wide vents on the side of the dome (*9*) that flush away hot and cold eddies that can degrade image quality. *—G.S.*

The steel case stretched so far beyond the width of the trailer's wheel base as it negotiated the hairpin turns that its delicate cargo threatened to furrow into the volcanic cinder embankment on one side or tumble down an abrupt slope on the other. In the right location, technology can evoke the otherworldly. Here among the cinders expelled from the bowels of Mauna Kea and in clear view of the ocean, there appeared to emerge an elemental confluence of air, earth, fire and water. As the convoy neared the summit, considered in the old religion practiced on Hawaii's Big Island to be the holy abode of the goddess of snow, it assumed the shape of a gigantic cross. A mule train of Ford Explorers and Toyota 4Runners formed the stem; a ludicrous overhang of steel casing became the arms of this emblem. And above, in the midst of a moonscape at 4,200 meters, the silvery dome of the Gemini North observatory waited in the stark June sunlight to receive the glass wonder needed to complete this monument to a secular religion.

Would the old gods be angered by this sacrilegious incursion? Perhaps; if you climb the catwalks to the top of that lustrous rotating hemisphere and stretch out your arms, you can proclaim yourself king of the world. At that moment, the top of your head will mark the highest point in the entire Pacific Basin.

The ever so careful delivery of the fragile mirror to the summit signaled the end of one of the riskiest parts of the Gemini project but also the start of six months of frenetic work. The schedule dictated that engineers had to connect and test all the telescope's major systems within half a year so that the observatory could witness "first light"—that is, produce its first cosmic snapshots—before Christmas.

That tight schedule was driven by a tight budget but also by an acute sense of competition. During a 10-month or so period beginning in May 1998, Gemini and other mammoth instruments, including the European Southern Observatory's Very Large Telescope in northern Chile and the National Astronomical Observatory of Japan, will have captured their first starlight. The Japanese telescope, known as Subaru (the Japanese name for the Pleiades star cluster), butts up from another rock-strewn cinder cone only a few hundred meters away.

Gemini North will not be the largest telescope in the latest generation of light collectors. And it lacks the full complement of optical and infrared cameras and spectrographs found on some of its rivals. But its builders are determined to beat the competition when collecting images in the infrared end of the electromagnetic spectrum. The infrared is the relatively unexplored region where astronomers probe for star-forming areas that are occluded by the dust that absorbs visible light. It is also where they seek the earliest galaxies, whose radiation is shifted toward these wavelengths as they move away from us at unimaginable speeds.

By mid-December, what distinguished Gemini North could be discerned in the observatory, by poking among the pieces of this toy kit for titans, some of which still lay strewn across the steel floor. As the bang of metal against metal echoed through the 36-meter-diameter dome, Matt Mountain, the loquacious Englishman who directs the program, gazed with evident pride toward the top of the telescope, 20 meters or so above. There the one-meter-diameter secondary mirror will focus the light gathered by the 8.1-meter-diameter primary mirror into a tight, steady beam. Up where most telescopes exhibit a thick truss work occupied by special instruments, only two slight, crisscrossing steel vanes stood between the primary and the heavens, like some bowlegged spider. "That spider emits radiation straight to the telescope beam," Mountain said. Radiation that makes cold steel glow like a hot andiron on an infrared detector can drown out the faint interstellar signal. "The thinner you can make the spider, the less emission you get," he noted.

Mountain, who swore his name was not a prerequisite for employment as director, rattled off a list of infrared-reducing design features, such as a silver coating on the mirror. The silver and other measures should diminish to 3 or 4 percent the background infrared radiation contributed by the telescope, less than a fifth the typical figure for terrestrial observatories. Mountain continued with the primer for designing advanced telescopes. He recounted how vents that open and shut like huge aluminum lips help to flush away image-distorting currents of turbulent air inside the dome, eddies that result from temperature differences between the telescope, the dome and the surrounding air. "We can take 300 or so tons of steel down to within one degree of ambient," Mountain said.

This attention to detail should allow Gemini to spot features as small as seven hundredths of an arc second in the near infrared. That will be sharper than the Hubble Space Telescope can manage with its relatively puny 2.5-meter telescope. An arc second is $^1/_{3,600}$ of a degree. With the finer resolution of Gemini, an astronomer could theoretically read the NASA logo on the International Space Station at a distance of 350 kilometers—if it glowed in the infrared.

Trained as an astronomer, Mountain has spent much of his career building and refining infrared instruments. Before Gemini, he put together the infrared spectrometer on the neighboring U.K. Infrared Telescope on Mauna Kea—and later managed the early stages of an upgrade of that telescope's optics.

The night before his trek to the summit, Mountain had been up until past midnight tending to his one-year-old son's croup. The nocturnal habits of the astronomer had trained Mountain well for fatherhood—and this insomniac bent would be needed in the next few weeks as first light marked a new birth of sorts. The tall, slightly heavyset 42-year-old with a thatch of brown curls may not have been hired for his name. But his easygoing, hands-off management style qualifies him to mediate among the project's diverse camps, which include high-powered scientists and government bureaucrats from seven countries.

With Christmas little more than a week away, it was clear to Mountain that Gemini would not make its first infrared pictures of the firmament until mid-January at the earliest. That should have amounted to nothing more than a tiny crimp in a schedule set more than four years earlier. But in truth, neither Mountain nor project manager Jim Oschmann

The mirror itself is a masterpiece: no gemstone has ever been cut with greater symmetry.

COAXING REFLECTIONS from a piece of glass was a task that fell to four Gemini engineers and technicians who transported the mirror by hand from a wash station to a vacuum chamber in the neighboring Canada-France-Hawaii Telescope

really knew what work would remain until they ordered the dome slit opened to the night sky and turned the gaze of the 342-metric-ton behemoth on the pinpoint of a star.

Expectancy filled the cavernous dome. Brown-coverallled engineers and technicians hung like monkeys from the telescope frame while repairing the accordion folds of the metal mirror cover. In the gnawing cold of the unheated dome, technicians installed optical fibers and electrical cabling. "I need two more lungs," proclaimed staff electrician Andrew Gushiken, reacting to the reduced oxygen, 40 percent less than that enjoyed by the snorkelers and surfers a few kilometers below. Workers made final adjustments both within and without the mirror cell, the giant blue cylindrical structure that holds the mirror and bends it into the proper shape under computer control. Nearby a whiteboard bore a scribbled warning to anyone contemplating a break: "No Observing on the Observation Level."

"One month late for first light is acceptable, but we can't slip any more than that," Mountain emphasized, slicing the air with both hands. "The credibility of this program and future programs depends on it." If the schedule drags on, it could set back plans to move the engineering team to northern Chile, where, as Gemini's name suggests, an identical twin will open its eye on the universe before its northern sister turns two. With Gemini North and South, an astronomer will be able to formulate an observing program that includes the full sky, from star-forming regions in the Magellanic Clouds to the galaxies of the Hubble Deep Field. It is the only new-generation telescope to boast this capability.

Time also pressed on Mountain and his team because Gemini is a public work. It not only furnishes a broader celestial panorama but also supplies time on the sky to more astronomers than any other large U.S. telescope does. The Geminis will become the People's Telescopes, the national eight-meter observatories for the U.S., the U.K., Canada, Australia, Argentina, Brazil and Chile. Unlike telescopes built with private money, the Geminis will be at the disposal of any astronomer from these countries who can convince a review board of the merits of a proposal.

The U.S. government committed itself to half the cost of the Gemini program—but it also imposed a cap of $88 million so that it would not get caught paying more than its share. Delays in the north could drive up costs and might jeopardize Gemini's ability to ask for funds to outfit the telescope with a full complement of instruments in coming years.

Throughout its history, the project has struggled against a fiscal noose. The minimalist design features that Mountain pointed out are as much a testament to the rigors of cost accounting as they are to clever engineering. The spartan top of the telescope limits infrared noise, but at the expense of a wide-field camera that many astronomers wished for to survey a broad section of sky. By sacrificing this and other amenities, the Gemini team kept the telescope within its now $184-million budget. The one $8-million increase went for better sensors and components to coat the mirror with silver in Chile.

Japan, in contrast, has spent $350 million for its one telescope, sparing no expense to seize a prominent role in state-of-the-art astronomy. "We could have put in three or four Geminis for that much," Oschmann commented.

Mountain's sensitivity to schedule and cost was also grounded in the controversy that dogged Gemini's early years. Mere months after he was hired as project scientist in 1992 (he was promoted to director in 1994), Gemini almost lurched to an unceremonious halt when the University of Arizona challenged the award of the contract for casting the mirror to Corning, the low bidder. At the university's Mirror Laboratory, headed by the prominent J. Roger Angel, "they believed the contract was theirs by right," Mountain said.

Angel's group objected that this gargantuan contact lens—eight meters wide but only 20 centimeters thick—would distort incoming starlight by flexing in the slight air currents inside the dome. The design, the university contended, would not hold up as well as its own mirror, consisting of a thin face backed with a stiff honeycomb of borosilicate glass. In the intense debate that followed, an inde-

(CFHT) dome (*left*). In the chamber, a thin layer of aluminum evaporated on the glass disk (*center*). Later, Gemini's John Filhaber and CFHT coating specialist Barney Magrath, who held the flashlight, inspected the highly reflective finish (*right*).

pendent committee impaneled by the National Science Foundation recommended that the contract be redirected to the University of Arizona.

During the next 11 months, the Gemini team had to justify the most minute design points. "To show the level of intellectual debate," Mountain recalled, "the competitors from the university turned up at a meeting with a yard-long piece of window glass cut in a circle and shook it and said, 'This is how floppy the Gemini mirror is going to be.'"

"This was my first experience with the U.S. astronomical community," he added. "And I was saying, what the hell have I done [in taking the job]." The imbroglio nearly killed the project. But a separate design review committee—appointed by the National Science Foundation and the Association of Universities for Research in Astronomy—upheld the Gemini team's initial decision and let the program proceed on its original course.

Mountain had made the ascent of Mauna Kea from Gemini's offices in the port city of Hilo to observe one of the many milestones on the way to first light. The engineering detail working the summit had crossed off a number of checklist items in recent weeks. Its members had coated the primary mirror and moved it into the cylindrical mirror cell. The time had come to place the mirror in its home and attach it to the towering telescope frame.

As the work proceeded, Mountain and Oschmann looked down from the service platform on the telescope frame onto a swimming-pool expanse of shimmering concave metal that rested on a platform at one side of the dome. On the scaffolding beside the mirror, Larry Stepp, the project optics manager, and optomechanical engineer Eric Hansen tightened bolts to batten down the mirror so that an earthquake cannot jolt it from its cell. They turned their wrenches with the slow deliberation that an eye surgeon would use in taking a scalpel to a cornea. If a wrench had dropped, it could have produced an indelible scratch.

"I tell you what I'm not impressed with is these parts," Stepp called up to Mountain and Oschmann, lamenting the need to make manual adjustments above the mirror surface. On the Gemini team, Stepp had assumed the role of protector of the mirror, the one who constantly urged the most cautious path to ensure that this $10-million-plus glass gem remained intact. Anyone who worked above the exposed mirror asked Stepp's permission. Mountain and Oschmann sometimes had to overrule Stepp's deliberateness to keep things on track.

Stepp's caution was understandable, however. The mirror itself is a masterpiece: no gemstone has ever been cut with greater symmetry. From peak to valley across its surface, the mirror varies typically no more than 16 nanometers (billionths of a meter), about half of that specified originally by Gemini in its contract with REOSC. No point is more than 140 nanometers away from absolute smoothness. "If you [took this] mirror and stretched it across the Atlantic Ocean, the tallest wave would be one foot," Mountain said.

The mirror surface is a matter of competitive pride for all the new telescopes. After the Gemini mirror was polished, a scientist from Subaru called the Gemini office and asked for the results. When finished, the Subaru mirror exceeded Gemini's surface quality by four nanometers. Gemini, in turn, gave the Subaru results to REOSC when it was polishing the mirror destined for Gemini South at Cerro Pachon in Chile.

The voyage of the mirror cell a few meters across the dome floor should have taken only a few minutes. Yet it consumed an hour and a half. The 80-metric-ton cell rested on a kind of pneumatic hovercraft, which vibrated haltingly forward. Time and again, the transport tripped on a gap between the dome floor and the rotating center platform on which the telescope sits. Two workers took turns furiously tightening a cable to yank the cell along. Another jumped up and down on the cable, adding his own weight to the effort.

To keep things moving forward, dozens of such makeshift solutions have had to be crafted. Two days earlier John Filhaber, charged with integrating Gemini's myriad systems, helped three colleagues lug the secondary mirror, a roughly 60-kilogram (130-pound) disk of glass worth more than $1 million, across the concrete floor at an adjacent observatory. Clad in white surgeon masks and clean-room caps, coats and booties, the four men cradled the mirror as if moving a piece of furniture. One untoward jolt as they made their way from the wash station to the vacuum coating chamber and the precious slab would have been lost.

Filhaber would have preferred to forgo this risky move. But the Gemini coating chamber—the most advanced ever built, according to the project's publicity literature—had broken during an all-night marathon 10 days earlier. The chamber contains a magnetron that uses a plasma of argon ions to knock aluminum atoms off a metal sheet and deposit them in an ultrapure reflective film on the mirror glass. (The entire eight-meter mirror was covered with only as much aluminum as it takes to manufacture a beer can.)

The Royal Greenwich Observatory, then England's oldest scientific institution, had built the chamber. But last year that venerable organization, beset with budget problems, had apparently been more occupied with its own imminent demise than with Gemini's contract. "They were building this at the end of their lifetime, and it showed," Filhaber complained.

By early December, Filhaber had been striving for months to get the coating machine to work properly instead of tending to his other duties to make Gemini's diverse subsystems work together. The chamber still wasn't 100 percent, but the team could postpone the coating of the primary mirror no longer. So one long day he and three technicians passed a seven-hour stretch with eyes glued to gauges that measured the current coursing through the magnetron. "It had never run this long without failing," Filhaber said. "We weren't even breathing."

Then, with only 20 minutes to go and one last segment of glass to cover, the voltage went to zero and the current soared. An electrical short had shut the machine down. At first it seemed like a disaster. The magnetron could have nicked the surface of the mirror. Restarting the machine would cause a ripple in the coating; they might even have to strip off the aluminum and start over. "We used the metaphor of *Apollo 13* coming back from the moon. Our lives weren't in danger, but our mirror was, and our mirror was our life," he declared.

The 35-year-old Filhaber is a confessed daredevil who surreptitiously staged nighttime climbs of the George Washington and Brooklyn bridges while a student at Columbia University. Moreover, he added with customary brashness, "I have this uncanny ability to make just anything work." He saw the setback as a challenge and set about lining up the magnetron by eye in order to finish the coating. Holding their breath, Filhaber and team restarted the machine and finished the job, leaving the mirror with a good enough coating for first light.

With Gemini's machine still out of order, Filhaber and crew had to borrow the coating chamber at the neighboring Canada-France-Hawaii Telescope Observatory, into which they now placed the secondary mirror without a hitch. In late January, Filhaber left the project. His family had not adjusted well to life in provincial Hilo, an occupational hazard for anyone who lives in the isolated environments where telescopes reside.

The milestone that marks first light is an arbitrary formality. For Gemini, it did not mean that the telescope was ready to hand over to astronomers to search the heavens each clear night. Rather it would constitute the judgment of Gemini's project director, a pair of its scientists and its public relations manager that several of a multitude of images received on a borrowed infrared camera could be shown to the world without a shower of brickbats from the astronomical community.

The true first light occurred in late December—and it bore an uncanny resemblance to a high school science project. Starlight that was reflected from the great, glass paraboloid below glowed as a dot a few millimeters in size on a piece of cardboard. The paper served as a two-cent substitute for the $1-million secondary mirror, which had yet to be mounted on the telescope frame. The dot—a reflection of Jupiter—allowed for calibrations in the big mirror.

In late December and through January, the project crept along through other checkpoints that might merit the first-light imprimatur. Because of mechanical and software problems, the schedule nonetheless slipped past its mid-January deadline. On January 29, however, Gemini was ready to take the sky for yet another first-light rite, a series of images with both the primary and secondary mirrors in place.

Except for the green emanations of a computer screen, blackness filled the Gemini dome at 9:30 P.M. With a low mechanical hum, the dome slit opened, immediately bathing the interior in the light from a full moon. The telescope

SUNSET ON MAUNA KEA reflects off the Gemini dome (*left*), one of whose first star images was captured in early February and inspected (*below*) by project manager Jim Oschmann (*in foreground*) and project director Matt Mountain. The Subaru dome (*far left*) received first-light images in January.

PETER MICHAUD *Gemini Observatory*

stood at attention, pointing toward the zenith. Amazingly, it trained directly on Castor and Pollux, the two brightest stars of the constellation Gemini.

Hours later, after wrestling with a parade of software glitches, a star was born on the Gemini computer screens. This nameless creature, designated only number 1253 in one of the innumerable cataloguing systems astronomers love to compile, emerged as a skewed, false-color orange blob in both the summit control room and on the computers at the base offices in Hilo, where most astronomers will spend their nights observing the sky. On top of the mountain, Oschmann eagerly made manual adjustments to the mirror actuators to correct for the vertical elongation characteristic of astigmatism. A few minutes later a well-rounded sphere appeared.

Oschmann's twiddling had brought the resolution from 10 arc seconds down to one arc second in the course of minutes, a process that had sometimes taken years for older, four-meter telescopes. In Hilo, Mountain had watched the images on a computer terminal—and Oschmann's doings over a teleconferencing monitor. An air of jubilance prevailed. But Mountain's look was glum and sullen. It was not because the *Honolulu Advertiser* had displayed a front-page photograph that morning of the Orion nebula taken by the Subaru telescope, an image he dearly wished could have belonged to Gemini. He later explained that his feelings had more to do with the enormity of launching a big science project: "It was so hard to get to this point, and there was a realization that the hard work had just begun."

Seeing the same newspaper, Oschmann had wanted to post the Subaru photograph on the summit and write underneath: "How many days until we get to this, guys?" But Mountain's insight about the difficulties that lay ahead proved to be the more prescient one.

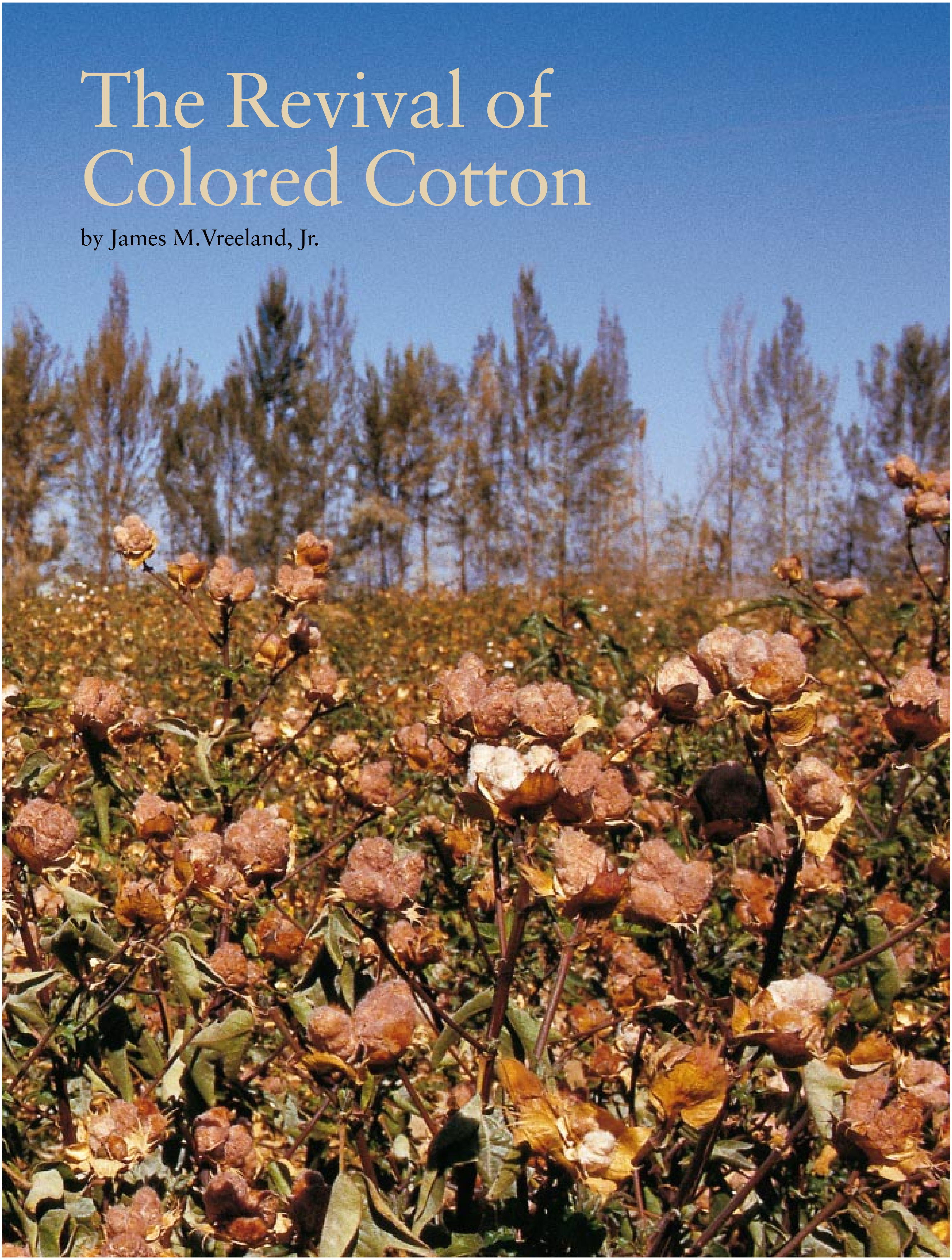
The formal declaration of first light had to be postponed beyond the middle of February. The bet that all the systems could be assembled quickly and made to work immediately had not paid off. The lightweight top end of the telescope—a feature that had reduced cost and that was designed to help viewing in the infrared—would now prove a weak link. One of the telescope's software and hardware systems would not move the secondary mirror fast enough to counteract the image blurring that occurred from the frame's shaking in the wind—and would require a major hardware and software fix. Impressive first-light images for general release would still be possible in the weeks to come, if the telescope were blessed with a string of calm, clear nights. But the crew had to wait for a subsiding of the snow, the ice and, in particular, the high winds that plague any 4,000-meter perch in winter—even in Hawaii. The added delay—and the $30,000 per night to operate the telescope—would create renewed budget pressures.

First light really marks the beginning of an intensive 15-month stretch when engineers and astronomers work together to hone the instrument to demanding subarc-second specifications. To achieve the telescope's full potential, the team will deploy an adaptive optics system that will compensate for the atmospheric turbulence that can ruin the telescope's imaging.

If all goes well for Gemini, sometime in the middle of 2000 astronomers will take full control of the telescope. Long before the handover next year, many of the engineers will take their brown coveralls and move to northern Chile. There they will get a chance to learn from past mistakes as they assemble a southern clone of the Mauna Kea machine. Mountain has tried to keep his team looking even further ahead than the completion of Gemini South. In their rare spare moments, he asks them to contemplate what it would take to build a 50-meter telescope, perhaps one made up of a series of connected segments, a design employed by the renowned Keck telescopes on Mauna Kea. Each of these segments might match the size of Gemini's primary mirror. This quest for size—what some astronomers call "aperture envy"—may never end. The dimensions of the universe dictate that a telescope can never be too big. SA

The Revival of Colored Cotton

by James M.Vreeland, Jr.



Peruvian weaving done in the plain twining fashion

PATRICIA J. WYNNE

One afternoon in 1977 I was struggling to work in the National Museum of Anthropology and Archaeology in Lima, Peru, in a small conservation laboratory that I shared with a resident population of fleas, rats, a snake and a monkey. I was examining pre-Columbian textiles through a stereoscopic microscope, thinking about how best to preserve them. A graduate student in archaeology, I had come to Peru several years earlier to participate in an excavation at the Chan Chan site in the northern Andes and had just returned with a modest grant from the Organization of American States to continue my studies. Little did I know that what I would see through the microscope that day would set me off on a different trail altogether.

Inside the cotton fibers' walls I noticed some intriguing dark masses that imparted color to the fabric. Because the distinct brown spots did not appear to be the result of dye, I began to ask around at universities in Lima: Was it possible that some cotton was naturally pigmented? The answer—often derisively given—was categorically no: cotton is white. The coloration apparent in the microscope must be, the experts reasoned, the result of oxidation or of some other discoloration that came about as the now antique fabric had aged.

A new arrival on the Western fashion market, naturally pigmented cotton originally flourished some 5,000 years ago. Its revival today draws on stocks first developed and cultivated by Indians in South and Central America.

Unconvinced, I flew up to Trujillo, where I had worked several years before at Chan Chan with Victor Antonio Rodriguez Suy Suy, a professor of anthropology at the National University of Trujillo and a descendant of the Mochic ethnic group. He met me at the airport and informed me straightaway that there was such a thing as naturally colored cotton. In fact, he drove just outside the airport and pointed to land alongside the road. In the sunken fields, which were clearly of pre-Hispanic origin, we could see rustic cotton plants clinging to the sandy soil. Cotton plants bearing reddish fibers! Entranced, I spent the next few months traveling the area, searching for plants and textiles with fibers that were naturally ecru, deep chocolate and many other shades of brown, and even mauve. It was challenging work because the descendants of the Mochica Indians of the north coast guarded their plants jealously.

Nevertheless, I was hooked. I gave up my archaeological studies, turned to ethnoarchaeology and, for the next 20 years, sought out all the information I could find about naturally colored cotton in museums and libraries and at ancient sites and by talking with everyone I met. Ultimately, the people who taught me the most were the Mochica Indians, who, some 2,000 years ago, cultivated cottons of myriad hues and who had quietly maintained some of these cultivars.

Before they were bred into predominantly creamy white strains centuries ago, cotton plants were well known for producing an array of colors. But following the advent of the cotton gin and inexpensive industrial dyes, white cotton reigned supreme. Colored plants were marginalized, surviving only in seed banks kept by some agriculture departments here and there around the world and in small, traditional communities in a handful of places, including Mexico, Guatemala and Peru. These pigmented cottons have undergone a revival recently, and many people are now familiar with them and with organically grown white cotton. But few people know that the story of cotton in its resplendent tones began some 5,000 years ago in the Andes. Virtually all the colored cotton plants we in the West use commercially and interbreed today come from pre-Columbian stocks created by the indigenous peoples of South America.

Ancient Practices

Five millennia ago early farming societies in the Americas selected, domesticated and improved two local species of cotton: *Gossypium hirsutum* and *G. barbadense*. The former was cultivated in northern Central America and the Caribbean, the latter—famous for having the longest, finest fibers of all cottons—in western South America.

The archaeological evidence regarding cotton domestication in these regions is extensive, but for brevity's sake, I will mention only some of the more important sites. The oldest cotton fiber recorded so far in Central America comes from the Tehuacán site near Oaxaca in Mexico and was produced some time around 2300 B.C. Chocolate-brown fibers, unique to *G. barbadense*, have been unearthed at the most ancient levels of Huaca Prieta, a settlement on the north Peruvian coast that was occupied between 3100 and 1300 B.C. This chocolate-brown fiber and a light-brown one can be seen in

JAMES M. VREELAND, JR.

MAUVE COLORED COTTON was found growing in a few places on Peru's north coast (*opposite page*). The plant, which had been carefully cultivated and maintained over many millennia, is now producing naturally colored cotton for commercial uses. Other swatches reveal several—but by no means all—of the natural colors of cotton that have been selectively bred (*above*).

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PATRICIA J. WYNNE

PERUVIAN TAPESTRY from A.D. 1000 depicts a cotton plant complete with roots, leaves, stems, flowers and ripening cotton bolls spilling forth with naturally pigmented cotton (*left*). Traditional spinning bowl was used by some Andean Indian women, probably Inca, to set the spindle in as they plied the ball of cotton (*above*).

many of the fabrics made by Andean weavers, which have survived for millennia because of the arid coastal soils of northern Peru. (The dry air works to preserve the textiles, which would be damaged or destroyed by moisture.) It appears that these colors were intentionally differentiated and bred by ancient Peruvian fisherfolk, who made nets and lines from the darker shades because they were less visible to fish—a tradition and craft that continues today. Despite its extensive use from Oaxaca down through the Andes, there are no records of naturally pigmented cotton found in prehistoric sites north of Mexico. If it was introduced through trade or even cultivated locally, the records have disappeared or the pigments have weathered. The well-known "Hopi" cotton (*G. hirsutum,* variety *punctatum*) of the Southwest is actually white or off-white, although it is possible that chemical degradation could have occurred in the surviving samples.

Later records provide more detail than the prehistoric ones do, and they clearly show that pigmented cotton was used as tribute. Sixteenth-century Mexican documents, for instance, reveal that brown cotton constituted a principal form of payment from the lowlands peoples to the Aztecs. Other documents indicate that when the first Spaniards crossed the Peruvian desert in 1531 they marveled at the extensive fields of cotton growing in a range of colors unlike anything they had seen. Naturally colored cotton fabrics were among the first items collected as tribute and sold or shipped to the Spanish court, and those Indian textiles were more technically sophisticated than anything woven on European looms at the end of the 15th century.

Well-Traveled Seeds

As the New World was pried open by naturalists and merchants, cotton plants native to the Americas were transported around the world. Other naturally pigmented cotton plants are indigenous to Africa and Asia, including *G. herbaceum* and *G. arboreum.* Cotton has an ancient history in that part of the world as well: fibers from about 2200 B.C. have been discovered in the Indus Valley, and some from circa 2250 B.C. have turned up in Nubia. But it seems these Old World species have short staples—as the cotton fibers are called—making them much harder to spin and weave. In large part, they were ultimately displaced by the long-stapled newcomers.

Modern Egyptian cotton, for example, is derived from a South American progenitor (most probably *G. barbadense*), which was apparently brought by slavers to northern Africa from the New World. First described in 1820 or so, this strain originally produced a long, strong lint with a golden-brown color. It was interbred with local plants to yield new commercial selections: ashmouni, a brown stock; mitafifi, which was darker brown, had a longer lint and gave rise to American-Egyptian yuma cotton in 1908; and, finally, what is now called pima cotton. (Pima is the name of a Native American tribe, members of which helped to grow an extra-long staple variety of *G. barbadense*. Pima cotton, developed in Arizona, was obtained from an Egyptian form cultivated during the past century.)

In China the native pigmented species—the so-called Nankin varieties—had short staples just like the original Egyptian species, but they grew only in a pale off-white color. Although the literature is confusing on this point, it appears that 19th-century references to Nankin cotton could be describing a cultivar introduced from South and Central America. Nevertheless, it is clear that at some point cotton plants from the Caribbean—that is, *G. hirsutum* plants—did reach China.

Colored cotton plants from the eastern Mediterranean region and Asia apparently reached the U.S. during the colonial period. Cultivars of *G. arboreum* arrived, as did those of *G. hirsutum* and *G. barbadense*. Colored cotton was hand woven and spun, and even machine woven at times, in several southern states. In the heart of the Mississippi Delta, for example, golden-brown cotton has been grown for more than two centuries by a small group of rural Acadian spinners. Despite scattered pockets of colored cotton cultivation, however, it never took off commercially in the U.S. (It appears that Haiti and the former Soviet Union were the only two countries to produce colored cotton fabric on an industrial scale before the present day. Haiti did so for a short time in the 1930s, and the Soviets only when dyes were in short supply during World War II.)

The global spread of the various cotton cultivars—called upland cotton—followed the invention of the English spinning frame in 1769 and the cotton gin in 1794. The industrial revolution was up and running, and with the appearance of inexpensive chemical dyes, the fate of colored cotton was sealed.

Slanted variation on the plain twining pattern

PATRICIA J. WYNNE

White Supremacy

It was cheaper to use white cotton and dye it because the palette was unlimited and no specialized harvest techniques or facilities were needed, as they were for naturally pigmented cottons. By the 1900s most indigenous, colored cotton landraces, or cultivars, grown in Africa, Asia and Central and South America were replaced by all-white, commercial varieties.

During World War II, green and

COURTESY OF JAMES M. VREELAND, JR.

PRE-HISPANIC GRAVE in the Chancay Valley of Peru is heaped with naturally colored cotton bolls. The ancient people of this coastal area filled the body of the deceased with the cotton, which would absorb the bodily fluids, thereby aiding in the process of mummification. The arid sands of the region preserved the cotton (which was removed from the body when this grave was looted).

LINT FIBER greatly enlarged reveals the natural twist that made cotton such an easy material to spin. The dark masses impart the natural color.

PATRICIA J. WYNNE

brown cottons were produced for a limited time because dyes were not available. Because Soviet farmers were producing colored-cotton products, the U.S. government also instructed a famous agronomist, J. O. Ware, to study the Soviet cotton plants to determine whether they were commercially viable in the U.S. Ware and his colleagues concluded that the green and brown cotton plants yielded too little lint that was too short in staple length. Colored cotton was officially relegated to obscurity. Only in a few places were people still entranced by its possibilities.

A New Market for Old Plants

After disappearing for about a century, naturally colored cotton suddenly reappeared as a fashion item in the early 1990s. Big U.S. clothing manufacturers such as Patagonia, Levi Strauss and Esprit as well as several European companies began to buy "environmentally friendly" cotton—that is, cotton that is chemical-free. Cotton farmers use approximately 23 percent of the world's insecticides and 10 percent of the world's pesticides to combat pests such as the boll weevil. U.S. cotton farmers use some 35 percent of the total, making them the greatest consumers of cotton pesticides; Indian producers use the second greatest amount, nearly 11 percent.

These insecticides and pesticides, which include malathion, aldicarb, methyl parathion, trifluralin, deltamethrin and tribufos, are some of the longest-lived and most destructive. Trifluralin, for instance, disrupts the hormonal and reproductive systems of animals, and in the U.S. tribufos is classified as a possible human carcinogen. These compounds not only harm the workers who use them but also leach into soil, reaching groundwater, rivers and streams, killing fish and contaminating livestock. Once it has been harvested, white cotton is usually bleached—which involves chlorine-based processes that give rise to dioxins. The cotton is then dyed with a whole host of other chemicals, many of which include heavy metals that often end up in the wastestream.

Because of concerns about endocrine disrupters and rising cancer rates, consumers and manufacturers have increasingly been turning to organic cotton producers. Although the specifics of certification vary from country to country, an organic producer generally can get a stamp of approval if no pesticides have been used on the land for one to three years. (As some experts point out, however, pesticide residues are quite long-lived, and three years does not leave the soil pesticide-free.) The movement is gaining momentum, and currently some

FOUR SPECIES of cotton have different lint lengths. The two species found in Africa and Asia, *Gossypium arboreum* and *G. herbaceum,* come in naturally colored varieties, but both have lint lengths that range from short to medium. The two species from South and Central America, *G. barbadense* and *G. hirsutum,* have medium to long lint lengths.

PATRICIA J. WYNNE

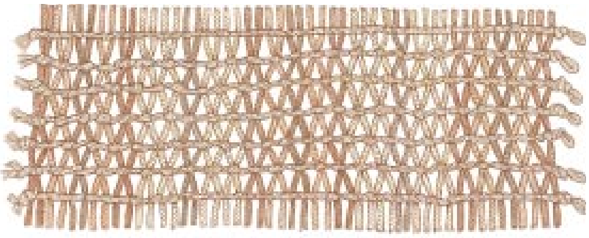
20,000 acres (8,000 hectares) in the U.S. and in half a dozen other countries produce organic cotton, including naturally pigmented cottons that do not have to be dyed with toxic chemicals.

The resurgence of interest in naturally colored cotton has been very gratifying for me and for my many colleagues in Peru. When I first started my investigations in 1977—sparked by those dark masses in the cotton fibers—I was told that not only were there no naturally colored cotton plants but also that the extensive and beautiful ancient hand-spinning and weaving traditions of northern Peru had disappeared. So when I went north on that seminal trip to visit Rodriguez Suy Suy, it was with great satisfaction that I located individual plants and, ultimately, entire fields of brown cotton that peasants and Indian artisans had stubbornly maintained.

The discovery that a rich textile tradition dating from 3000 B.C. had persisted into modern times interested many people throughout Peru. As a result, in 1982, I created and co-directed the Native Cotton Project with support from the Peruvian ministries of labor and tourism. Those of us involved with the project worked to revive even further the cultivation and use of colored cotton. The resuscitation of this ancient tradition offered rural farmers an alternative crop to grow, but it also required the governmental reversal of a century-long policy.

My co-workers and I discovered that beginning in 1931 the Peruvian government had issued a series of laws and decrees aimed at destroying perennial, pigmented forms of native cotton in an effort to protect the all-white varieties that were commercially viable. Quarantine measures had been implemented over a broad swath of the Peruvian coast to eradicate cotton pests by eliminating all the possible alternative plant hosts, including landraces of colored cotton, the Peruvian kapok tree (*Bombax discolor*) and even a lintless cotton (*G. raimondii*). Pesticides were liberally applied, and the long-standing, successful tradition of crop rotation was abandoned.

Although the pest-control program had proved to be an expensive and misbegotten failure, it was still being adhered to in the 1980s, with devastating consequences. Much of the genetic variation present earlier in the century had been irreversibly eroded, abandoned by Indian farmers or suppressed by a legion of new plant pathogens that arose after the massive pesticide application. Even the survival of the commercial all-white

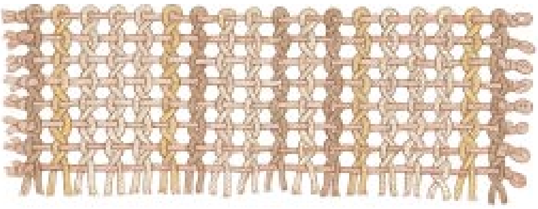


Zigzag form of twining

PATRICIA J. WYNNE

COTTON HARVESTING is done by hand in Peru (*top*). Women then sort the cotton, also by hand, for color and for quality (*right*). Finally, the cotton is ginned (*below*). The gins shown here were designed and patented in England over a century ago. Although they still work admirably well, most have been replaced recently by modern gins.

COURTESY OF JAMES M. VREELAND, JR.



Gauze weave from the Chancay Valley in Peru

PATRICIA J. WYNNE

cotton was severely threatened. In 1990 a new Peruvian "environmental code" finally made the eradication practice illegal. But pesticides remain pervasive. In the 1990s the annual consumption of pesticides in Peru reached an all-time high: about 18 pounds (eight kilograms) of pesticides were used per person per year, although experts say that only 1 percent of the insect pest damage is being controlled even now.

Slowly, over the past decade or so, we have been able to rebuild the stock of naturally colored cotton. Today the Native Cotton Project maintains 75 landraces of white and naturally pigmented cottons. Some 15,000 peasants and Indians who grow these cottons in dozens of plots throughout Peru are by far the largest single group of naturally colored lint producers worldwide.

FRANÇOIS PATTHEY *Grupo Inca*

COTTON CLOTHES in naturally occurring colors are produced in Peru by the author and his colleagues and sold internationally under the brand name Pakucho. Pakucho means "brown cotton" in the ancient Inca language.

The majority of them use organic methods, removing large pests by hand (children often drown the bugs in a water-filled jar) and growing plants that repel the insects. These techniques are pre-Columbian in origin. Archaeological sites from A.D. 1250 show that cotton was grown in rotation with cucurbits, a food crop in the squash family. In addition, ancient soil samples reveal the presence of pollen grains from another plant, Lippia. These seeds came from a weedy shrub, thought by most farmers to be useless. But years of questioning indigenous farmers turned up an octogenarian who identified the plant as mastrante. He grew it in a row next to his native cotton plants to control a pest called the cotton stainer (*Dysdercus peruvianus*). The old farmer did this by periodically cutting down several mastrante plants, drying them in the sun and, when the wind was right, igniting them. Pungent smoke from the desiccated shrubs wafted through the cotton fields, instantly driving out the cotton stainers, which ruin cotton by puncturing the seeds, releasing oils that stain the boll.

The Native Cotton Project grew steadily, and in 1993 we were contacted by a textile company in Arequipa that wanted to market naturally colored cotton products internationally. Our brand name became Pakucho ("brown cotton" in the ancient Inca language), and we now produce colored cotton products and textiles. The cotton is labeled organic by Skal, a Dutch inspection organization. Colored cotton is organic and drug-free: it is a lucrative cash crop for farmers who have been under pressure to convert their land to coca production for cocaine.

There are many revival efforts that resemble those of Pakucho and the Native Cotton Project. In the hills of Santander in Colombia, for instance, a small group of student-led peasant producers has brought back native cotton spinning and weaving as a rural development project. In the highlands of Guatemala the Ixchel Museum of Guatemala City is leading a revival project in communities where brown cotton, or *ixcoco,* was traditionally spun until the practice almost died out. And in the Bolivian Oriente, the Chiquitano Indians hope to revive organic cotton cultivation as well.

Indeed, the future of colored cotton looks bright in many places. It has attained near-celebrity status in the U.S. and Europe. And this year Peru's naturally pigmented and organically grown cotton exports will exceed $15 million—only fitting, because many thousands of years ago the Americas were the wellspring for virtually all the colored cotton we know and enjoy today.

The Author

JAMES M. VREELAND, JR., has been conducting research on the ancient textiles of Peru since 1968. He first discovered naturally colored cotton in Peru in 1977, while doing research for his doctoral studies at the University of Texas at Austin under the guidance of Richard P. Schaedel. Since that discovery, he has worked to understand the survival of the 5,000-year-old resource, as well as to ensure its revival among Peruvian Indian and peasant cotton farmers and artisans. He wishes to thank his many sponsors, including the Social Science Research Council, the Wenner-Gren Foundation for Anthropological Research and the National Science and Technology Council of Peru. Vreeland can be found at PAKUCHO@mail.interplace.com.pe or at http://www.interplace.com.pe/pakucho.htm on the World Wide Web.

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THE AMATEUR SCIENTIST

by Shawn Carlson

Detecting “Hot” Clouds

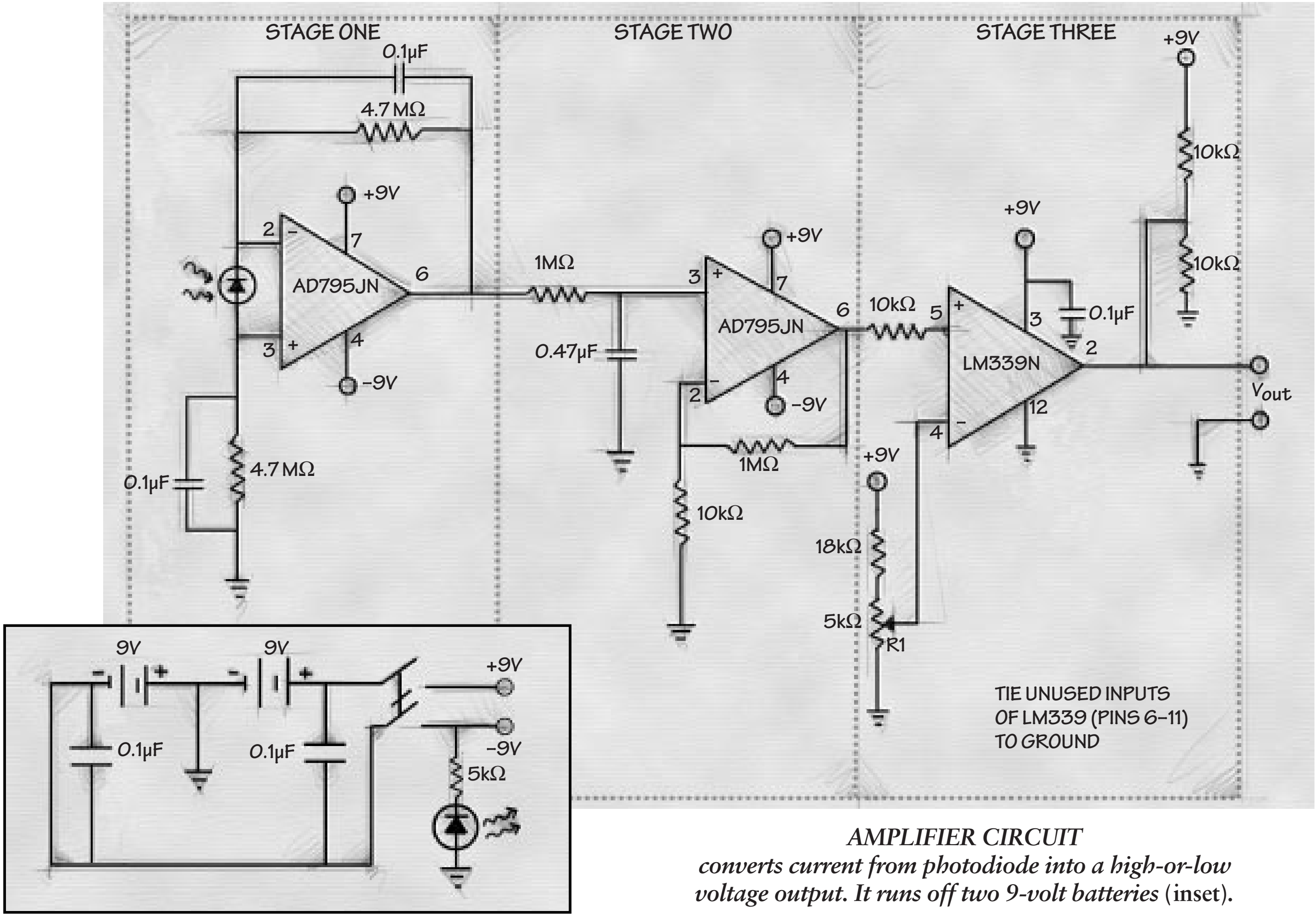
When not flying as an airline pilot, Monty Robson works to involve young people in science. Under his leadership, the Western Connecticut Chapter of the Society for Amateur Scientists has raised $50,000 toward a professional-quality telescope for a high school in New Milford. The telescope will be fully automated and connected to the Internet so that students far and wide can access everything the heavens have to offer.

Because any telescope can be ruined by rain and excessive wind, it is important to keep constant tabs on the weather. I’m designing the weather station for the automated observatory and thought I’d share with you my ideas for a cloud detector.

We humans can see clouds at night because they reflect light. But it is tough to build a weather sensor that relies on variations in the brightness of visible light, because the moon’s brightness also fluctuates. A cloudless sky with a full moon can be brighter than a cloudy sky with no moon. Fortunately, the moon and the clouds differ in one crucial respect: the moon delivers little infrared light to the earth’s surface, whereas clouds scatter infrared strongly. At night, as the air temperature drops, the ground vents some of its excess heat as infrared radiation with a wavelength of around 9 microns. If the skies are clear, most of this energy escapes into outer space. But a fluffy layer of condensed water vapor returns thermal energy back to the ground. That is why, all else being equal, a clear night is chillier than a cloudy one.

The reflected radiation can be observed with an infrared radiometer, which produces a voltage that increases with the intensity of the infrared light striking it. But there is a problem. Photons emitted by the earth’s surface have such a low energy that inexpensive silicon sensors, such as photodiodes, must be chilled with liquid nitrogen, lest the signal be swamped by the thermal jostling of atoms within the detector itself.

One simple way to avoid the cryogenics might be to take advantage of the telescope’s urban setting. Incandescent lights, including house lights and streetlights, are much hotter than the ground and so produce more energetic radiation. If enough photons from these sources scatter off the clouds, they should overcome the noise within a photodiode operating at room temperature. So I decided to try an unchilled radiometer. The early data look promising, especially for low, thick clouds, but I hope you will conduct your own experiments where you live and send me your results.



AMPLIFIER CIRCUIT
converts current from photodiode into a high-or-low voltage output. It runs off two 9-volt batteries (inset).

The infrared photodiodes at your local electronics suppliers are most sensitive to wavelengths around 0.9 micron, or 900 nanometers. But they also pick up some visible light—wavelengths between about 400 and 700 nanometers—so you must screen this light out. Some photodiodes, such as the NTE3033 that I purchased at Fry's Electronics for $4, are encased in an opaque plastic that blocks visible light but not infrared. Others, such as the SD3421 from Honeywell Micro Switch (call 800-367-6786 or 815-235-6838), will require an external filter. Edmund Scientific sells a circular filter 1 inch in diameter for $5 (call 609-573-6250 and ask for part no. H43948).

As used in this radiometer, the photodiode transforms the photon intensity into a very weak electric current, which must then be converted to a voltage and amplified. For the circuit [*see illustration on opposite page*], I chose the AD795JN operational amplifier, manufactured by Analog Devices (800-262-5643 or 617-329-4700 to find the nearest distributor), in part because it produces scarcely a whisper of electronic noise. You might experiment with lower-grade op-amps such as the TL082, available at Radio Shack. But old standbys such as the 741 op-amp are far too noisy.

The first stage of the circuit yields 10 millivolts for each nanoampere generated by the photodiode. The second stage boosts the signal again, but it also magnifies the circuit-generated noise. Conveniently, the signal I am looking for is very low frequency, because the night sky is of nearly constant brightness. Therefore, the circuit can cut noise by using a low-pass filter—consisting of a resistor and a capacitor—without affecting the signal. The filter blocks frequencies above 10 hertz, which account for two thirds of the noise generated by the AD795JN in this circuit. (Technically, the bypass capacitors in the first stage also fulfill this function.) Overall the second stage boosts the output of the first stage 100-fold while keeping the noise output to only a few tenths of a millivolt.

In complete darkness, stage two of my prototype gave a signal of 3 millivolts with random fluctuations of about 0.3 millivolt. When I placed the device inside a dark and windowless bathroom and pointed my TV remote under the door, the output jumped 300 millivolts.

The third and final stage uses a chip

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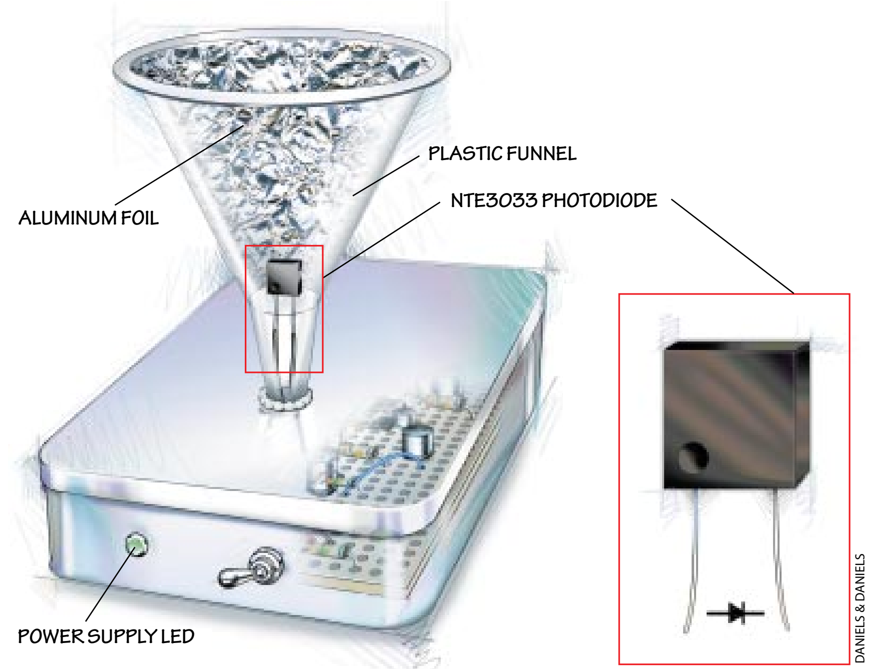


INFRARED RADIOMETER
directs light from the sky to a photodiode, which transduces it to an electric current.

called a comparator to check the output against a reference voltage that mimics a cloudless sky. The LM339, available from Radio Shack (part no. 276-1712) for about $1, has four comparators on a single chip, only one of which is needed here. The comparator turns the analog signal from the second stage into a two-state output to indicate cloudy or clear.

For use as a cloud detector, encase the circuit in a grounded and weatherproof metal box. Cement aluminum foil inside a large plastic funnel and mount the photodiode near the bottom [*see illustration above*]. This reflective horn guides skylight onto the sensor and blocks radiation from the ground. Mount the horn so that it points straight up. Under a starry sky, the second stage of my unit put out about 0.5 volt. When clouds rolled in, it increased to a little over 1 volt. It did not respond to moonlight.

To calibrate the instrument, point the horn straight up on a clear night and adjust the potentiometer R1 until the voltage at the comparator's negative input is 0.2 volt greater than the signal registered at its positive input. Then the output of the third stage should be approximately 0 volts. When you tip the reflective horn toward a light, the reading should jump to almost 5 volts. Test the detector on the next cloudy night. The circuit should generate about 0 volts when the horn is covered and about 5 volts when exposed to the cloudy sky. Readjust R1 if necessary. City dwellers and suburbanites should both be able to find a setting that reliably distinguishes between clear and cloudy skies. Given a suitable interface, this signal could be fed into a computer.

With minor changes, you can create other useful instruments. For example, if you read the output of the second stage directly with a digital voltmeter, you have an extremely sensitive near-infrared light meter. Because an object passing by will change the amount of infrared energy that reaches the sensor, the device can also be used as a motion detector. Replacing the infrared photodiode with one that is more sensitive to visible light makes a visible-light radiometer, which can do such things as measure the light pollution in the night sky and the energy output of bioluminescent organisms. SA

Those interested in learning more about Robson's telescope project can reach him directly at 860-354-1595. For more information about this and other projects from this column, check out the Society for Amateur Scientists's Web page at web2.thesphere.com/SAS/WebX.cgi. As a service to the amateur community, SAS can supply the electronics components for this project (photodiode, op-amps, comparator, capacitor and resistors only) for $30 plus $5 shipping until May 2000. Send a check to the society at 4735 Clairemont Square, Suite 179, San Diego, CA 92117, or call 619-239-8807.

I gratefully acknowledge informative conversations with George Schmermund and Russell Wallace.

by Ian Stewart

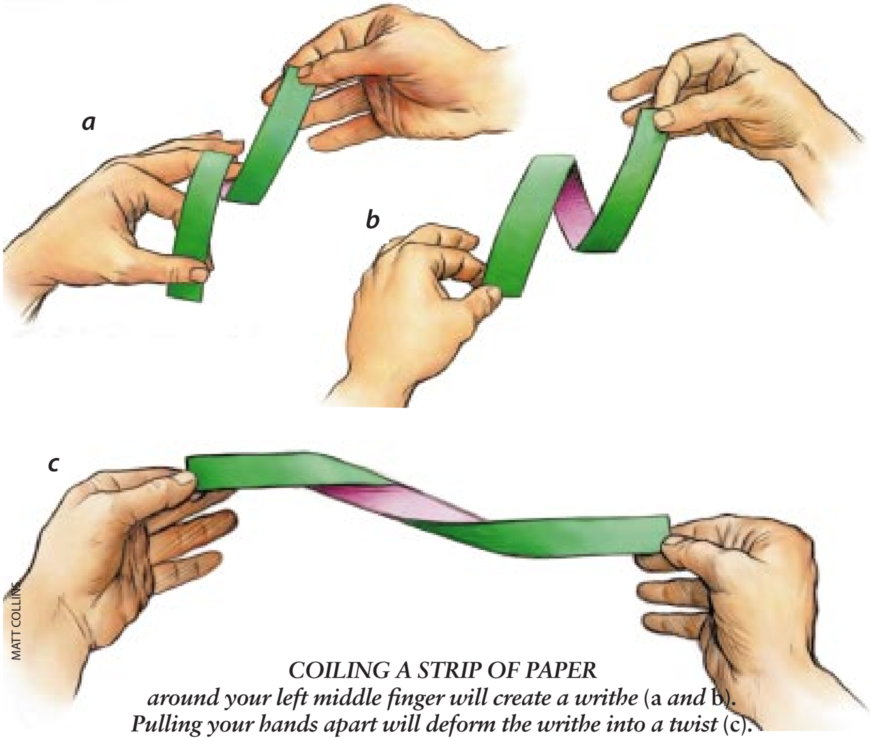
Tangling with Topology

Why does the telephone cord always get twisted? I'm thinking of those stretchable cords, the long helical coils attached to phones that hang on the wall. When you install the phone, the cord hangs nice and neatly. But as the weeks pass, it becomes more and more tangled. You can see the same effect with a rubber band if you hold its ends loosely between the thumb and forefinger of each hand and twiddle your fingers. Or you can start with a length of string between your fingers and thumbs and roll the ends. This kind of behavior is called supercoiling, and it also happens to undersea communications cables and to strands of DNA.

I know why the phone cord supercoils in my house. It's the same general mechanism that makes the rubber band and the string coil around themselves in that characteristic manner. When the phone rings, I pick it up with my right hand and twist it about 90 degrees. To speak into it, though, I then transfer the phone to my left hand, which imparts another 180 degrees of twist. When I've finished, I use my left hand to hang it on the wall again, imparting a final 90 degrees of twist to the cord. So every time I use the phone, I twist the cord by a full 360 degrees—and in the same direction every time.

If I kept the phone in my right hand, I could untwist the cord when I put the phone back. But that transfer between hands seals the cord's fate. The same kind of thing happens to the electric cable for my garden tools. After use, I coil it over my shoulder like a mountaineer's rope. Over time, the cable gets more and more twisted along its length. Something is converting coils into twists, but what?

The branch of mathematics that organizes how we think about this kind of question is topology—"rubber-sheet geometry," the geometry of continuous transformations. Topologists distinguish two different ways to loop a flat strip: twists and writhes. To understand the difference, it helps to make a strip of strong paper, eight to 10 inches long and half an inch wide. It's useful if one side is distinguishable from the other: for example, you can color one side red and the other side blue.



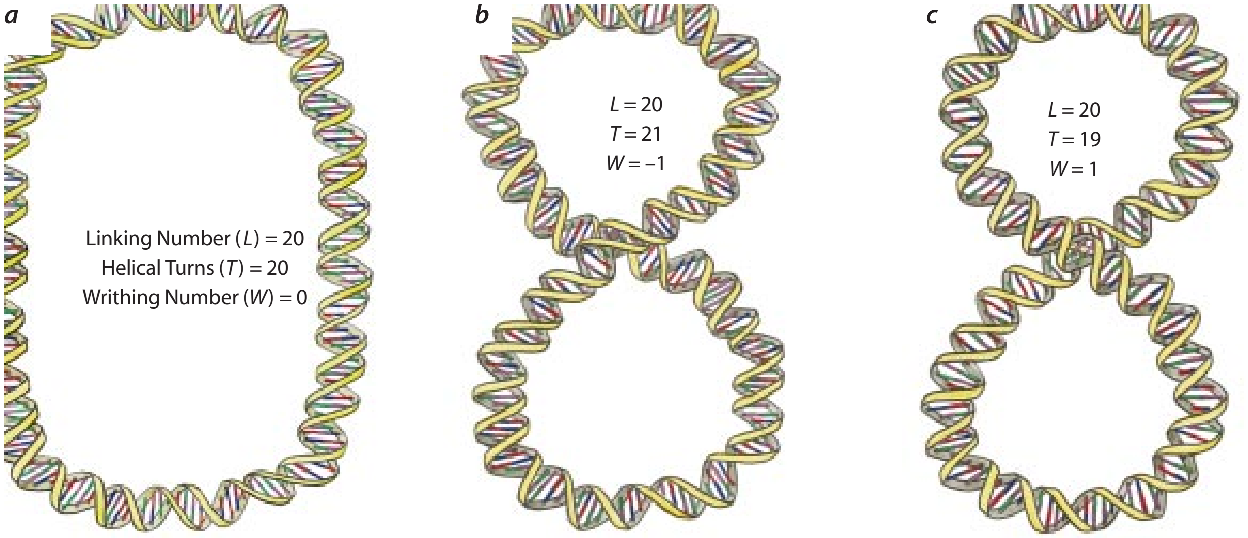
MATT COLLINS

COILING A STRIP OF PAPER around your left middle finger will create a writhe (a *and* b). *Pulling your hands apart will deform the writhe into a twist* (c).

Hold the strip flat and pointed directly away from your body, with your left thumb and forefinger holding the near end, and your right thumb and forefinger holding the far end. Now move your right hand to coil one loop of the strip around your left middle finger [*see illustration below*]. Then remove your left middle finger to leave a free loop. You have just inserted one coil, or writhe, into the strip. If, however, you gently pull your hands apart, the strip deforms into a different shape, called a twist. You could have gotten the same effect by holding the strip flat across the front of your body, keeping the left end fixed and twisting the right end through 360 degrees. So we see that one writhe can be deformed, topologically, into one twist.

Both writhes and twists have a direction—they can be "positive" or "negative." Once you've decided that a given writhe or twist is positive, then its mirror image is negative. The easy way to start is to declare that the writhe in the illustration is positive but that the twist is negative. This choice leads to the simple equation $T + W = 0$, where T is the number of twists and W the number of writhes. If you coil the strip of paper twice around your middle finger, you will be giving it two positive writhes—and if you pull your hands apart, the writhes will turn into two negative twists. Experiment with three or four writhes: you'll find that any given number of positive writhes can be turned into the same number of negative twists.

One can see the same phenomenon when twisting a piece of plain string. You can keep track of how the string supercoils by imagining that a flat band runs along its center. As you twist one end of the string, this band also twists, and the number of twists in the band will equal the number of complete turns you give to the string. If you keep the string taut, all it can do is twist, but if you move the ends toward each other, the string prefers



MATT COLLINS

CLOSED LOOP OF DNA obeys the formula $L = T + W$ *whether the DNA molecule is relaxed* (a) *or supercoiled* (b *and* c).

to writhe, and the supercoil appears.

The reason the string prefers to writhe is related to the fact that it is slightly elastic, in the sense that it is bendable but produces a restoring force when it bends. The more you bend it, the more strongly it tries to straighten out again. The preference for writhes over twists was first explained in 1883 by British mathematician Alfred G. Greenhill, who showed that a writhed shape has less elastic energy than the corresponding twisted one. The same is true even of paper strips, as you can confirm by experiment: unless you impart energy by holding the strip taut, it prefers to writhe. Greenhill proved that if an infinitely long rod is twisted by forces “at infinity,” it buckles into a helix. Recently three Australian mathematicians—D. M. Stump and K. E. Gates of the University of Queensland and W. B. Fraser of the University of Sydney—analyzed the elasticity theory of a twisted rod using more realistic modeling assumptions. They found specific formulas for the exact shape of the supercoil, useful in particular for engineers laying undersea cables, which can become twisted while being placed on the ocean bottom.

The situation for the phone cord is in principle more complicated because the cord starts out as a helix. Nevertheless, a phone cord also converts twists into writhes, just like a plain string, at least if you don’t allow its own helical coils to unravel, which is what usually happens. (You also get funny glitches in the phone cord where successive coils don’t fit together properly.) You can imagine a long fat string threaded through the helical coils with a long flat strip embedded in it, and as the cord gets twisted, so does that string, and so does the strip.

Like the phone cord, the DNA molecule, the hereditary material of living organisms, is a helix. More accurately, it is a double helix, in which two helical strands corkscrew around and around each other. Biologists have to understand the geometry of DNA’s double helix under a variety of conditions, and they find that it, too, undergoes supercoiling, with transitions from writhes to twists. It is important to understand these transitions when interpreting electron micrographs of loops of DNA. Moreover, as I hinted earlier, DNA and phone cords can do something that plain string cannot: they can ravel or unravel their own helical coils. One simple topological feature of DNA may give you a flavor of the much more sophisticated theories being devised by topologists and biologists. It concerns three features of a closed loop of DNA:

- The linking number L, which is the number of times one strand crosses the other when the molecule is laid out flat;
- The number T of helical turns in the DNA;
- The writhing number W, which measures the amount of supercoiling.

The basic formula is the elegant $L = T + W$, which generalizes our earlier formula for a flat strip, $T + W = 0$. The edges of the flat strip are not linked, so $L = 0$ in that case. For a given DNA loop, L is fixed, but we can trade writhes for twists or vice versa. The illustration above shows how this works for a DNA loop with a linking number of 20.

FEEDBACK

I received a lot of correspondence on the cake-cutting algorithms mentioned in the column “Your Half’s Bigger Than My Half!” [December 1998]. In particular, Saman Majd laid to rest my vague feelings of disquiet about moving-knife algorithms. In these, one or more knives moves slowly across the cake, and players have to shout when they are willing to accept the piece that is cut off. My worry was the element of reaction time. Majd’s idea is that in place of the moving knife, the players make marks on the cake (or on a scale model). First, choose a direction (say, north-south) and ask each of the n players, in turn, to mark the cake with a north-south line at the westernmost position for which they are willing to accept the cake to the west of the mark. (That is, where they estimate the “worth” of the left-hand slice to be $1/n$.) Whoever’s mark is farthest west cuts off that bit and exits the game.

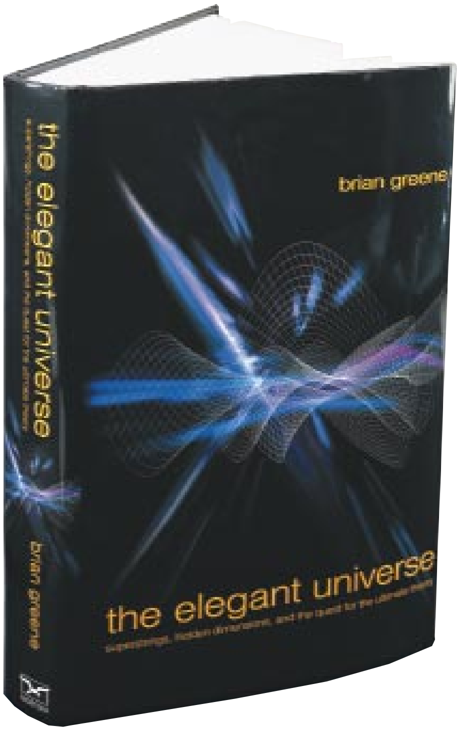
Now continue in the same general manner. The ordering of the cuts in the west-east direction substitutes for the timing, and the same idea can be used for all moving-knife methods. I withdraw my reservations! —*I.S.*

REVIEWS AND COMMENTARIES

AESTHETIC SCIENCE

Review by Chris Quigg

The Elegant Universe: Superstrings, Hidden Dimensions, and the Quest for the Ultimate Theory
BY BRIAN GREENE
W. W. Norton & Company, New York and London, 1999 ($27.95)



BETH PHILLIPS

Making connections is the essence of scientific progress. For monumental examples in the realm of physics, think of the amalgamation of electricity and magnetism and light; of the recognition that heat is atoms in motion, which brought together thermodynamics and Newtonian mechanics; and of the realization that the chemical properties of substances are determined by the atomic and molecular structure of matter.

These advances, and much of our recent progress in particle physics and cosmology, came about in large measure through the creative resonance between experimental discovery and theoretical insight, sometimes one taking the lead, sometimes the other. Another path to theoretical progress focuses on foundational issues of internal logic and self-consistency. The most recent strides—many would say leaps and bounds—along that path have attended the development of string theory, the subject of Brian Greene's thoughtful and important book, *The Elegant Universe*. Greene, a professor of physics and mathematics at Columbia University and an adjunct professor at Cornell University, is a leading contributor to string theory and a key agent in the growing reunion of physics and mathematics. *The Elegant Universe* presents the ideas and aspirations—and some of the characters—of string theory with clarity and charm. It is both a personal story and the tale of a great intellectual movement.

The conceptual tension that faces physics at the millennium has been building for half a century. All of modern physics rests on two pillars. One is Albert Einstein's general relativity, which describes the world on the largest of scales—stars, galaxies and the immensity of the universe itself. The other is quantum mechanics, which describes the world on the smallest of scales—atoms, nuclei and quarks. Experiments have confirmed the predictions of both general relativity and quantum mechanics to a remarkable degree. But—as we currently understand these two theories—they cannot both be right. The violent fluctuations on ultramicroscopic scales implied by the uncertainty principle of quantum mechanics are at odds with the smooth geometry of space-time that is the central feature of general relativity.

Why has this battle of titanic ideas not paralyzed physics? At most of the distance scales that physicists contemplate, from less than a billionth of human scale out to the farthest reaches of the universe, the dissonance between quantum mechanics and general relativity does not arise. That is why many physicists are content to note the problem and go—productively—about their business. But when we consider stupendously short distances to analyze the earliest history of the universe, we run up against the fundamental incompatibility between general relativity and quantum mechanics.

Over the past three decades, an intrepid band of theoretical physicists and mathematicians—first in tiny groups, now in a veritable army—have concluded that the time is ripe to address this grand conflict between the two great pillars of our understanding. The picture they are developing is called string theory. It holds that the fundamental constituents of the universe are not the elementary particles that we idealize as having no size, like geometric points, but tiny strings. The resonant patterns of vibrations of the strings are the microscopic origin of the masses of what we perceive as particles and the strengths we assign to the fundamental forces. Because strings have a finite, though fantastically tiny, size, there is a limit to how finely we can dissect nature. That limit—set by the size of strings—comes into play before we encounter the devastating quantum fluctuations that rend space-time. Thus, the conflict between quantum mechanics and general relativity is resolved.

Searching for Symmetry

String theorists undertake their campaign to reconcile general relativity and quantum mechanics even without detailed experimental results, which Greene calls "the shining light of nature," to guide them from one step to the next. Lacking experiment's guiding hand, it is possible that one or more generations of physicists will devote their careers to string theory without getting any experimental feedback. They risk investing a lifetime of effort for an inconclusive result.

Why take the risk? The string theorists are not simply sticklers for rigor. They are animated by ambition, by the hope that resolving the conflict between general relativity and quantum mechanics will resolve at a stroke many other issues—explaining the properties of the elementary particles and forces, plumbing the true nature of a black hole. “In his long search for a unified theory,” Greene writes, “Einstein reflected on whether ‘God could have made the Universe in a different way; that is, whether the necessity of logical simplicity leaves any freedom at all.’ With this remark, Einstein articulated the nascent form of a view that is currently shared by many physicists: If there is a final theory of nature, one of the most convincing arguments in support of its particular form would be that the theory couldn’t be otherwise.”

String theory holds that the fundamental constituents of the universe are not the elementary particles that we idealize as having no size, like geometrical points, but tiny strings.

Early in the study of string theory, physicists learned that the theory does not make sense if space-time is made up of the three space dimensions plus one time dimension of ordinary experience. String theory also requires extra space dimensions that must be curled up to a very small size to be consistent with our never having seen them. Whether we can probe them directly or not, these extra curled-up dimensions—six of them, in most forms of string theory—have physical consequences. As Greene explains it, “a tiny string can probe a tiny space. As a string moves about, oscillating as it travels, the geometrical form of the extra dimensions plays a critical role in determining resonant patterns of vibration. Because the patterns of string vibrations appear to us as the masses and charges of the elementary particles, we conclude that these fundamental properties of the universe are determined, in large measure, by the geometrical size and shape of the extra dimensions. That’s one of the most far-reaching insights of string theory.”

String theory is still a work in progress. In fact, the equations of string theory seem so complicated that physicists have managed to write down only approximate versions. Within the past few years, string theorists have realized that all the approximate formulations might be seen as different limiting cases of an 11-dimensional theory whose fundamental entities include two-dimensional membranes. Although it is only partially understood, this new theory, termed M-theory, has given unforeseen unity to the approximate versions of string theory that previously seemed distinct and unrelated [see “The Theory Formerly Known as Strings,” by Michael J. Duff; Scientific American, February 1998].

If string theory arises from metaphorical travel to the realm of infinitesimal distances and unattainably high energies, how can we hope to test it? Edward Witten of the Institute for Advanced Study in Princeton, N.J., urges that string theory already can claim experimental confirmation for its prediction of gravity. As Greene explains, “Both Newton and Einstein developed theories of gravity because their observations of the world clearly showed them that gravity exists. On the contrary, a physicist studying string theory . . . would be inexorably led to it by the string framework.”

One reason that string theory appeals so powerfully to theoretical physicists is that it is the most symmetrical theory ever devised. Symmetry is the concept physicists use to relate phenomena and circumstances that seem—on first examination—to be different. James Clerk Maxwell showed that such disparate phenomena as light, electricity and magnetism are fundamentally intertwined; Einstein showed that all states of motion are related. String theory encompasses these symmetries and more. It incorporates the grandest symmetry that physicists have imagined: supersymmetry, a quantum-mechanical extension of space and time. Supersymmetry relates the two quantum-mechanical categories of elementary particles, so that each of the known fundamental particles must have a superpartner whose spin differs by half a unit. Intensive searches for supersymmetry—or for indirect indications of the existence of supersymmetry—preoccupy many particle physicists around the world. Although supersymmetry can exist without string theory, the discovery of supersymmetry would supply extremely strong encouragement for string theory.

String theory might also be able to resolve one of the great puzzles of cosmology. Astronomical observations have shown that Einstein’s cosmological constant, which governs the cosmic evolution of the motions of distant galaxies, is quite small, if not exactly zero. Yet according to our current understanding of the fundamental interactions, quantum fluctuations throughout space tend to create a cosmological constant that is many, many times larger than observation allows. Can string theory show why the cosmological constant is tiny?

The Significance of Scale

For most of the 20th century, physicists have been living through—no, making—a change in the way humans think about their world. Physicists have known since the 1920s that to explain why a table is solid, or why a metal gleams, we must explore the atomic and molecular structure of matter. That realm is ruled not by the customs of everyday life but by the laws of quantum mechanics. The recognition that the human scale is not privileged, that we need to leave our surroundings the better to understand them, has been building since the birth of quantum mechanics. As it emerges whole, fully formed, in our unified theories and scale-changing shifts in perspective, the notion seems to me both profound and irresistible. I find it fully appropriate to compare this change in perception with the shifts in viewpoint we owe to Copernicus and Einstein. And just as the realization that we are not at the center of the universe ultimately enlightened and empowered—not diminished and dispirited—us humans, so, too, the recognition that our size is not the only, or the most important, scale for comprehending nature will be a source of insight and inspiration.

If string theory succeeds, its success will represent the culmination of the idea that we understand the universe best when we consider it on many scales. Here is Greene's summation: "Although we are technologically bound to the earth and its immediate neighbors in the solar system, through the power of thought and experiment we have probed the far reaches of both inner and outer space. During the last hundred years in particular, the collective effort of numerous physicists has revealed some of nature's best-kept secrets. And once revealed, these explanatory gems have opened vistas on a world we thought we knew, but whose splendor we had not even come close to imagining."

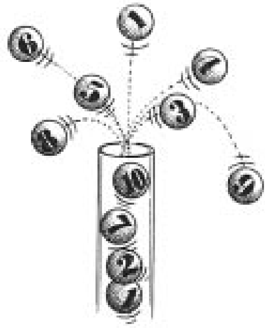
Will string theory succeed? We do not know. After all, no one yet understands completely what string theory is, and the tools needed to extract its predictions are still being developed. It is certainly not the only fruitful path to follow: experiments at the great accelerators and surveys at the great observatories, together with the theoretical developments that motivate or respond to them, will surely bring dramatic advances in our understanding of what nature is and how it works. But the insights that string theory has already brought illustrate anew the power of the question "Why not?" to open our eyes to new possibilities. String theory is a beautiful dream, beautifully told in *The Elegant Universe.*

CHRIS QUIGG is a theoretical physicist at Fermi National Accelerator Laboratory in Batavia, Ill. He is the author of Gauge Theories of the Strong, Weak, and Electromagnetic Interactions *(Perseus Books, 1997).*

THE EDITORS RECOMMEND

THE JUNGLES OF RANDOMNESS: A MATHEMATICAL SAFARI. Ivars Peterson. John Wiley & Sons, New York, 1998 ($14.95).

From a purely operational point of view, mathematician Mark Kac once said, "the concept of randomness is so elusive as to cease to be viable." Peterson examines a number of processes that seem random but may not be. In flipping a coin, he points out, "we know from experience (or theory) that we're likely to obtain an equal number of heads and tails in a long sequence of tosses. So if we see twenty-five heads in a row, it might be the legitimate though improbable result of a random process. However, it might also be advisable to check whether the coin is fair and to find out something about the fellow who's doing the flipping." Peterson looks at randomness in rolling dice, human concourse, slot machines, the synchronous flashing of fireflies in Southeast Asia and several other fields, presenting the mathematics imaginatively and clearly. Discussing the electronically manufactured random numbers that govern the operation of slot machines and other casino games, he says: "The trouble is, just as no real die, coin, or roulette wheel is ever likely to be perfectly fair, no numerical recipe produces truly random numbers. The mere existence of a formula suggests some sort of predictability or pattern."



FROM *THE JUNGLES OF RANDOMNESS*

THIS NEW OCEAN: THE STORY OF THE FIRST SPACE AGE. William E. Burrows. Random House, New York, 1998 ($34.95).

"When the history of this century is written," Burrows says, "the story of mankind's first breaking gravity's relentless hold and touching places beyond Earth will be one of its most exciting and important chapters." Burrows tells the story engagingly, beginning long before this century with an account of the human effort to fly. And then to overcome gravity by developing rockets. Thence into what he calls the first space age, which might have arrived later than the 20th century had it not been for the cold war—"the great engine, the supreme catalyst, that sent rockets and their cargoes far above Earth and worlds away." Sputnik, the manned missions to the moon and the unmanned exploration of other planets in the solar system—all the milestones of the first space age appear in the rich tapestry Burrows has woven. But now, he says, the first space age has ended and the second has begun. Its features are an enduring human presence in space, the use of space to serve society's needs (by means of such devices as communications satellites and orbiting telescopes) and, inevitably, space weapons. If we are spared devastation by the weapons, then someday, perhaps, astronauts will set forth on the long voyage to a nearby star: "the ultimate, fantastic human odyssey."

EDISON: A LIFE OF INVENTION. Paul Israel. John Wiley & Sons, New York, 1998 ($30).

Edison's name is on 1,093 U.S. patents—more than any other person's. It is a measure of his renown that his surname alone suffices for the title of this book. Israel, managing editor of the Rutgers University edition of Edison's papers, has explored thoroughly the five million pages of documents housed at the Edison National Historic Site in West Orange, N.J., and so he is well positioned to discuss the eminent inventor's achievements. That he does with care and clarity. The well-known inventions—the incandescent lightbulb, the phonograph, the kinetoscope for motion pictures, the carbon transmitter for telephones—are all here in detail, and so are the lesser-known ones as well as some Edisonian projects that did not succeed. Israel also paints a clear portrait of the man. One learns, among other things, of Edison's difficult relationships with his children, his indifference to his appearance and his singular notions about diet. (In his last years, when he was suffering from stomach trouble, "he consumed nothing more than a pint of milk every three hours.") Edison may well have been the "Inventor of the age," as he was orotundly described in the Grand Prize that he won at the Universal Exposition of 1878 in Paris, but he was in addition a complex and intriguing human being.

FROM *EDISON*

LEONARDO'S MOUNTAIN OF CLAMS AND THE DIET OF WORMS. Stephen Jay Gould. Harmony Books, New York, 1998 ($25).

Polymath Gould, who holds professorships in zoology, geology and biology, presents here the eighth collection of his monthly essays from *Natural History*. The art of the essay is not much practiced now, but Gould is a master of it: the beguiling subject, the juicy feast of facts and thoughts related to the subject, and the surprising connections made between the subject and other topics—all rendered in smoothly polished prose. The title derives from two of the essays, one on Leonardo's seemingly prescient studies of sea-creature fossils in the Alps and what moved him to make the studies, the other on the Diet of Worms in 1521 and the Defenestration of Prague in 1618 as representative of the dark side of human behavior, to be contrasted with the glorious side as depicted by the paintings of Rubens and the architecture of Prague—and what evolutionary biology has to say about why humans are capable of such horror and such glory. Gould offers 21 essays in all, covering a great sweep of human affairs and natural history.

DINOSAURS OF UTAH. Frank DeCourten. University of Utah Press, Salt Lake City, 1998 ($45).

Of books on dinosaurs there are many, but this one aims at a wider target. DeCourten says he "became increasingly disenchanted with dinosaur publications that focused almost exclusively on the animals themselves, with little mention of the habitats and environmental history of the areas they occupied." So he focused on Utah, which is a rich source of dinosaur remains, and has produced a work that examines dinosaurs in the geologic and historical setting there—historical in this case meaning the Mesozoic era in which they flourished for millions of years and then, quite abruptly as geologic time goes, met their mysterious end. The book is carefully constructed and is immensely aided by its abundant illustrations—22 color plates by Carel Brest van Kempen (showing dinosaurs as they might have looked in life), 41 photographs and 112 figures—drawings and charts, mostly done by DeCourten. The concluding chapter, "Doing Paleontology," gives a sense of the hard work required to find dinosaur remains: "Because there is still no way to locate dinosaur fossils from satellites or airplanes, and no remote sensing techniques can reveal the presence of fossil bones over a broad area, the actual finding of scientific treasures requires walking ... and walking ... and walking."


CAREL BREST VAN KEMPEN

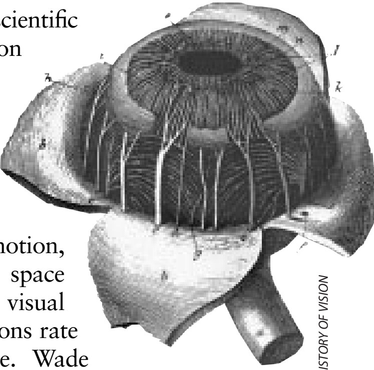
ENERGIES: AN ILLUSTRATED GUIDE TO THE BIOSPHERE AND CIVILIZATION. Vaclav Smil. MIT Press, Cambridge, Mass., 1998 ($25).

"Energy is the only universal currency: one of its many forms must be transformed to another in order for stars to shine, planets to rotate, plants to grow, and civilizations to evolve." Thus Smil begins his teeming cross-disciplinary book—"a hybrid," he calls it, "combining a quasi-encyclopedic sweep with the brevity of mini-essays," together with some 300 illustrations, old and new. The 82 essays are grouped under the headings of sun and earth, plants and animals, people and food, preindustrial societies, fossil-fueled civilization, and transportation and information; they cover a broad span of knowledge.

Dip into the book anywhere, and you will find a bracing fact or connection. Examples: Total runoff of the earth's rivers averaged 38,000 cubic kilometers during the 1980s, which was more than 5 percent below the mean during the late 17th century. The relation between the energy cost of walking and speed has a clear U shape: the energy cost is highest at a bit less than one meter per second, lowest at about 1.6 and moderate at about 2.4; the energy cost of running, however, is basically constant for speeds between three and 5.5 meters per second. The theoretical capacity of windmills increases with the cube of the wind speed; this in turn is proportional to the height above the ground raised to the power of 0.14; in other words, for a given wind speed at the surface, a machine with a shaft 10 meters above the ground will be only about 60 percent as powerful as one with its shaft 30 meters above the ground. And so on, in a dazzling procession.

A NATURAL HISTORY OF VISION. Nicholas J. Wade. MIT Press, Cambridge, Mass., 1998 ($55).

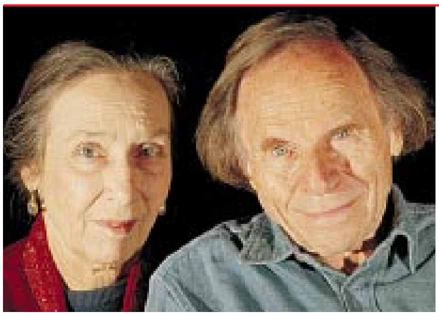
Wade, professor of visual psychology at the University of Dundee in Scotland, offers what he calls "an unconventional history of vision because it is based almost entirely on descriptions of visual phenomena in the (usually translated) words of the natural philosophers who reported them." His tale concerns what scholars learned about vision subjectively—that is, from their own visual experiences or by observing the visual experiences of others. It ranges from the time of the ancient Greeks to the appearance, about 160 years ago, of instruments that made objective and scientific studies of vision possible. Light and the eye, color, subjective visual phenomena (such as afterimages), binocularity, motion, space (including space perception and visual acuity) and illusions rate a chapter apiece. Wade presents much of his story in the words of the people who made the observations. He has also gone to some trouble to find fine engraved portraits of most of those people. The result is a sober, scholarly, handsome and rewarding book.


FROM A NATURAL HISTORY OF VISION

WE WERE BURNING: JAPANESE ENTREPRENEURS AND THE FORGING OF THE ELECTRONIC AGE. Bob Johnstone. Basic Books, New York, 1999 ($27.50).

It is a bit hard to remember now the profound concern that many Americans felt during the 1980s about what appeared to be a Japanese juggernaut that was sweeping all before it in the consumer electronics industry and that was threatening to drive American firms out of the electronics market. Today the predominant view in the U.S. is, as Johnstone puts it: "Japanese-style capitalism, so fashionable in the late 1980s, has been found wanting. The American way has triumphed." That complacency is misplaced, Johnstone says. "Sooner or later, Japan will bounce back."

He credits the success of the Japanese to a number of entrepreneurs who drove such firms as Sharp, Sony and Yamaha to their triumphs; and he describes ably the technology that they developed for making television sets, camcorders, watches, calculators and the many other products that pour forth from the nation's electronics industry. Japan still has such people, he says. "The point of this book," he writes, "has been to demonstrate that, though unseen and undervalued, there are entrepreneurs in Japan and that such individuals have played a key and hitherto unrecognized role in Japan's rise to prominence as an economic power. Until very recently, however, such creative forces have been stifled by ineffective government policy. Now the time has come to release their talents." SA



WONDERS

by Philip and Phylis Morrison

Circumnavigators All

DUSAN PETRICIC

What is now commonplace at one time amazed the world. That pipe fitter's troubling dream, the space station Mir, now counts about 50,000 trips around the world during a wearing decade in orbit. Much farther out in space hundreds of unmanned geostationary satellites orbit high over the equator every 24 hours; the sports bar at the corner can aim its television dish to watch Manchester United and never needs to shift. Those satellites move in sync with the earth's surface. We don't call that circumnavigation, although as deck passengers we daily circle the axis of the spinning earth. Only when we change surface position do we call it travel. To keep up with the sun across the U.S., you need to fly west at near-supersonic speed. But fast circumnavigators in low-earth orbit experience dawn and dusk a dozen times and more every 24 clock-hours.

It was in 1873 that the novelist Jules Verne first turned the feat of circumnavigation from a historic landmark to popular drama. His way-cool London clubman managed to go around the earth in 80 days, by ship, balloon, train, elephant, even sailing on land across Nebraska. The exact day count escaped the adventurer, for he forgot that all his assorted vehicles were day by day overtaking the sun in the sky. The fiction stimulated fact in an epoch when scheduled public travel was speeding up under steam. The undaunted young woman who signed herself Nellie Bly, a spectacular correspondent for the *New York Globe,* drew praise from Verne himself after her 1889 trip, which began in New York, went via Suez and encircled the globe. She cut a real week off the fictional Londoner's time.

In 1500 circumnavigation was a high challenge not yet met. Portuguese ships had for a long lifetime pioneered the sea route step by step, south around Africa, past India to the fragrant East Indies. In 1492 Christopher Columbus opened a new way for Spain, westward to the unexpected Americas. Ferdinand Magellan was a tough, ambitious officer of the Portuguese court, admired for his deeds both in combat and in travel out to the easternmost limits of Lisbon's reach. Not yet 40 years old, he fell out of royal favor for reasons no longer clear. His king rejected a bold plan the veteran had formed: lead a flotilla westward by sea to the lucrative clove-and-cinnamon East, first across the Atlantic, then across the Pacific—newly found by the Europeans and not yet traversed by any ship of theirs. Magellan took the plan to the Spanish, who lacked access to the Spice Islands east of Java. After a couple of years, young Charles V of wealthy Spain and his advisers agreed to back the risky scheme.

The earth's axis is not a fixed point but wanders every year or so in a complex rosette about 100 feet across.

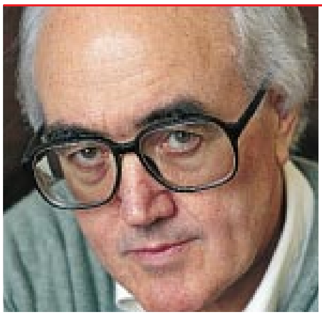
Charles's new subject, Captain General Magellan, sailed out of the river mouth below Seville in September 1519 with five well-armed serviceable ships, nothing special. His command had about 300 Spanish and foreign sailors and officers and five expert Portuguese pilots. Only one ship, *Victoria,* of 85 tons, returned to Seville, under Captain Juan de Elcano in September 1522 with about 20 men (a few stragglers arrived later). Their captain general did not return; he lay dead in the Philippines, lost in an hour's confused combat with local forces. Yet Magellan was the first man to cross all global longitudes during his lifetime—he died about 300 miles to the west of the easternmost port he had reached during his earlier service to Portugal.

The ordeal of his voyage was extreme: thirst, famine and scurvy took a fierce toll. Columbus had to sail the open ocean for only five weeks, Magellan for 14. On the final leg of their voyage, the officers of *Victoria* learned in Cape Verde that their day count was slow by one day; the ship had celebrated Easter on Monday, surely a sin, if a venial one. Very slowly, more seafarers tried circumnavigation. It took a century until all four main maritime powers had succeeded, and it was a century more before circumnavigation became more of an option than an end in itself.

The centenary of a striking circumnavigation under sail was marked in June 1998. In 1898 Captain Joshua Slocum, a veteran New England ship's master, had returned to Newport, R.I., in his 35-foot sailboat *Spray* from the first trip ever made around the world alone. His life and writings are celebrated by those 10,000 strong who sail the high seas in cruising yachts; every year 100 or so of them make it to Cape Horn. Of that doughty band, some will become full circumnavigators by sail. Well-organized races enroll those very

Continued on page 131

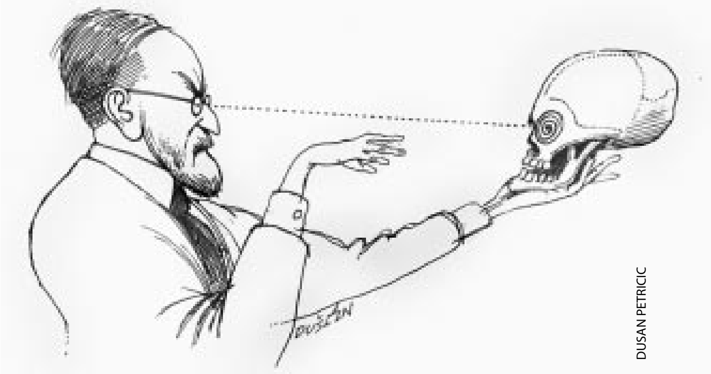
COMMENTARY



CONNECTIONS

by James Burke

Zzzzzzz



DUSAN PETRICIC

A recent bout of press hysteria about a stage hypnotist (whose subjects claimed he had caused claimed he had caused them long-term anguish) reminded me of how it all started. With hysteria, I mean. In 1880, when Josef Breuer, eminent Viennese medic, started treating a lady named Bertha Pappenheim for what he thought was hysteria (symptoms: convergent squint, disturbances of vision, paralysis, contractures of arms and legs) with a radically new, "gaze deep into my eyes" technique. The treatment was so effective that he and the colleague working with him later kicked off the entire science of psychoanalysis. This made Breuer's colleague so famous I only have to say that his first name was Sigmund.

Freud then shot off to Paris to bend the ear of anybody who'd listen. He seriously underwhelmed his professor, the hottest shot in French neurology, Jean-Martin Charcot (a.k.a. the "Napoleon of Neurosis" from the way he put one hand in his coat when demonstrating and was a general egomaniac and showman), because Charcot was too busy persuading the world that as far as the brain was concerned, mental was really physical. At this time, the brain was considered the "most advanced" system of the body, controlling the nervous system and therefore responsible for all disease. Pretty much everybody since the Greeks had thought some kind of magic fluid ran down through the nerves from various parts of the brain to various parts of the body. Mind over matter, you could say.

Some time around 1820 Kaspar Spurzheim and Joseph Gall (two Viennese doctors … what was it about Vienna?) had come up with a variation on this theme. Their idea was that the brain was composed of 37 organs, each one of which controlled a specific personality characteristic. The more developed one of these control centers in the brain was, the bigger it was, and the more of a bump it made on your skull (a large bump behind the left ear meant you were a good lover, in case you want to check). Back in 1815 Spurzheim had lectured in Edinburgh on gray-matter matters and inspired two locals, George and Andrew Combe, to set up the Phrenological Society.

Phrenology was an instant smash hit (with, among others, Queen Victoria) because once you'd found the bump you were interested in you could maybe do exercises to make it even bigger. In the upwardly mobile self-improvement environment of the mid-19th century, the ability to enlarge your bump of knowledge was irresistible. Phrenology even gave hope to social reformers who wanted to reduce the size of criminal-tendency bumps. For George Combe, things came to a head when he decided to splice the knot. What could he do but examine the dome of his prospective bride? She passed the test, and he married her because "her anterior lobe was large; her Benevolence, her Conscientiousness, Firmness, Self-esteem and Love of Approbation amply developed." She was also rich.

He married her because her anterior lobe was large. She was also rich.

Even hardheaded (sorry, last cranial joke) businessmen fell for all this guff. Henry Maudslay, a man so down-to-earth that he invented the screw-cutting lathe, without which the industrial revolution might not have happened, advised all young men to check out the skull of their beloved. (Maudslay had also invented a machine that measured things to within one ten-thousandth of an inch, so he was into quantification.) One of Maudslay's pupils was a young Napoleonic War draft dodger named Richard Roberts, to whom I have alluded before for his invention of a machine that made rivet holes automatically on the Britannia Bridge and the *Great Eastern* steamship.

Early in his career Roberts had worked as a pattern maker for the great ironmaster John Wilkinson, who ran one of the first blast foundries in a place named Coalbrookdale (guess what you would see if you went there). It was Wilkinson who made the switch from charcoal furnace fuel to coal and started turning out pig iron by the ton. Around about 1770 he came up with yet *another* one of those inventions without which there might have been no industrial revolution: a machine that bored out cannon barrels from solid metal. Then, in spite of the state of Anglo-French relations at the time (down the toilet), he smuggled the technology across the English Channel, where the French used it to make cannons, which they then shipped off to a bunch of people in the U.S. with a different kind of revolution in mind. Meanwhile James Watt jumped at the precision with which Wilkinson's machine could bore out cylinders accurately enough for his new engine to be steam-tight.

Wilkinson made enough out of all this to get buried in an iron coffin (three times, till they got the right fit) and to provide financing and experimental equipment for his sister's husband, a failed preacher-turned-scientist named Joseph Priestley. Who hit the jackpot when he and Mrs. Priestley moved in next door to a brewery in Leeds. Well, you can't fail to notice carbon dioxide in such circumstances, can you, so Priestley put it in water and invented soda. To be perfectly fair, he also discovered oxygen, wrote the definitive book on electricity and became pals with every science biggie of the day, including Ben Franklin. This last relationship was not entirely to the taste of the "king and country" mob, who burned down Priestley's lab and forced him to leave for America in 1794.

One of Priestley's other equipment suppliers (and fellow member of the Lunar Society, a group of innovators and liberal thinkers who met at every full moon, when the night roads were easier) was potter Josiah Wedgwood, whom you'll know if you're into formal crockery. Wedgwood made a million because he called a dinner set he designed "Queen's ware." Social climbers by the thousands bought the stuff. And the empress of Russia. He made neoclassical all the rage, because it was based on the style of the vases and statuary and pediments and plinths (and anything else he could carry) pilfered from Pompeii and environs by Wedgwood's antiques-collecting friend, Sir William Hamilton, envoy extraordinaire to the court of Naples. Who sometimes turned up for meetings with the Lunatics.

Another Lunatic was Erasmus Darwin, well known for boozing and having turned down George III's offer to take him on as royal physician. Wedgwood's eldest daughter married Darwin's son and ended up the mother of Charles Darwin, about whom no more need be said, except that his cousin was Francis Galton, a man estimated to have had an IQ of 200 and deeply into statistics. On one occasion Galton carried out a survey into the effectiveness of prayer and another on the body weight of three generations of British aristocrats (who says IQ is everything?). Galton is perhaps more (in)famous for having coined the term "eugenics." At one point, he also became an enthusiastic member (and eventually general secretary) of the British Association for the Advancement of Science.

In 1853 one of the association's regular attendees, James Braid, wrote a paper with a riveting appendix entitled "Table-Moving and Spirit-Rapping." As part of Braid's investigations of mental therapeutics, trances and animal magnetism, he also discovered how to induce "a particular condition of mind and body," which he believed was good for the health. Josef Breuer would one day agree. Braid christened his new trick "hypnotism."

Have to stop now. My eyelids ar SA

Wonders, continued from page 129

few who compete in sailing solo around the planet, now documented by onboard video camera.

With a similar purity of purpose, the first ever nonstop, nonrefueled flight around the world was completed in 1986. The slender, white monoplane *Voyager,* a flying fuel tank composite built of woven fibers held in epoxy resin, made it from Edwards Air Force Base in California and back in nine days and small change. The two brave pilot-engineers, Dick Rutan and Jeana Yeager, landed with 2 percent of their fuel load to spare. Like most financing, construction and operations, the original plane design (by Rutan's brother, Burt) was a gift of professional skill and devotion from the community of those who build and fly their own planes.

For lighter-than-air flight lofted by hydrogen but under engine power, the silver dirigible *Graf Zeppelin* rounded the world to and from New Jersey in 1929 with paying passengers, taking 21 days. The full tour by free balloon, powered only by the winds that blow, has not succeeded through the end of 1998 after many modern attempts.

We close with news of a lightning-fast annual Race around the World, one whose winner crosses all the time zones in about five minutes. Location, location, location: circle near enough to a pole where all meridians meet. Our real globe is no idealized sphere; its actual axis is not a fixed point but wanders every year or so in a complex rosette about 100 feet across. At the Amundsen-Scott South Pole Station, an airplane taxiway of packed snow a mile long encloses the uncertain pole of the moment. Every spring 200 overwintering research personnel conduct the race, three laps around through every degree of longitude. Last year's contestants included a big tractor towing "a hungover passenger in an easy chair on a cargo sled" and two Carnegie Mellon University cyclists on fast mountain bikes.

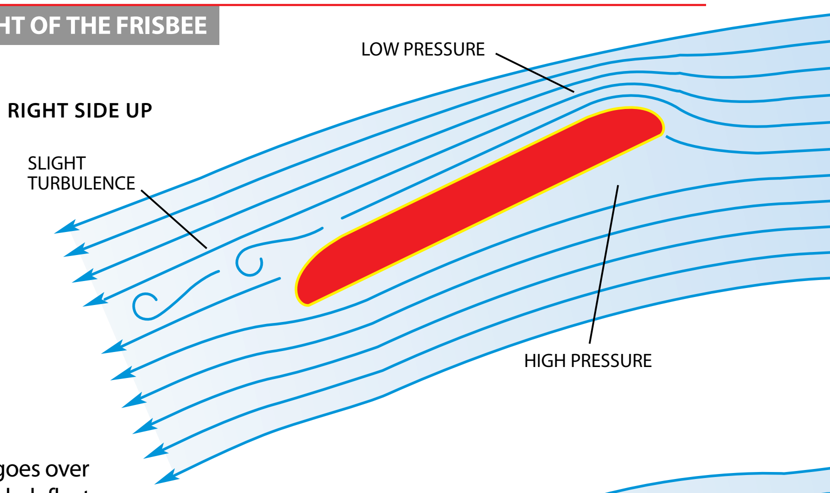
The winner was cyclist Matt Newcomb, an observation engineer, in his goose-down parka, the thermometer standing in the –20s. It will be hard to top this lighthearted realization, delightfully absurd but quite real, of the old grade-school geography puzzle about north and south at the earth's axis. SA

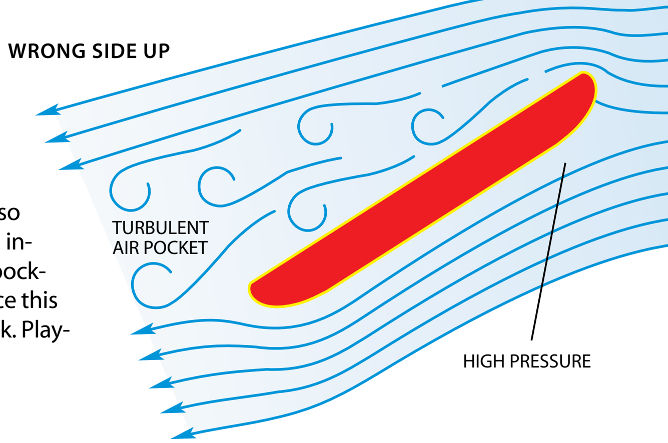
WORKING KNOWLEDGE

THE FLIGHT OF THE FRISBEE

by Louis A. Bloomfield
Professor of Physics, University of Virginia
Author of How Things Work:
The Physics of Everyday Life

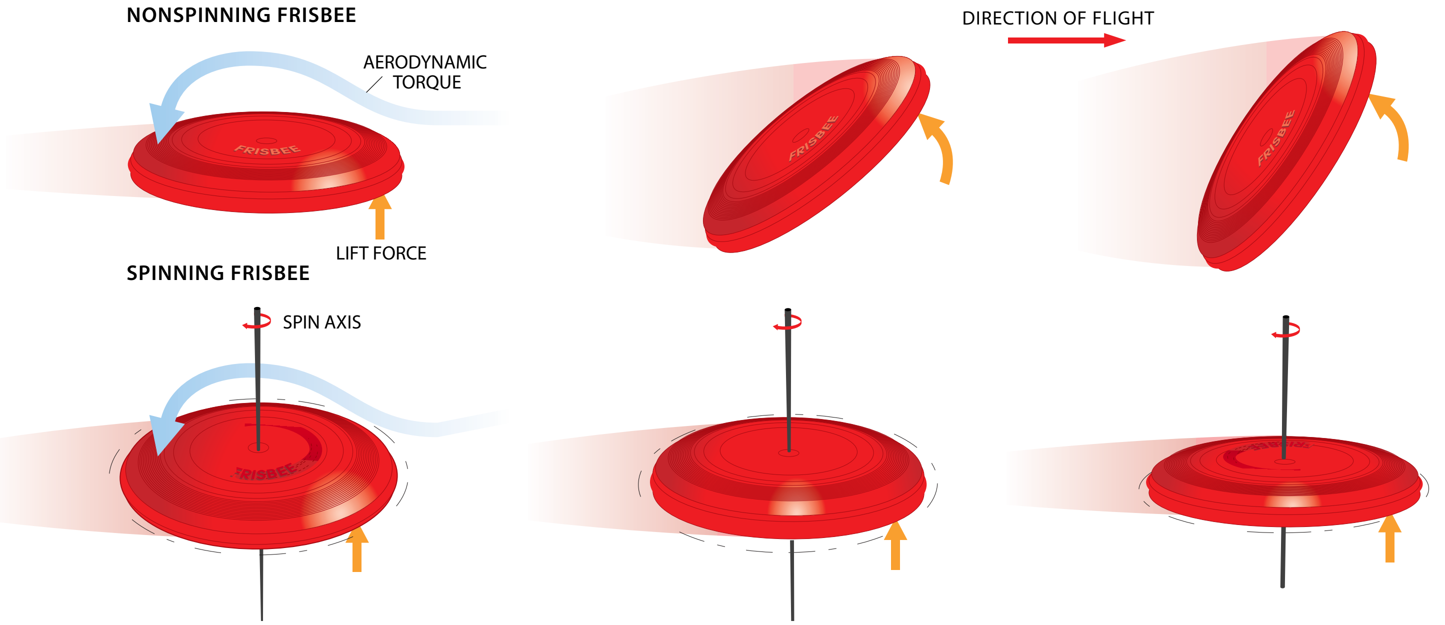
Modern Frisbees don't look much like tins from Bridgeport, Conn.'s, Frisbie Pie Company—the decades-old platters behind the name. But they fly through the air for the same reasons. Both are essentially spinning wings that stay aloft thanks to aerodynamic lift and gyroscopic stability.





FORWARD FLIGHT splits rushing air at the disk's leading edge: half goes over the Frisbee; half goes under. Because that edge is tipped up, the disk deflects the lower airstream downward. As the Frisbee pushes down on the air, the air pushes upward on the Frisbee—a force known as aerodynamic lift. The upper airstream is also deflected downward. Like all viscous fluids, flowing air tends to follow curving surfaces—even when those surfaces bend away from the airstream. The inward bend of the upper airstream is accompanied by a substantial drop in air pressure just above the Frisbee, sucking it upward.

Limits to the airstream's ability to follow a surface explain why a Frisbee flies so poorly upside down. When the upper airstream tries to follow the sharp curve of an inverted Frisbee's hand grip, its inertia breaks it away from the surface. A swirling air pocket forms behind the Frisbee and destroys the suction, raising the air resistance. Once this air resistance has sapped the inverted disk's forward momentum, it drops like a rock. Players can take advantage of this effect in a hard-to-catch throw called the hammer.



ILLUSTRATIONS BY GEORGE RETSECK

ROTATION is crucial. Without it, even an upright Frisbee would flutter and tumble like a falling leaf, because the aerodynamic forces aren't perfectly centered. Indeed, the lift is often slightly stronger on the forward half of the Frisbee, and so that half usually rises, causing the Frisbee to flip over. A spinning Frisbee, though, can maintain its orientation for a long time because it has angular momentum, which dramatically changes the way it responds to aerodynamic twists, or torques. The careful design of the Frisbee places its lift almost perfectly at its center. The disk is thicker at its edges, maximizing its angular momentum when it spins. And the tiny ridges on the Frisbee's top surface introduce microscopic turbulence into the layer of air just above the label. Oddly enough, this turbulence helps to keep the upper airstream attached to the Frisbee, thereby allowing it to travel farther.