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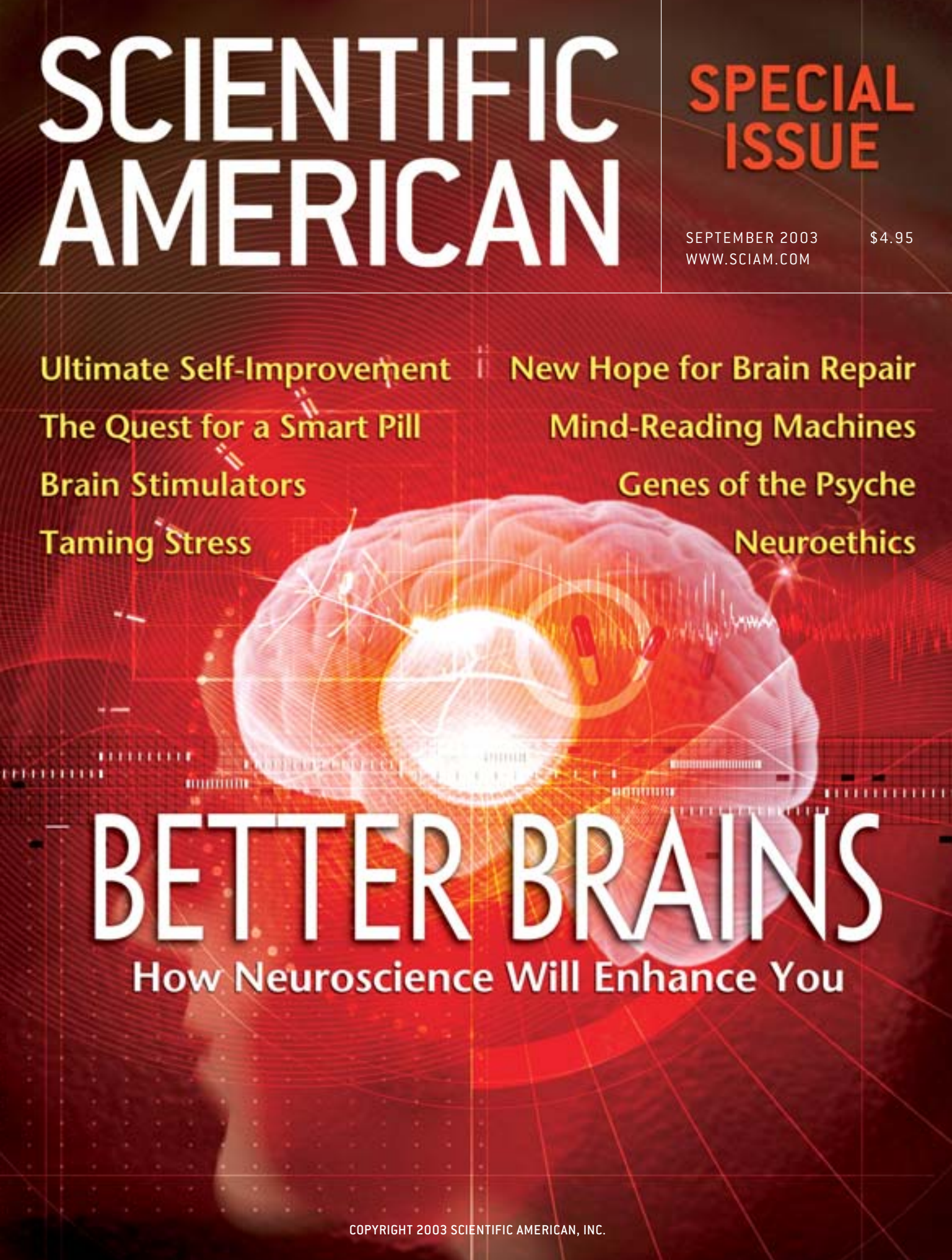

BETTER BRAINS

How Neuroscience Will Enhance You

september 2003

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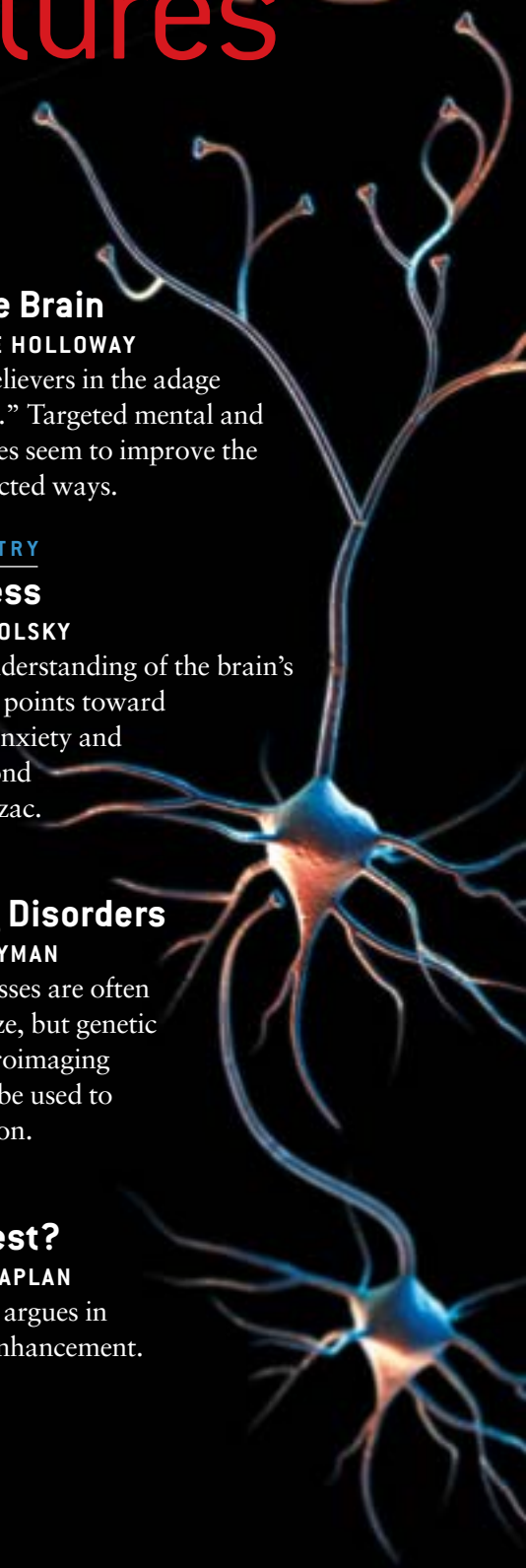
features

SPECIAL ISSUE: BETTER BRAINS



MIKE MEDICINE HORSE *Hybrid Medical Animation*

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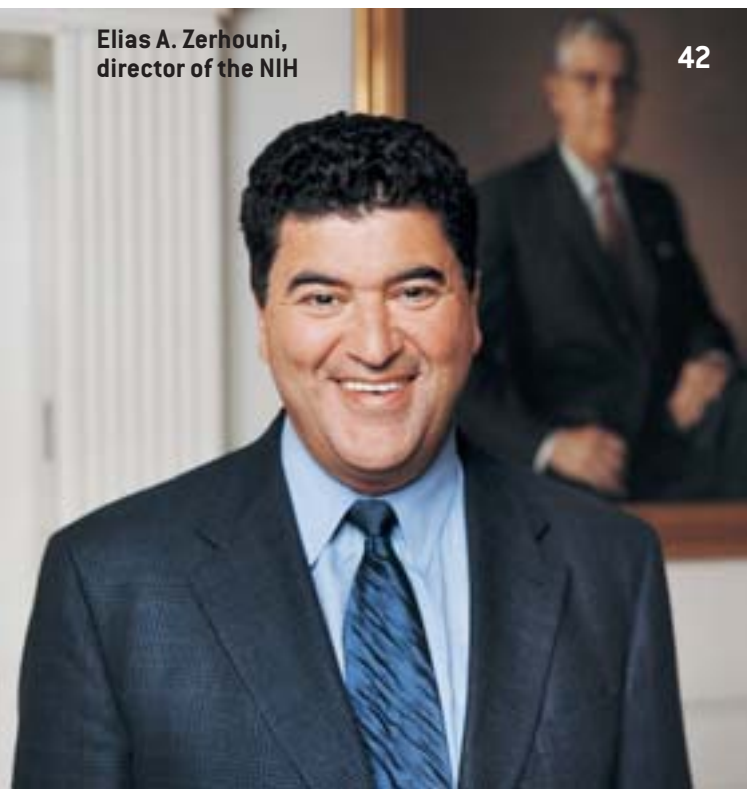

columns

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A Vote for Neuroethics

By the third decade of the new millennium, the power of computing will be such that we should be able to scan and download a blueprint of every axon, dendrite, presynaptic vesicle and neuronal cell body, thus creating a software-based facsimile of someone's brain. Human and machine will have become one. Or so observes Ray Kurzweil, the technologist-turned-futurist who has championed the marriage of the biologic and the cybernetic. "Our immortality will be a matter of being sufficiently careful to make frequent backups," he remarks in all earnestness.

Kurzweil's vision is often cited in popular accounts about the future of machine intelligence. But, in the end, his grandiose statements serve merely as technophilic conceits.

We are, to be sure, in the midst of dynamic change in neuroscience. Yet it is much subtler than Kurzweil's embrace of what he calls "spiritual machines." The current upheaval is rooted in advances in psychopharmacology, neuroimaging and genetics. The ultimate goal is not for us all to become cousins of the Terminator or Max Headroom. Rather it is to correct neural defects and to take normal people (whatever "normal" means) and make improvements from baseline—what Peter Kramer, the *Listening to Prozac* psychiatrist, famously calls "better than well." That could signify growing new cells to replace old ones suffering from the ravages of Alzheimer's or Parkinson's disease. Or it could mean slipping your kid a memory pill while he or she crams for AP calculus.

The ethical issues raised by advances in neuroscience are with us already. They both overlap and outflank the ones raised by genetic engineering. Changing the brain, with or without gene alteration, speaks to what it means to be human. Drugs or magnetic fields that modulate cognition may bend the very definition of who we are.

The list of moral and social issues attached to neurotechnologies is long enough to position ethicists alongside traffic engineers and medical technicians on a list of hot jobs that appears in the *U.S. News and World Report* annual career guide. What kind of privacy safeguards are needed if a machine can read your thoughts? Will cognition enhancers exacerbate differences between rich and poor? Or, instead, will they relegate social diversity to the status of historical artifact? What happens if we deduce through neuroimaging the physiological basis for morality? Oh, and by the way, what happens to free will?

Columnist William Safire, who is chair of the Dana Foundation, a sponsor of neuroscience research, has popularized the term "neuroethics." The nascent field held one of its first conferences in May 2002 at Stanford University to begin to map a strategy to deal with both the ethics of neuroscience and the neuroscience of ethics. Do we really need a new subdiscipline of a subdiscipline? After all, we have bioethics, which already compartmentalizes a larger field that has been around since Aristotle and Hippocrates.

Our vote is a decided yes for moving ahead. The technologies of mind and brain are special. They differ from genomics and other biomedical fields in one telling respect: most scientists and ethicists alike acknowledge that the essence of what we are is not all in our genes. But as one commentator has pointed out, it is much more difficult to argue persuasively that it is not all in our heads.

THE EDITORS editors@sciam.com

TECHNOLOGIES that have come out of neuroscience have raced ahead of the ethical issues they raise.

MATT COLLINS

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On the Web

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FEATURED THIS MONTH

Visit **www.sciam.com/ontheweb** to find these recent additions to the site:

Harvesting Hydrogen Fuel from Plants Gets Cheaper

A major roadblock to widespread use of hydrogen-powered electric vehicles, which emit only water vapor as a by-product and could thus cut greenhouse gas emissions substantially, is the cost and trouble associated with producing a suitable supply of hydrogen. Last year scientists reported having developed a technique to harness the fuel from biomass, but the catalyst required for the reaction was too expensive to be commercially viable. The same researchers have discovered another catalyst that works just as well—at a fraction of the cost.

Drug Boosts Sense of Touch

The sense of touch can be significantly improved using drug therapy, new research suggests. Amphetamines administered in conjunction with finger stimulation can apparently increase a fingertip's sensitivity by 23 percent. The findings could lead to treatment options for the elderly or injured who have difficulty performing tasks that require fine touch—buttoning a shirt, for example.

Ask the Experts

Are humans the only primates that cry?

Kim A. Bard, a reader in comparative developmental psychology at the University of Portsmouth, provides an answer.

COURTESY OF HUBERT R. DINSE (*hand*)

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Letters

EDITORS@SCIAM.COM

IN AN INFINITY OF UNIVERSES, an endless number of possibilities must exist, as Max Tegmark argues in "Parallel Universes" [May]. It's tempting to wonder if every other *Scientific American* board of editors who published that article got as bleary-eyed reading the scads of letters it generated. Many of the notes were thoughtful—and thought-provoking—such as this one, which Anita Brubaker sent via e-mail: "If Tegmark's multiverse theory is true, then one of the many existing universes has no pain, no death and no suffering. On the other hand, one universe's inhabitants experience maximum pain. Has Tegmark demonstrated the existence of what are usually called heaven and hell?" More cosmic commentary on the May issue follows.

PROBLEMS WITH PARALLELS

I have a problem with Max Tegmark's use in "Parallel Universes" of "infinity," which I understand to state that there are infinite universes, and hence all possible arrangements of matter and energy must exist somewhere. The particular arrangement of matter and energy we observe in this universe is the culmination of causal processes that have led up to it. One can imagine all sorts of variations—Abraham Lincoln at our dinner table, our conscious brain inside the skull of a whale, an intact planet Earth lying at the center of the sun. But if there are no means by which such events could come about, then they never will, even given infinite time and universes.

Ethan Steele
Tucson, Ariz.

Tegmark's argument for other universes parallel to ours is inconclusive because of the systematic neglect of an alternative explanation and a shortage of empirical evidence. Tegmark presents four levels of parallel worlds where twins of himself could abide. On Levels I and II, his twins are outside our horizon, where we cannot sense them. How, then, does he infer their existence? He does so partly by extraordinary extrapolation beyond the cosmological data into the realm of speculation and partly by smuggling in a key unstated premise. This premise is that our existence is accidental rather than planned. How could science establish such a result? In Level IV, Tegmark introduces his own speculation. If an infinite unobservable entity is needed to explain the unreasonable effectiveness of mathematics, then, as the scientist-turned-priest John Polkinghorne suggests, theism might also be considered.

In all three cases, the evidence supports the conclusion of either many universes or design, but the design option has been suppressed, with a misleading result. Thus, the inference of parallel universes is not "a direct implication of cosmological observations" but requires a crucial implicit injection of ideology.

J. Brian Pitts
via e-mail

The article says that there are $2^4 = 16$ possible arrangements of 4 particles. But I remember $n!$ as the arrangement formula for n distinct objects. If the formula is valid in this case, 4 particles can be arranged in $4 \times 3 \times 2 \times 1 = 24$ different ways. When applied to our universe, the number of arrangements becomes much, much higher and the distance to the nearest duplicate universe far greater.

L. Moriamé-Deseck
St. Laurent du Var, France

If light could have traveled only 42 billion light-years since the big bang, how could any matter lie beyond that horizon?

Jeremy Gernand
Houston

TEGMARK REPLIES: *Regarding Steele's points: when predicting what we expect to observe, we must take probabilities into account. Although even bizarre matter arrangements*

could come about via freak thermal fluctuations, they would be rare and short-lived. In contrast, more prosaic universes, like one with Tucson being named Nuscot, would be about as likely as our own.

I disagree with Pitts. The assumption that space and its matter content do not end abruptly 42 billion light-years away is hardly an "extraordinary extrapolation," because we observe great regularity out to that distance. It is, however, an assumption, and I encourage keeping an open mind about whether our cosmological observations are best explained by parallel universes, design or something we haven't yet thought of.

In the formula Moriamé-Deseck refers to, n! *is the number of arrangements of* n *individually distinguishable particles, such as billiard balls each painted a unique way. Elementary particles like electrons are indistinguishable, so there are only* 2^n *possibilities.*

Last, for Gernand: the big bang happened not merely here but everywhere at the same time, so the matter beyond our horizon didn't need to travel to get there.

PROFIT AND PATIENTS

"The Orphan Drug Backlash," by Thomas Maeder, raised, but did not answer, the question of whether the Orphan Drug Act has allowed some companies to reap excessive profits. In the case of Genzyme's Ceredase (alglucerase), Maeder might have reviewed the central role the NIH played in discovering the missing enzyme and in conducting the clinical trials that led to its approval for treatment of patients with Gaucher's disease.

Not only did NIH researchers identify the enzyme and obtain patents covering the basic method for harvesting it from the human placenta, the agency also conducted the pivotal clinical trial that Genzyme used to file its New Drug Application. The NIH paid Genzyme almost $9 million to produce the enzyme for clinical studies. Moreover, Genzyme was allowed to charge patients for alglucerase before it was approved for marketing.

We described these events in October 1992 in "Federal and Private Roles in the Development and Provision of Alglucerase Therapy for Gaucher Disease," published by the Congressional Office of Technology Assessment. That paper is available at the CyberCemetery, maintained by the University of North Texas Library (http://govinfo.library.unt.edu/ota/).

Judith L. Wagner
Bethesda, Md.
Michael E. Gluck
Washington, D.C.

MISSILE INTERCEPTOR begins a test flight.

BE PREPARED

Regarding "Misguided Missile Shield" [Perspectives]: a demand for perfect realism in testing a complex weapon system like missile defense is unrealistic. More testing is necessary—more tests, however, are scheduled.

Perspectives states that a "patchy" missile shield could create a false sense of security and that it "would be much easier" to smuggle nuclear bombs into the U.S. than to launch missiles. But the enemy will not necessarily choose the easiest way—as we learned in 1941, when Japan chose a risky and expensive air strike over sabotage. We expected sabotage and planned our defense accordingly. Japan, though, chose the hard way and scored a major strategic victory.

In reality, no defense is perfect; every system and policy is patchy. Like it or not, we are obligated to prepare for every means of attack possible. We ought not be misled by the simplistic, all-or-nothing assumptions missile defense critics ask us to pick and choose from; after all, our enemies do not play that game.

David M. Sawyer
Former captain, U.S. Army Reserve
Winston-Salem, N.C.

A STRONGER INTERNET

After reading Albert-László Barabási and Eric Bonabeau's article on "Scale-Free Networks," I would like to contribute an idea to save the Internet from destruction. Currently, increasing protection of the hubs from viral epidemics merely invites cleverer attacks, each of which has the potential to defeat the entire network if it can breach the defenses in just one place. A better strategy would be to artificially alter the random versus scale-free balance of the Internet itself. This can be done by slightly biasing traffic to encourage more lower-level, node-to-node links. The bias can consist of an advantage in bandwidth.

Rolf Schmidt
Inverness, Scotland

SYNESTHESIA AND LANGUAGE

It's easy to understand why 98 percent of the people tested chose the blob as "bouba" and the pointed shape as "kiki" ["Hearing Colors, Tasting Shapes," by Vilayanur S. Ramachandran and Edward M. Hubbard]. Bouba is made up of bum-shaped B's and kiki of K-like spikes.

John Wilson
Nepean, Ontario

RAMACHANDRAN AND HUBBARD REPLY: *Non-English speakers, whose alphabet shapes do not resemble either a B or a K, also answer the same way. Many such contrasting shapes exist. For example, if you show English speakers a blurred line and a sawtooth edge and ask, "Which is 'shh' and which is 'rrr'?" they almost always pick the blurred line for shh and the sawtooth for rrr—even though no letters resemble these. Or if you display a very blurred line versus a slightly blurred line, people spontaneously associate the former with "shh" and the latter with "sss."*

50, 100 & 150 Years Ago

FROM SCIENTIFIC AMERICAN

Biological Joe ▪ Pilot Gustave ▪ Dedicated Louis

SEPTEMBER 1953

FORCE OF NATURE—"What holds the nucleus of the atom together? In the past quarter century physicists have devoted a huge amount of experimentation and mental labor to this problem—probably more man-hours than have been given to any other scientific question in the history of mankind. By all the laws of known forces, the particles in an atom's nucleus should flee from one another, instead of clinging together so strongly that we must build enormously energetic machines to pry them apart. The glue that holds the nucleus together must be a kind of force utterly different from any we yet know. Japanese physicist Hideki Yukawa, as early as 1935, suggested a new particle for the nucleus, whose emission and absorption is supposed to transmit the nuclear forces. This particle, when Yukawa invented it, was of course purely hypothetical. Today it is known as the meson. —Hans A. Bethe"

STALIN AND LYSENKO—"Trofim D. Lysenko, who since 1948 has been the ruler of Soviet botany and a symbol of Soviet science, seems to have lost his throne with Stalin's death. He was denounced recently in a Soviet botanical journal and in the general organ of the Soviet Academy of Sciences. A translation of a remarkable document by Lysenko himself was published in the U.S. recently by *Science*. It was a eulogy of Stalin written for *Pravda,* and in it Lysenko gave credit where credit was due. Stalin, he disclosed, was the real author of the Lysenko theories: 'Comrade Stalin found time even for detailed examination of the most important problems of biology.... He directly edited the plan of my paper 'on the situation in Biological Science,' and in detail he provided me with directions as to how to write certain passages.'"

SEPTEMBER 1903

TATTOOS—"The word 'tattoo' is derived from the Polynesian *tattau,* and was first anglicized by Captain Cook. The practice has been defined by Maurice Berchon as 'that strange and very ancient custom which consists in the introduction under the cutaneous epidermis, at different depths, of coloring matter, in order to produce some design which will be of very long duration.' In Japan tattooing is chiefly confined to the lower classes, who are decorated with such figures as are seen on porcelain [*see illustration*]. Cinnabar and Indian ink are the pigments used."

THE ART OF TATTOOING in Japan, 1903

WHITEHEAD GLIDER—"Experiments with an aeroplane [glider] have been carried out recently by Mr. Gustave Whitehead, of Bridgeport, Conn., who has been studying the subject of mechanical flight for upward of fifteen years. The method of soaring used by Mr. Whitehead consists in running with the aeroplane against the wind, preceded by an assistant who draws it with a rope when it leaves the ground. Mr. Whitehead is now constructing a motor of 10 horse power, which he expects will not exceed 40 pounds in weight, aluminum being used as far as possible. This is to be used on an improved aeroplane with which the inventor hopes to be able to rise vertically in still air, travel horizontally, and descend vertically again." [*Editors' note: There is no convincing evidence that Whitehead ever built a successful motorized airplane.*]

SEPTEMBER 1853

DEDICATION—"Professor Louis Agassiz' search for things new and strange in the rice swamps of the South was crowned with complete success, but he contracted the malignant fever of the country, from which he barely escaped with his life. Among other novelties which he found there was a fish without ventral fins, and it is related as expressive of his unextinguishable enthusiasm in matters of science, that when slowly recovering, a friend called to see him and said to him, 'I am sorry to hear, Professor, that you have been dangerously ill.' 'Ah, yes,' said Professor A., 'I have been very sick but no matter, I have found a fish without ventrals.'"

RISE OF THE MACHINES—"In 1846 we believe there was not a single garment in our country sewed by machinery; in that year the first American patent of a sewing machine was issued. At the present moment thousands are wearing clothes which have been stitched by iron fingers, with a delicacy rivaling that of a Cashmere maiden. Sewing machines have not taken the bread from a single female in our land."

INFORMATION

Public Not Welcome

LIBRARIES CUT OFF ACCESS TO THE SCIENTIFIC LITERATURE **BY W. WAYT GIBBS**

In June the journal shelves at the Health Sciences Library of the University of Pittsburgh began showing holes. Where current issues of *Leukemia Research* were once stacked, now stands a small cardboard sign: "Issues for 2003 are available only in electronic form." The cardboard tents have replaced print copies of hundreds of journals, from *Fertility and Sterility* to *Cancer Detection and Prevention* to the *Journal of Pediatric Surgery*. And at the library's computer terminals, where employees and students of the university can tap into the fast-growing digital collections, other signs advise that "You need an HSL Online password to use these computers." Restrictions in the contracts the university has signed with publishers prohibit librarians from issuing passwords to the public.

NO PEEKING: Visitors will have a harder time finding journals to read in university libraries.

CHIEN-CHI CHANG *Magnum*

A patient newly diagnosed with leukemia, a parent concerned about a risky operation her child is facing, a precocious high school student—whatever their motivation, ordinary citizens have for decades enjoyed free access to the latest scientific and medical literature, so long as they could make their way to a state-funded university library. That is rapidly changing as public research libraries, squeezed between state budget cuts and a decade of rampant inflation in journal prices, drop printed journals in droves. The online versions that remain are often beyond the reach of "unaffiliated" visitors.

"We are in the midst of a massive transformation to the digital library," says Patricia Mickelson, director of the University of Pittsburgh's medical library. Scientists and doctors find the electronic resources much more convenient, she says, "and we just can't afford both the electronic and print versions."

Part of the problem, adds Deborah Lordi Silverman, the library's journal manager, is that the thousands of journals are put out by just a handful of publishers, who bundle their

titles into "big deals" covered by a single contract. "The kicker with these deals is that in exchange for a guaranteed price, they say you can't cancel anything," Silverman complains.

Research libraries are likely to continue carrying print copies of general-interest journals, such as *Science, Nature* and the *New England Journal of Medicine*. And a few powerful institutions—among them the Massachusetts Institute of Technology and the University of California at San Francisco—have insisted on "walk-up" clauses in their contracts that allow any patron full access to their online journals at workstations within the library. But they are the exception; as a rule, Silverman says, publishers insist that their online journals remain "protected" from the general public.

Pressured by a boycott among some high-profile scientists in 2001, certain journals began offering free public access to back issues a year or more after publication. But most charge high per-view fees for recent articles.

The restrictive tactics have enabled publishers to squeeze more dollars from their subscribers. But the restrictions may turn out to be a strategic error, as the industry faces a backlash on several fronts. In June, Minnesota Representative Martin Sabo introduced a bill, the Public Access to Science Act, that would forbid publishers from claiming copyright on "scientific work substantially funded by the federal government"—a large fraction of basic and medical research. "It defies logic to collectively pay for our medical research only to privatize its profitability and availability," Sabo argues.

Also in June, a nonprofit group called the Public Library of Science announced that it plans to launch in October the first of two elite life science journals that will be free online to all readers. Funded by $9 million in start-up money from the Gordon and Betty Moore Foundation and backed by prominent scientists such as Harold E. Varmus, former director of the National Institutes of Health, the group plans to recoup its expenses by charging the scientists who submit their papers for publication. Print subscriptions will also carry a modest fee.

And M.I.T., the University of California system and about 140 other universities have set up so-called open-access archives in which researchers can deposit their papers before they are published, much as ArXiv.org has done for physics. According to Stevan R. Harnad, a cognitive scientist at the University of Quebec and a longtime advocate of such archives, the number of papers in these repositories grew from about 20,000 two years ago to 1.3 million at the beginning of 2003. They still capture a small fraction of the two million or so peer-reviewed articles published each year by journals. But the long-term threat to the highly profitable business of journal publishing is unmistakable.

THE PRICE OF ADMISSION

The fees that many journals charge to view a single article—usually for only 24 hours—can be steep.

American Journal of Pathology	$8
Genes and Development	$8
Cancer Research	$10
Cancer	$25
Cancer Cell	$30
Cell	$30
Current Biology	$30
Neoplasia	$30

SOME GOOD WITH THE BAD

Laboratory findings do not always reflect everything that goes on in the body. Low levels of ionizing radiation might actually be beneficial—see "Nietzsche's Toxicology," on page 28.

BIOPHYSICS

Fatal Attachments

EXTREMELY LOW ENERGY ELECTRONS CAN WRECK DNA

BY GRAHAM P. COLLINS

That high-energy ionizing radiation harms DNA when it smashes through cells comes as no surprise. Each particle can pack a million times as much energy as a photon of visible light. Yet recent experiments have demonstrated that even remarkably low energy electrons set off by ionizing radiation can break up key molecular components of RNA and DNA. The result has implications for understanding the biological effects of low levels of radiation and for the improvement of radiotherapy treatments.

A particle of high-energy ionizing radiation does not inflict most of its damage by knocking atoms around directly. Instead all along its track it sends electrons flying, like a bowling ball crashing through pins. Each of these "secondary" electrons receives a modest one to 20 electron volts (eV) of energy—comparable to that of a photon in the visible to ultraviolet range. Ionizing radiation knocks loose about 40,000 such electrons for every mega-electron volt of energy that it carries.

Prior to about 2000, the conventional wis-

dom held that DNA could be harmed by secondary electrons only while they had more than about 10 eV—enough energy to ionize the DNA. Then a collaboration led by Léon Sanche, Darel Hunting and Michael A. Huels of the University of Sherbrooke in Quebec studied the effects of electrons with as little as 3 eV and found that even those could break both strands of a DNA molecule's double helix. The electrons seem to exert their destructive power by attaching to one of the DNA's component molecules; the resulting negative ion then breaks down. The decay fragments can in turn damage the other strand by chemical reaction. The cell's DNA-repair machinery can correct a single lesion, but closely spaced or complex lesions are likely to defeat its restorative abilities.

URANIUM EMITS alpha particles (helium nuclei), each of which can generate 160,000 low-energy electrons in tissues.

Tilmann Märk's group at the University of Innsbruck in Austria has now extended the lower energy limit to well below 1 eV. Rather than studying whole DNA molecules, the group collided a low-energy electron beam with beams of gaseous uracil, thymine and cytosine (bases that form the information-carrying rungs of an RNA or DNA molecule) and deoxyribose (one of the backbone molecules). According to Märk, even electrons with near-zero energy "destroy deoxyribose very effectively, [producing] a number of fragment ions." As in the whole-DNA experiments, the electrons appear to act by attaching to the molecules in question, which then break up by losing a hydrogen atom or a larger fragment.

Both collaborations have also studied the effects of low-energy electron attachment to halo-uracil molecules, in which a halogen atom such as bromine replaces a hydrogen atom. More than 40 years ago researchers discovered that substituting bromo-uracil for thymine in DNA increases a cell's sensitivity to radiation (thymine is like bromo-uracil except that a methyl group replaces the bromine). Some studies have suggested that fluoro-uracil, used in chemotherapy, also radiosensitizes tumor cells. (Its main therapeutic effect, however, is inhibition of DNA or RNA synthesis.) This year the Innsbruck group found that chloro-uracil is 100 times as sensitive as ordinary uracil to breakup by electrons.

Of course, reactions in dilute uracil gas in a vacuum are a far cry from reactions within a DNA molecule in vivo with numerous closely attached water molecules. To address this issue, Märk says that his group "plans to enclose these molecules in a cluster of water molecules and then study the interactions with electrons." Huels and his co-workers, meanwhile, are studying bromo-uracil in situ in strands of DNA with a view to enhancing its effectiveness in radiotherapy. They have found that bromo-uracil's radiosensitizing effect depends on the DNA structure and the base sequence where the bromo-uracil is incorporated. "This may allow us to target specific sites in tumor cells directly," Huels says.

CATCHING SOME RAYS

At typical background levels of radiation near sea level in the U.S., each cell in your body sees on average about seven secondary electrons a day. Those electrons will come, however, in bunches of 1,000 per cell every few months. The dose averages to a scary-sounding (but actually relatively harmless) 200 mega-electron volts per kilogram per second. About 40 percent of that dose comes from radioactive nuclei naturally present in the human body. Lung tissue would experience much more because of short-range alpha particles (helium nuclei) emitted by inhaled radon and its daughter nuclei.

The electromagnetic fields emitted by power lines, cell phones and other consumer electronics are emphatically *not* ionizing radiation. According to the American Physical Society, scientific research shows "no consistent, significant link between cancer and power line fields."

U.S. DEPARTMENT OF ENERGY *SPL/Photo Researchers, Inc.*

HORMESIS

Nietzsche's Toxicology

WHATEVER DOESN'T KILL YOU MIGHT MAKE YOU STRONGER **BY REBECCA RENNER**

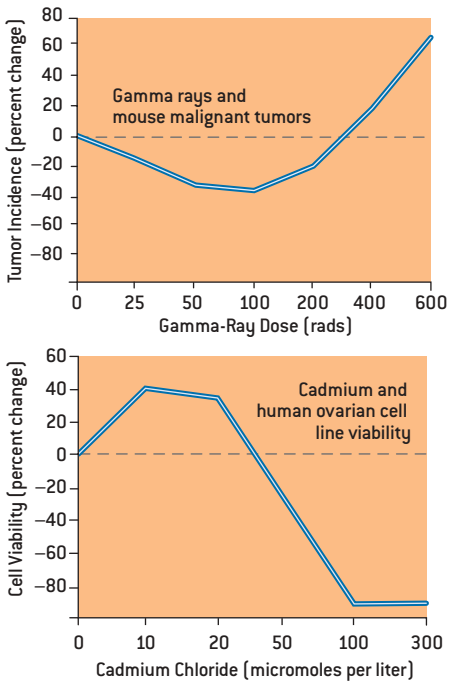
If dioxin and ionizing radiation cause cancer, then it stands to reason that less exposure to them should improve public health. If mercury, lead and PCBs impair intellectual development, then less should be more. But a growing body of data suggests that environmental contaminants may not always be poisonous—they may actually be good for you at low levels.

Called hormesis, this phenomenon appears to be primarily an adaptive response to stress, says toxicologist Edward J. Calabrese of the University of Massachusetts at Amherst. The stress triggers cellular repair and

maintenance systems. A modest amount of overcompensation then produces the low-dose effect, which is often beneficial.

This idea may sound bizarre, but such adaptation to stress is common, says physiologist Suresh Rattan of Århus University in Denmark. Exercise, for instance, plays biochemical havoc with the body: starving some cells of oxygen and glucose, flooding others with oxidants, and depressing immune functions. "At first glance, there is nothing good for the body about exercise," he notes. But even couch potatoes know that moderate exercise is worthwhile. Rattan says that the cellular insults from exercise prompt the defense system to work more efficiently.

Over the past decade, Calabrese has compiled thousands of examples of hormesis from published scientific literature. Many findings challenge and even flout established theories about what is harmful. For example, the prevailing theory is that any increase in radiation exposure increases the risk of cancer. But biologist Ronald Mitchel of Atomic Energy of Canada has shown that a single low dose of ionizing radiation stimulates DNA repair, delaying the



A PINCH OF POISON seems beneficial in some cases when compared with control groups, as shown by the effects of gamma rays on the emergence of mouse tumors (*top*) and of cadmium exposure on human ovarian cells (*bottom*).

LUCY READING; ADAPTED FROM J. R. MAISIN ET AL. IN *RADIATION RESEARCH*, FEBRUARY 1988 (*top*) AND TETSUYA ABE ET AL. IN *BIOCHEMICAL PHARMACOLOGY*, JULY 1, 1999 (*bottom*); AS REPRODUCED BY EDWARD J. CALABRESE AND LINDA A. BALDWIN IN *TRENDS IN PHARMACOLOGICAL SCIENCES*, JUNE 2001

POLLUTION STANDARDS that factories—such as this chemical plant on Lake Baikal, Russia—must meet may change if hormesis proves to be a widespread phenomenon.

RALPH WHITE *Corbis*

onset of cancer in mice; high doses produced the opposite effect, as expected. Prolonged exposure to extreme temperatures is also harmful, but Rattan has found that heating up human skin cells to 41 degrees Celsius (106 degrees Fahrenheit) twice a week for an hour slows aging in the cells.

Even well-established environmental headaches display some hormesis. The definitive rat study that linked high doses of dioxin to cancer, published in 1978 by Richard Kociba of Dow Chemical and his colleagues, also found that low doses reduced the incidence of tumors.

"Adaptation to such stresses is absolutely essential," Mitchel remarks. "If we couldn't adapt to changes in our environment, we would die." Such adaptation at the molecular level is seen in most primitive forms of life and has been evolutionarily conserved all the way up to humans, he adds.

Hormesis challenges the existing hazard-assessment process underlying environmental regulations, Calabrese says. Toxicologists usually determine the relation between exposure to contaminants and health risks by conducting animal experiments. They start out by giving lab animals a high dose that produces clear adverse effects. Then they work downward until they can estimate a concentration that doesn't cause harmful effects. For chemicals that don't cause cancer, they obtain a safe dose for humans by applying uncertainty factors to account for differences between mice and men and among individual people. The resulting safe dose for humans is then usually deemed to be about 0.01 to 0.001 the safe dose for mice. For carcinogens, toxicologists assume that exposure to any amount increases the risk.

But Calabrese suspects that in many cases, the benefits of hormesis may occur at levels higher than the recommended safe doses for humans. Thus, it might be possible to refine pollution standards so that we can reap the benefits of hormesis while still being protected against adverse effects in the environment. Or at the very least, it might be reasonable to stop worrying about exceedingly low exposures.

Researchers investigating adaptive stress responses aren't the only ones interested in effects at low doses. Scientists studying endocrine disruption are also joining in. They are concerned that contaminants that mimic hormones can have significant harmful effects at very low doses if exposure occurs during a susceptible developmental window. In some sense, endocrine disruption appears to be the opposite of hormesis, in which low doses could have unsuspected harmful effects because of the contaminant's chemical similarity to hormones.

Advances in molecular biology are giving toxicologists the tools to investigate low-dose phenomena, according to Joseph V. Rodricks, health sciences director at Environ, environmental consultants in Arlington, Va. Instead of monitoring the onset of disease or cancer, toxicologists are beginning to use modern molecular biology tools to identify the critical early precursors to illness. They then monitor how the precursors vary at low doses.

Hormesis has much to prove if it is to revolutionize toxicology, Rodricks notes. Many of the hormetic dose-response relations that Calabrese has compiled raise more questions than answers, he says. For example, the dioxin study looks like hormesis if all types of cancer are combined, but hormesis doesn't show for individual types of cancer. Despite such skepticism, Rodricks is one of many toxicologists calling for a National Research Council review of this phenomenon.

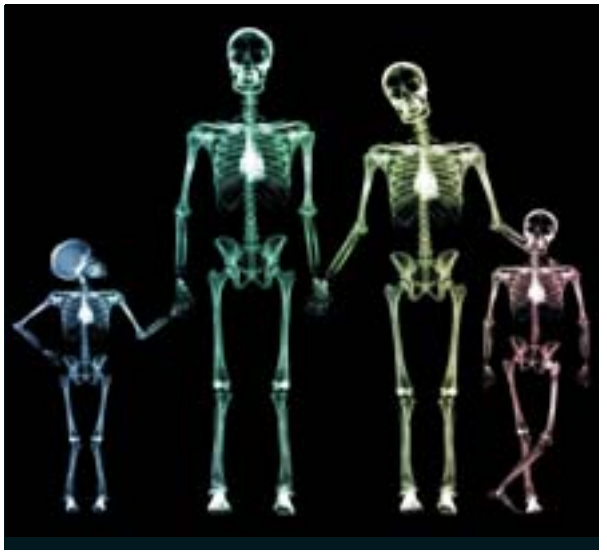
Rebecca Renner writes about environmental issues from Williamsport, Pa.

SECURITY

Handicaps in CAPPS

COMPUTERIZED PASSENGER SCREENING IS NOT SO EASY **BY WENDY M. GROSSMAN**

Does the person in the next seat intend to blow up the plane? The Transportation Security Administration (TSA) believes it can answer this question via a proposed second-generation system known as Computer-Assisted Passenger Pre-Screening, or CAPPS II. In terms of the variety of information, the system goes much further than the 1.0 version—and may be too complex to pull off without huge additional funding.



NOTHING TO HIDE: The proposed computerized passenger pre-screening system would examine airline travelers in detail.

The original system, which began in 1998, requires U.S.-based airlines to pass reservation data through a secret, government-supplied algorithm intended to identify fliers who pose a risk to safety. It was implemented at a time when airline safety focused on bombs in checked suitcases. (It was also meant to be temporary, to be replaced by a system that matches passengers to their checked luggage, the standard outside the U.S.) After September 11, 2001, officials extended CAPPS to include all passengers and required airlines to refuse to board anyone with a matching or similar name to those on the government's "no-fly" list without permission from law-enforcement officials.

The proposed CAPPS II will be an attempt to build a "threat-assessment tool" that would be the world's first fully automated system to check passenger backgrounds. The most recent proposals would compare name, date of birth, home address and home telephone number with private-sector databases, potentially including credit and criminal records.

But as Edward Hasbrouck, author of *The Practical Nomad* and an expert on travel industry infrastructure, points out, this information is not typically listed in passenger name records, which are the data that the Transportation Security Administration planned to use. To work, CAPPS II would require "the most profound change that has ever been proposed in the basic concepts of how passenger information is exchanged," Hasbrouck says. Right now airlines outsource their computerized work to external reservations systems such as Sabre. Passenger data are collected by tens of thousands of travel agencies; the agencies in turn use a variety of third-party software to run their businesses and interface with the reservations systems. As a result, data formats are not standardized across the industry, which has protocols that predate the Internet. Moreover, passenger name records and passengers do not necessarily match up one to one: a group traveling together may have one record with only travel agency information in it.

Altering current practices to suit CAPPS II will be costly. Hasbrouk thinks that $1 billion is a "conservative lower-end estimate" and that the TSA has grossly underestimated the complexity of the necessary changes. (The agency has requested $35 million for 2004 for developing CAPPS II, part of $1.7 billion overall for passenger screening.)

Still, such a system could possibly succeed: "Technically, there is almost nothing that can't be done given enough time and resources," comments retired FBI profiler Bill Tafoya. But with limited understanding of other cultures and the fact that data mining is only as successful as the mind-set that produces the search criteria allows it to be, he favors a risk-based assessment system. An example is the one proposed by the Reason Public Policy Institute, a Los Angeles–based think tank. Its system would identify high-, average- and low-risk passengers and focus security attention accordingly. That approach isn't perfect, either: Terry Gudaitis, a former terrorist profiler for the CIA who now works for Psynapse Technologies, a security firm in Washington, D.C., notes that someone with a clean record and registration as a trusted traveler would be a target for identity theft. And terrorists would have a sub-

NEED TO KNOW: CAPPS OFF

The extensive data on passengers that CAPPS II would collect has aroused the ire of privacy groups and civil liberties organizations. Their protests led to calls to boycott Delta Airlines for testing CAPPS II earlier this year and to the Transportation Security Administration for putting the system on hold while it reviews the privacy issues. (CAPPS II was supposed to have started at the end of 2002.) To justify its cost and invasiveness, CAPPS II would have to work spectacularly well: some 45 million people fly every month in the U.S. Even a tiny percentage of false positives will create the perception that innocent fliers are being harassed. And only one false negative could result in a catastrophe.

DIGITALVISION

stantial incentive to try to get themselves accepted as low-risk.

The fundamental problem, Gudaitis observes, is the "developmental nature of human beings." For example, the same terrorists who carried out the 9/11 attacks flew to their starting points. "During that flight they were not a threat," she notes. "So what was the pattern of profile, the behavioral change that occurred in an hour's time span? They disembarked and got on another plane."

Wendy M. Grossman writes about information technology from London.

MATERIALS SCIENCE

Photovoltaic Finesse

BETTER SOLAR CELLS—WITH WIRES WHERE THE SUN DON'T SHINE **BY DANIEL CHO**

HELIOS, NASA's experimental unmanned plane—shown passing the Hawaiian island of Lehua this past June—used Sunpower's solar cells to reach a record altitude of 96,863 feet.

CARLA THOMAS *NASA*

Solar cells remain small players in an energy-guzzling world, in part because they don't convert light into electricity very well. Although photovoltaics made of advanced materials such as gallium arsenide can achieve nearly 30 percent efficiencies, the cost makes them suited only for use in space. The efficiencies of typical commercial cells have languished for years at about 15 to 16 percent. In the past couple of months, however, several firms have announced substantial gains that could make these cells more attractive.

Solar modules are often installed in limited spaces, such as rooftops. Eric Daniels, a vice president at photovoltaic manufacturer BP Solar, says that for this reason, many customers are willing to pay a premium for cells with a higher conversion efficiency. (Solar modules typically cost around $4 to $8 per watt.)

Today's commercial photovoltaics are based on crystalline silicon. Light striking the semiconductor excites electrons within it. The excited electrons move toward one of the electrodes, generating electricity. To boost efficiency, manufacturers must either increase the amount of sunlight absorbed or cut back on power losses caused by electrical resistance. Companies employ various tricks to this end. One is to make the rear surface of the cell internally reflective so that some light passes through the cell twice. Another is to cover the top of the cell with a layer of amorphous silicon, which absorbs sunlight better than the crystalline form does.

In March, BP Solar announced a photovoltaic cell with an efficiency of 18.3 percent. That same month Sanyo introduced a solar cell that is 19.5 percent efficient. In May, Sunpower Corporation in Sunnyvale, Calif., announced that it had solar cells boasting efficiencies of more than 20 percent.

Sunpower owes its edge in part to its unique rear-contact cell design. Most solar cells have their fronts covered with a fine network of wires to carry away the current produced within the semiconductor. Thin as they are, these wires cover up valuable space that could otherwise be collecting sunlight. Sunpower has moved all the wires and connectors to the back face.

In their original incarnation in NASA's unmanned solar plane, Helios, Sunpower's rear-contact cells had an efficiency of nearly 23 percent. (Helios crashed into the Pacific last June, but NASA has ruled out the solar cells as the culprit.) The company sacrificed a few percentage points to adapt their cells to mass production, cutting the price just enough to attract the first high-end buyers. Production quantities of the new cells will be available sometime next year.

BEYOND SILICON'S SUNNY SIDE

Crystalline silicon probably cannot dominate the photovoltaic industry forever, admits Dick Swanson, founder of Sunpower. Some scientists have calculated that the maximum possible efficiency for crystalline silicon solar cells is 25 percent. But no one has developed a commercially competitive substance. Thin-film photovoltaics made of amorphous silicon or semiconductor compounds such as cadmium telluride have yet to deliver comparable performance. Organic solar cells currently have efficiencies in the single digits. No one seems to expect these other materials to overtake silicon for at least 10 years. In fact, in 2002 BP Solar abandoned its thin-film manufacturing to concentrate on its crystalline silicon products.

NAVIGATION

Next-Generation GPS

GLOBAL POSITIONING INCHES TOWARD A MAKEOVER **BY STEVEN ASHLEY**

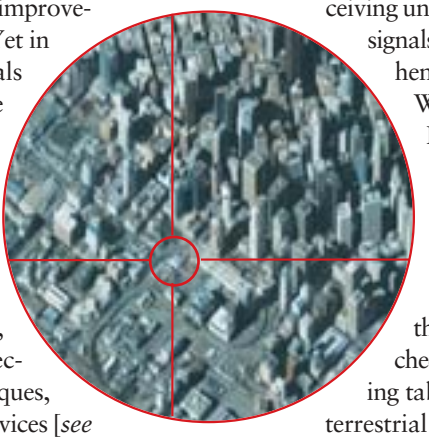
Some 20 million people now regularly use Global Positioning System (GPS) technology, relying on signals emitted by 24-plus U.S. NavStar satellites orbiting the earth (20,000 kilometers up) at any one time. GPS geolocation proved indispensable during the Afghan and Iraq wars. Every day shipping firms track delivery trucks while backcountry trekkers pack handheld GPS units that guide them through pathless wilderness. Motorola, Nextel and other firms are building cell phones fitted with GPS chipsets. One company is even designing a tiny, implantable GPS sensor.

From some perspectives, there does not seem to be much room for improvement in ubiquitous GPS. Yet in fits and starts, U.S. officials have begun planning the next generation of satellite navigation technology, known as GPS III (the current system is the second generation). The driving forces are better accuracy and reliability, concern about more effective signal-jamming techniques, alternative geolocation services [*see sidebar at left*], and new, more sophisticated applications, such as intelligent highway and traffic-safety systems.

Soon the U.S. Air Force is expected to request proposals for two-year development contracts worth up to $25 million. Initial launch of a GPS III satellite may occur as early as 2010. Competitors for the multibillion-dollar program—Boeing and the combination of Lockheed Martin and Spectrum Astro—have indicated their interest.

Per Enge, director of Stanford University's GPS Laboratory, sees three "megatrends" in the near-term evolution of GPS technology. The first is frequency diversity, which in fact is already being addressed as aging GPS II satellites are replaced periodically. When completed, the constellation of modernized orbiters will furnish civilian users with three new positioning signals. It will, moreover, provide U.S. armed forces with two additional signals that, being higher power, can better resist jamming. The extra frequencies afford redundancy to help fight timing errors resulting from ionospheric refraction of GPS signals, Enge states.

The second big trend concerns overcoming radio-frequency interference (RFI). "GPS broadcasts are extremely low power—equivalent to that of five lightbulbs," Enge explains. "With received power levels of 10^{-16} watt, the signal can be easily overwhelmed by nearby radio emitters." GPS receivers cut through the noise by matching the phase of the received ranging code with a replica code stored locally. When the wave phases align exactly, the receiving unit can use the timing of the signals as a precise reference and hence locate itself accurately. When deployed, so-called RFI hardening will permit the GPS receiver to double-check its calculations by keeping tabs on television and other terrestrial broadcast signals, which also employ this type of coding and emanate from well-known antenna sites.



HERE I AM—at least to within two meters or so, the current civilian resolution of GPS.

Enge's third GPS megatrend revolves around the installation of "integrity machines—systems that guarantee that the positioning error is smaller than a stated size." In July the U.S. Federal Aviation Administration brought online an enhanced-reliability GPS signal technology for guiding civil aviation. Called the Wide Area Augmentation System, the concept was developed by the FAA in cooperation with researchers at Enge's Stanford lab and elsewhere. Employing what are known as differential GPS techniques, the system obtains updated error-correction information from communications satellites in geosynchronous orbit. The revised data derive from ground-based reference receivers that monitor incoming GPS broadcasts and characterize the degree of distortion. "The fact that a geolocation signal had a two-meter error yesterday says nothing about today," Enge says.

DIGITALGLOBE

INDEPENDENT POSITION

The U.S. isn't alone in advancing global navigation technology. The European Space Agency and the European Commission have begun work on a system called Galileo. The Europeans intend Galileo to offer a positioning resolution of a meter—equivalent to those to be transmitted by the second-generation GPS civilian frequencies. Discussions continue, but European and U.S. officials have not yet determined whether Galileo will be competitive, complementary or fully interoperable with the GPS system. Reportedly, however, Galileo will work with the less well-known and less well-maintained Russian Glonass navigation satellites.

The European network, which may have its first satellite in orbit by 2008, raises questions about possible use of its relatively advanced geolocation capabilities by potential armed opponents of the U.S.: the Europeans are negotiating with China to participate in the Galileo project.

DATA POINTS: CLOSE TO HOME

Astronomers have detected dozens of extrasolar planetary systems, but the one found by the Anglo-Australian Planet Search, a team surveying the southern skies, bears the greatest resemblance to our own system. The star, called HD70642, is similar in size and age to our sun and has a Jupiterlike body in a nearly circular orbit. (Most other extrasolar gas giants orbit elliptically.) The planet is sufficiently far from its star that smaller, rockier planets, which are more likely to harbor life, may lie in between. The researchers announced the discovery at a Paris meeting and will publish the work in *Astrophysical Journal Letters*.

Jupiter's distance from the sun:
778 billion kilometers

New planet's distance from HD70642:
494 billion kilometers

Orbital period of Jupiter:
11.86 years

Orbital period of new planet:
6.11 years

Number of stars known to have planets:
111

Distance to HD70642:
90 light-years

Number of sunlike stars within 150 light-years:
2,000

SOURCES: National Science Foundation; http://exoplanets.org (star count as of July 18, 2003).

TRANSPLANTATION

Reviving Retinas

Retinal transplantation has proved difficult, in part because a tough scar of glial cells (structural nerve cells) forms around damaged areas. This barrier prevents transplanted cells from becoming an integral part of the retina. Scientists recently implanted new retinal cells into mice genetically engineered to be deficient in key proteins involved in scarring. The implanted cells could migrate away from the transplant site and extend into the optic nerve, although the researchers have yet to determine whether the implanted cells improved vision. The team is also working on a drug that will break down the glial barrier to allow a transplant in normal mice and, eventually, humans. "You could use this chemical to kill the glial cells, then after the transplant they would grow back," says Dong Feng Chen of Harvard University's Schepens Eye Research Institute, one of the report's authors. The paper is in the August *Nature Neuroscience*.

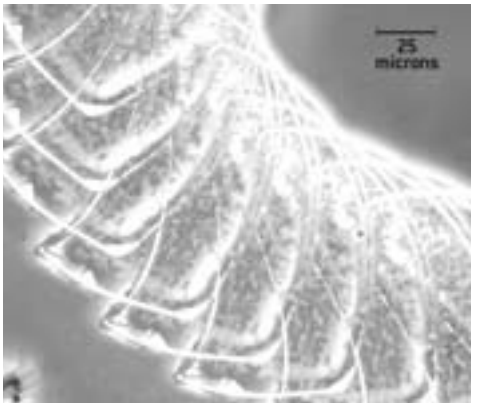
—Dennis Watkins

MICROMECHANICS

Bacterial Motor Works

Mixing microbes with machines is getting popular with engineers of micromechanical systems. Some, for instance, have coaxed the gyrating flagella of bacteria to act as pumps and valves. Now researchers are yoking microbes to lift and move objects, much like outboard motors on boats. The common *Serratia marcescens* "sticks gratuitously to surfaces," making them easy to attach to devices, says microbiologist Linda Turner of the Rowland Institute at Harvard University. Up to 50 can coat a blood cell–size plastic bead, and when the bacteria are packed densely, their flagella influence one another, thereby improving coordination. Turner hopes to guide the bacteria, which swim at about a millimeter a minute, with light or chemical cues. Carpets of the microbes could shuffle chemical-laden compounds around faster than diffusion alone or help to swirl and mix treacle-like fluids. She showed off the motors at the July meeting of the American Society for Microbiology.

—Charles Choi



BACTERIA UNDERNEATH a silicone panel carry it from right to left, as photographed in five-second intervals.

LINDA TURNER *Rowland Institute*; ILLUSTRATION BY MATT COLLINS

ALLERGY

Peace with Peanuts

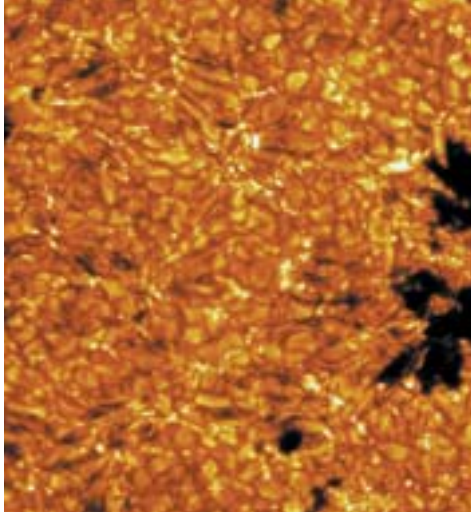
There is new hope for the estimated 1.5 million peanut allergy sufferers in the U.S. Robert A. Wood of Johns Hopkins University and his colleagues found that children with low levels of the antibody peanut immunoglobulin E—about one third of allergic children—have at least a 50 percent chance of outgrowing their allergy. Wood, whose study is in the July *Journal of Allergy and Clinical Immunology*, also warns that the allergy recurred in rare cases.

Of course, scientists could genetically modify peanuts so they don't trigger any reaction. But the controversy over transgenic food has led to searches for naturally existing hypoallergenic peanuts. After examining more than 370 peanut varieties (out of 14,000 known to exist), the U.S. Department of Agriculture announced on July 10 that it had found a peanut without one of the two major allergy-causing proteins. "If we find one variety that's lacking one allergen and another variety that's lacking the other allergen, they can be bred to create a variety that lacks both," observes Soheila Maleki, the USDA scientist conducting the search.

—Dennis Watkins

ASTRONOMY

New Light on Old Sol



GRANULES and other structures dot the sun's surface.

No, those are not popcorn kernels—they are granules on the sun's surface. A team led by Tom Berger of Lockheed Martin Solar and Astrophysics Lab in Palo Alto, Calif., snapped the highest-resolution photographs ever taken of the sun. The images, discerning features just 75 kilometers wide, reveal a surprising amount of structure in the photosphere, once thought to be flat and featureless. The granules, each about the size of Texas, result from heat burbling up from the sun's interior; sunspots and other dark "pores" appear sunken into the surface. Faculae—extra-bright areas between granules—appear to rise above the surface; they may account for the increased output during solar maximums. The team presented the images at the June meeting of the American Astronomical Society.

—*Philip Yam*

PHYSICS

Speed Control

Light zips through a vacuum at 186,000 miles per second, but superhot or frigid gases and crystals enable physicists to slow it down, speed it up and even stop it. Now scientists from the University of Rochester find that gemstones can also act as brakes and gas pedals for light and, crucially, do so at room temperature. Researchers first zap the mineral alexandrite with a laser that excites the electrons inside, altering how the crystal absorbs light. Another laser pulse is then shot in. If the laser frequencies are close, the second light signal will slow down by a factor of three million before exiting the crystal. Increasing the frequency difference can shift the peak of the second pulse and make it appear as though the entire pulse traveled faster than light. Such control over light could help improve fiber-optic network speeds and light-based computers. The findings are in the July 11 *Science*.

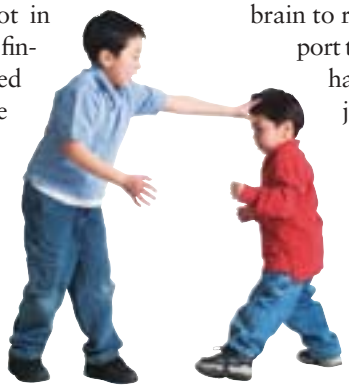
—*Charles Choi*

PERCEPTION

Punch Buggy Black and Blue

Two squabbling kids complaining that each has punched the other harder may both be telling the truth. Researchers at University College London conducted tit-for-tat experiments in which pairs of subjects were told to give as good as they got in terms of being rapped on the finger. The violence escalated rapidly: subjects increased the force they used by 38 percent on each turn. The scientists speculate that the subjects underestimated the amount of force they applied because when the brain has to plan a movement, it may attenuate the sensation of that movement. Freeing neural resources in this way may better prepare the brain to receive outside stimuli. To support their theory, the researchers also had subjects return the force via a joystick, rather than directly with their own finger; this method bypasses the brain's predictive mechanisms. Sure enough, the subjects accurately reproduced the force they received. The findings appear in the July 11 *Science*.

—*Philip Yam*



TAKE THAT: Accurately gauging the force of a hit depends on whether you are on the giving or the receiving end.

TOM BERGER *Lockheed Martin Solar and Astrophysics Lab (top);* RUBBERBALL *Getty (bottom)*

BRIEF POINTS

- **Aspirin may offer a new way to fight infections. Salicylic acid, aspirin's chief metabolite, can regulate two genes of *Staphylococcus aureus* and reduce the bacterium's ability to cling to the body's cells.**

  Journal of Clinical Investigation, July 15, 2003

- **Smoggy goodness: Trees can grow twice as fast in the city as in the country. Evidently, urban pollutants neutralize ground-level ozone that damages plant tissue.**

  Nature, July 10, 2003

- **Quarks had only been seen coming in pairs and triplets; now physicists have found a quarky fivesome. Weighing a hefty 1.5 billion electron volts, the "pentaquark" resulted from the coalescence of a neutron (one up and two down quarks) and a K^+ meson (one up and one antistrange quark).**

  Physical Review Letters, July 4, 2003

- **Genetic depression: Stressful life events are 2.5 times as likely to trigger depression in people who have the "short" version of the serotonin transporter gene, 5-HTT, as in those who have the "long" form.**

  Science, July 18, 2003

BY THE NUMBERS

Fertility Volatility

FLUCTUATING U.S. BIRTH RATES ELUDE DEFINITIVE EXPLANATION **BY RODGER DOYLE**

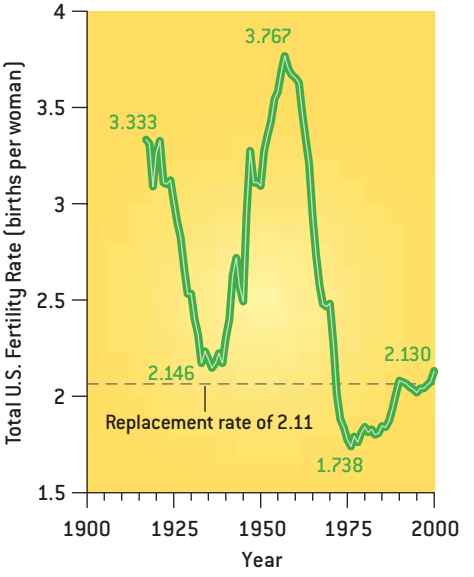
American fertility has gone through dramatic changes in the past century, including the "baby boom" after World War II and the "baby bust" of the 1960s and 1970s, which brought births below the replacement level of 2.11 births per woman for the first time in recorded history. In contrast, the average American woman in 1800 gave birth to seven children.

Back then, the U.S. was an agrarian society, so children had economic value. Cities saw a trend toward lower fertility: Families in Nantucket, for example, began limiting the number of children as early as the 1730s. Raising kids was costly, and, being whalers, residents had less incentive to have many children. Birth rates began dropping nationally during the 19th century because of urbanization and the decreasing supply of farmland, which lessened the need for extra hands. The most popular methods of family limitation were coitus interruptus, followed by the douche and the condom. By 1930 the U.S. birth rate had fallen to about a third of that recorded in 1800.

Explaining the fluctuations in fertility since World War II is far more controversial. Economist Richard A. Easterlin of the University of Southern California theorizes that the postwar boom has roots in the 1930s, when fertility was low because of the Great Depression. Children born then came of age in the 1950s and, being fewer in number, enjoyed high wages relative to those of their fathers. Well-off, they could afford to raise families. When their children—the baby boomers—came of age beginning in the 1970s, they were in surplus and so had low wages relative to their fathers and hence low fertility. The slight increase in fertility since the late 1990s could be the effect of the baby boomers' grandchildren entering the labor market or simply of the lower divorce rates of recent decades.

Competing theories emphasize the role of contraceptives. Sociologist Norman B. Ryder of Princeton University says that the baby boom resulted mainly from inadequate contraception and cites the failure rate of condoms and diaphragms:18 and 23 percent, respectively. As a result, in the 1950s about a quarter of couples who used contraceptives failed to prevent or delay pregnancy. Reliability improved in the 1960s thanks to the pill. Henri Leridon of the National Demographic Institute in Paris also points to the role of contraceptives, claiming that they were more important in causing the baby bust of the 1960s and 1970s than economic or social changes.

Improvement in contraception—the best methods are now more than 99 percent effective—means that another baby boom is unlikely anytime soon. Total fertility rates, which now hover around the replacement level, show no signs of plunging to the extraordinarily low levels of the European Union—now under 1.45—partly because of a high fertility rate among the growing Hispanic population, which in 2000 stood at 3.11. In comparison, rates for whites and blacks in 2000 were 2.11 and 2.19, respectively.



SOURCE: National Center for Health Statistics. The total fertility rate is the number of births a woman would have in her lifetime if, at each year of age, she experienced the average birth rate occurring in the specified year. The replacement rate assumes current mortality conditions and no net immigration.

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RODGER DOYLE

FURTHER READING

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"Nature, Mr. Allnut, is what we are put in this world to rise above."
—Katharine Hepburn to Humphrey Bogart in *The African Queen,* 1951

The Domesticated Savage

Science reveals a way to rise above our natures

By MICHAEL SHERMER

Evolutionary biologist Jared Diamond of the University of California at Los Angeles once classified humans as the "third chimpanzee" (the second being the bonobo). Genetically, we are very similar, and when it comes to high levels of aggression between members of two different groups, as I noted in last month's column on "The Ignoble Savage," we also resemble chimpanzees. Although humans have a brutal history, there's hope that the pessimists who forecast our eventual demise are wrong: recent evidence indicates that, like bonobos, we may be evolving in a more peaceful direction.

One of the most striking features in artificially selecting for docility among wild animals is that, along with far less aggression, you also get a suite of other changes, including a reduction in skull, jaw and tooth size. In genetics, this is called pleiotropy. Selecting for one trait may generate additional, unintended changes.

Like silver foxes, humans have become more agreeable as we've become more domesticated.

The most famous study on selective breeding for passivity began in 1959 by Russian geneticist Dmitri Belyaev of the Institute of Cytology and Genetics in Siberia. It continues today under the direction of Lyudmila N. Trut. Silver foxes were bred for friendliness toward humans, defined by a graduating series of criteria, from the animal allowing itself to be approached, to being hand fed, to being petted, to proactively seeking human contact. In only 35 generations the researchers produced tail-wagging, hand-licking, peaceful foxes. What they also created were foxes with smaller skulls, jaws and teeth than their wild ancestors.

The Russian scientists believe that in selecting for docility, they inadvertently selected for paedomorphism—the retention of juvenile features into adulthood—such as curly tails and floppy ears found in wild pups but not in wild adults, a delayed onset of the fear response to unknown stimuli, and lower levels of aggression. The selection process led to a significant decrease in levels of stress-related hormones such as corticosteroids, which are produced by the adrenal glands during the fight-or-flight response, as well as a significant increase in levels of serotonin, thought to play a leading role in the inhibition of aggression. The Russian scientists were also able to accomplish what no breeder had ever achieved before—a lengthened breeding season.

Like the foxes, humans have become more agreeable as we've become more domesticated. Whereas humans are like chimpanzees when it comes to between-group aggression, when it comes to levels of aggression among members of the same social group, we are much more like peaceful, highly sexual bonobos. Harvard University anthropologist Richard W. Wrangham proffers a plausible theory: as a result of selection pressures for greater within-group peacefulness and sexuality, humans and bonobos have gone down a different behavioral evolutionary path than chimps have.

Wrangham suggests that over the past 20,000 years, as humans became more sedentary and their populations grew, selection pressures acted to reduce within-group aggression. This effect can be seen in such features as smaller jaws and teeth than our immediate hominid ancestors, as well as our year-round breeding season and prodigious sexuality; bonobos were once called the "pygmy chimpanzee" because of their paedomorphic features. (Emory University psychologist Frans B. M. de Waal has documented how bonobos in particular use sexual contact as an important form of conflict resolution and social bonding.) Wrangham also shows how Area 13 in the human limbic frontal cortex, believed to mediate aggression, more closely resembles in size the equivalent area in bonobo brains than it does that same area in chimpanzees.

A plausible evolutionary hypothesis suggests itself: limited resources led to the selection for within-group cooperation and between-group competition in humans, resulting in within-group amity and between-group enmity. This evolutionary scenario bodes well for our species—if we can continue to expand the circle of whom we consider to be members of our in-group. Recent conflicts are not encouraging, but in the long run there is a trend toward including more people (such as women and minorities) within the in-group deserving of human rights. SA

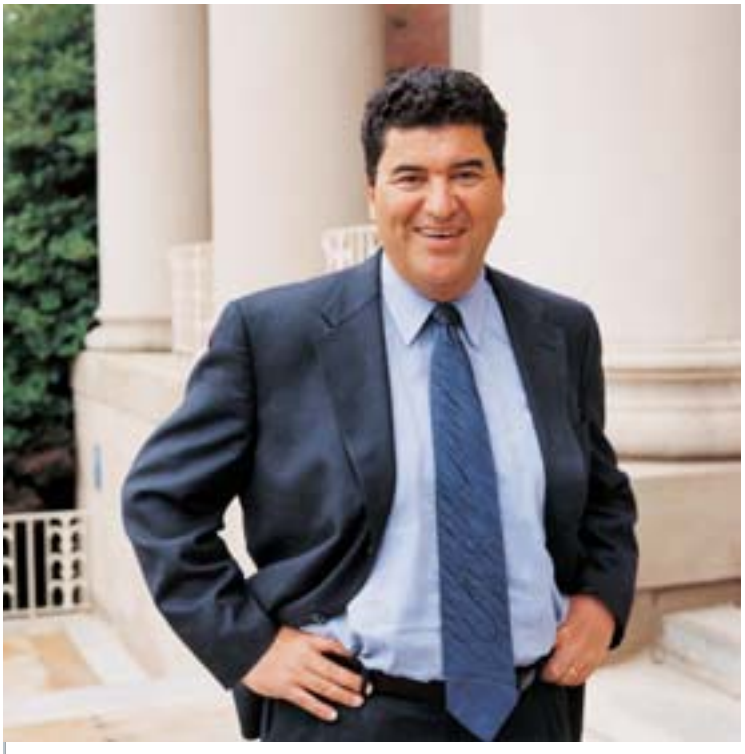
Michael Shermer is publisher of Skeptic *(www.skeptic.com) and author of* Why People Believe Weird Things.

BRAD HINES

A Biomedical Politician

Detractors initially worried that he might be a White House shill, but Elias A. Zerhouni says his medical thinking guides his stewardship of the National Institutes of Health By CAROL EZZELL

It's a cold, rainy morning in early April, but things are getting quite heated in the hearing room for the House Appropriations Committee on Capitol Hill. Representative Patrick J. Kennedy of Rhode Island is remonstrating against the Bush administration. The National Institutes of Health has been given $1.625 billion for bioterrorism research, Kennedy charges, but it is not studying how to manage panic-stricken populations following a bioterror attack. Kennedy is trying to bait the administration's top health officials, who have been called onto the carpet for the annual ritual of justifying their budget requests. Throughout the drama, NIH director Elias A. Zerhouni makes calm, measured responses, at times calling on Anthony S. Fauci, head of the NIH's antibioterrorism efforts, for his input.



HARRY ZERNIKE

ELIAS A. ZERHOUNI: BIOPOWER BROKER

- A registered Independent who has served in science advisory capacities under both Democratic and Republican administrations.
- Born in Algeria, Zerhouni became a U.S. citizen in 1990. He met his wife, pediatrician Nadia Azza, when both qualified for the Algerian national swim team in high school.
- Started Surgi-Vision, a firm in Gaithersburg, Md., that sells magnetic resonance imaging sensors small enough to fit inside blood vessels.

Since he took the reins of the NIH on May 20, 2002, Zerhouni has often faced Congress—which he calls a "major, major constituency" of his institution. As the first NIH director since the terrorist attacks of September 11, Zerhouni has been responsible for the country's ramped-up research efforts to counter bioterrorism. He is also in the hot seat to account for how the agency is spending its recent dramatic funding increases, which have doubled over the past five years, from $13.6 billion in 1998 to a projected $27.3 billion in 2003. And he is the lightning rod for criticism of the Bush administration by scientists who allege that political appointees are stacking science advisory committees to hew a conservative line on issues such as sexual practices and AIDS.

The 52-year-old Zerhouni—who was previously executive vice dean of the Johns Hopkins University School of Medicine, where he has spent most of his career—has confronted these challenges with directness tempered by diplomacy. At the April hearing, he countered Kennedy's ire with polite answers. But when asked about the issue privately, he bristles at the notion that the NIH has misplaced its priorities by focusing on making enough smallpox vaccine and developing a safer, next-generation version. "Panic would really set in if we told people, 'We're worried about your mental state, but we're not worrying about how many doses of vaccine are available,'" he declares.

Researching new vaccines to guard against a potential bioterror attack is only a small part of the sci-

entific scope of the NIH. Although roughly 4,000 scientists and technicians work on the sprawling NIH campus in Bethesda, Md., most of the agency's funding is spent on grants to the 50,000 researchers the NIH supports at universities and institutes around the country. Both groups of scientists study everything from cancer, heart disease and AIDS to rare genetic disorders that strike only a handful of people.

Zerhouni is a radiologist, which makes him an unusual choice to lead an agency whose research has increasingly focused on molecular biology and biochemistry. He is, however, a member of the prestigious Institute of Medicine and is renowned for refining an imaging technique called computed tomographic (CT) densitometry to help physicians discriminate between noncancerous nodules in the lung and lung cancers, based on the calcium content of the tumors.

The CT densitometry technique first got Zerhouni into government work. In 1985 Zerhouni consulted on President Ronald Reagan's colon polyps. After imaging Reagan's colon, he recommended against surgery. "They followed my advice not to operate," Zerhouni recounts, "and I became a medical consultant to the White House." He was subsequently tapped to serve on the National Cancer Institute's Board of Scientific Advisors from 1998 to 2002.

TESTIFYING before Congress is a regular task for NIH director Zerhouni—here, about the cause of SARS.

Still, Zerhouni remarks that the call from the George W. Bush White House personnel office came as a total surprise. "To be honest with you, when I was called I thought it was a mistake," he remembers. "I said, 'Are you sure you want to talk to me?'" Many NIH observers had similar reactions once his nomination leaked to the press in March 2002. E-mails flew around asking, "Anyone know this guy?" and "Zer-who-ni?"

Some scientists fighting against the White House ban on the use of federal funds for embryonic stem cell research were concerned about him as a choice. Zerhouni had established a privately funded institute for cell engineering at Johns Hopkins to allow scientists there to study human embryonic stem cells. Researchers speculated that, with his own private institute in place, Zerhouni would see no need for the federal funding of embryonic stem cell work and had cut a deal with the Bush administration not to try to overturn the ban.

Zerhouni flatly denies the allegation, stating that there was "no such thing" and that no one in the White House ever asked his stance on the issue prior to naming him. Indeed, he asserts that President Bush's announcement in August 2001 that federal money could only be used to study just 60 groups of human stem cells that had already been generated from human embryos actually broadened the scope of research; previously even such cell-line experiments were off-limits for federally funded scientists. "So I was personally in favor of the president's policy," he emphasizes, making it unlikely that he would try to lift the federal ban.

"I don't think Elias made any deal" with the White House about stem cell policy, states Harold E. Varmus, former NIH director and now president of Memorial Sloan-Kettering Cancer Center in New York City. Varmus is more concerned with the challenge Zerhouni will face in guiding the NIH to a "soft landing" of low to modest budget increases following its five-year budget doubling. "To fall from 15 percent increases per year to 3 percent a year places incredible stress on the NIH system," Varmus comments, because it means that scientists just starting their careers will find it impossible to get grants. "The current administration is bartering away our future [with tax cuts], and the NIH is going to suffer," he warns.

Zerhouni acknowledges that the slow-growth budgets envisioned for the NIH's immediate future could harm biomedical research if not managed carefully. He has assembled advisory groups to come up with a "road map" for how the NIH will manage with essentially constant resources, but the plans are still being finalized.

Varmus says that political pressure on the NIH is greater than it used to be. He avers that there is "some truth" to news stories that investigators are sanitizing their grant applications so as not to include phrases like "anal sex" that might squelch their chances by offending socially conservative politicians. But he claims that such anecdotes are being given too much attention. A "much deeper danger," he cautions, arises from the Bush administration's efforts to centralize government and to micromanage various agencies from the White House or departmental level. Although previous administrations treated the NIH "like a university within government," Varmus observes, things have changed. The Department of Health and Human Services, within which the NIH falls, has been more hands-on in hiring directors for the different NIH institutes and centers, he alleges, and has placed undue restrictions on travel as a cost-saving measure and a way of centralizing control.

Zerhouni remarks that he "hears these stories" about heavy-handed management of the NIH from above and about political influence on science advisory committees. But most have proved unfounded. "If there is any instance, they should let me know," he suggests. He'll be pacifying many more Kennedys before his NIH days are over. SA

ROLL CALL/NEWSCOM

THE BRAIN IS STILL AN ENIGMA. BUT THAT WON'T STOP US FROM TRYING TO ENHANCE MENTAL FUNCTIONING

BY GARY STIX

ULTIMATE SELF-IMPROVEMENT

The realization that the brain is more changeable than we ever thought has TRANSFORMED NEUROSCIENCE.

THE DECADE OF THE BRAIN CAME and went quietly. For the promoters who conceive and execute campaigns to raise public awareness and research dollars, duration is measured only in days, weeks, months or, rarely, years—never more than a decade. Any longer would exceed the natural life span of the potential audience and sponsors for the message conveyed: The Century of Kidney Disease Awareness? One Hundred Years of Schizophrenia?

Organizers of the Brain Decade coped with the difficulty of deciphering the world's most complex machine by setting out a series of comparatively modest challenges for the 1990s. A representative of the Dana Alliance for Brain Initiatives, which established a series of research objectives for the Decade, assigned generally high marks for meeting the stated goals: the identification of defective genes in familial Alzheimer's and Huntington's disease and the development of new treatments for multiple sclerosis and epilepsy, among other advances.

Left largely untouched was one of science's grand challenges, ranking in magnitude with cosmologists' dream of finding a way to snap together all the fundamental physical forces: we are still nowhere near an understanding of the nature of consciousness. Getting there might require another century, and some neuroscientists and philosophers believe that comprehension of what makes you *you* may always remain unknowable. Pictures abound showing yellow and orange splotches against a background of gray matter—a snapshot of where the lightbulb goes on when you move a finger, feel sad, or add two and two. These pictures reveal which areas receive increased oxygen-rich blood flow. But despite pretensions to latter-day phrenology, they remain an abstraction, an imperfect bridge from brain to mind.

Neuroscience, the attempt to deduce how the brain works, has succeeded in unraveling critical chemical and electrical pathways involved in memory, movement and emotion. But reducing the perceptions of a John Coltrane solo or the palette of a Hawaiian sunset to a series of interactions among axons, neurotransmitters and dendrites still fails to capture what makes an event special. Maybe that's why neuroscience fascinates less than it should. Maybe that's also why the De-

cade of the Brain passed with little notice. It's just too early to tackle the really big questions. Did you know that we are now in the midst of the Decade of Behavior? No? You're not alone.

Even though the Brain Decade came too early to yield the really big answers, intensive worldwide study during the 1990s of the many neural constituents did lend new perspectives on the brain and new tools for enhancing it. Drugmakers know that a pharmaceutical can treat disease effectively, even if they don't know fully how and why it works. The knowledge produced by neuroscientists, not only during the Decade of the Brain but also during the 10 decades that preceded it, has brought us to a juncture where we can begin to devise therapies for neurodegenerative diseases. But the upshot may be more than a drug that helps an Alzheimer's patient remember his name. This special issue of *Scientific American* describes new insights, not just into improving disordered brains but also into how neuroscience is finding ways to make good brains better.

The most important realization to emerge during the Brain Decade is that the organ being feted is more changeable than we ever thought. Even in maturity, some areas of the brain can renew themselves—a fact astonishingly contrary to a century of neurologists' dogma. That certain areas of the adult brain can generate new cells holds important ramifications for drug development and clinical practice. Careful reactivation of the molecules that foster such neurogenesis might counter the death of neurons that occurs in Alzheimer's and Parkinson's disease.

As more becomes known about this phenomenon, it may help demonstrate how to treat some forms of psychiatric illness. Investigators continue to test the hypothesis that Prozac and other selective serotonin reuptake inhibitors may exert an effect on mood by initiating neurogenesis. Understanding this process and the rewiring of connections that occurs among brain cells may suggest other, more effective agents against depression.

Beyond producing new nerve cells, the brain also rewires itself in response to experience. A deep understanding of so-called neural plasticity may reveal how far we can go with physical therapy, not only to repair the brain but also that torso-length extension of the central nervous system called the spinal cord. Christopher Reeve could not stand up on his 50th birthday, as he had wished. Still, neurologists marvel at the *Superman* actor's unprecedented recovery of limited movement in his extremities after long incapacitation from spinal injury.

The technological milestone of the past decade was the emergence of magnetic resonance imaging for taking detailed pictures of brains enmeshed in tasks ranging from doing arithmetic to listening to Mozart. Functional MRI, as the technique is known, may not provide a direct route to the essence of our conscious selves, but it could establish the basis for a more definitive form of lie detection than the polygraph and maybe even rudimentary methods of mind reading. More important, the technology, perhaps coupled with genetic testing, will create a more sound basis for diagnosing brain disorders than do current methods that rely on checklists of symptoms.

An understanding of the complex chain of neurotransmitters, "second messengers," transcription factors, genes and other miscellaneous molecules needed to make a long-term memory is leading to drugs that may ultimately help more than those beset with Alzheimer's or more benign forms of dementias that plague the aged. Physicians are sure to write off-label prescriptions for memory enhancers for the pupil preparing for finals or the chief executive readying a speech for the annual shareholders' meeting.

The prospect of enhancing normal brain function is real. And with it will come a host of

ethical issues concerning who has access to what. Will a "smart divide" separate an elite who can afford to self-administer a memory pill from the rest of society that copes with rote learning by burning the midnight oil? Neuroscience, perhaps more than any other biological subdiscipline, will force us to confront questions of equity. The Decade of the Brain may have passed with little fanfare, but the scanty knowledge that we now possess—that new brain cells emerge in old adults, for one—has already begun to yield powerful insights for clinical medicine. SA

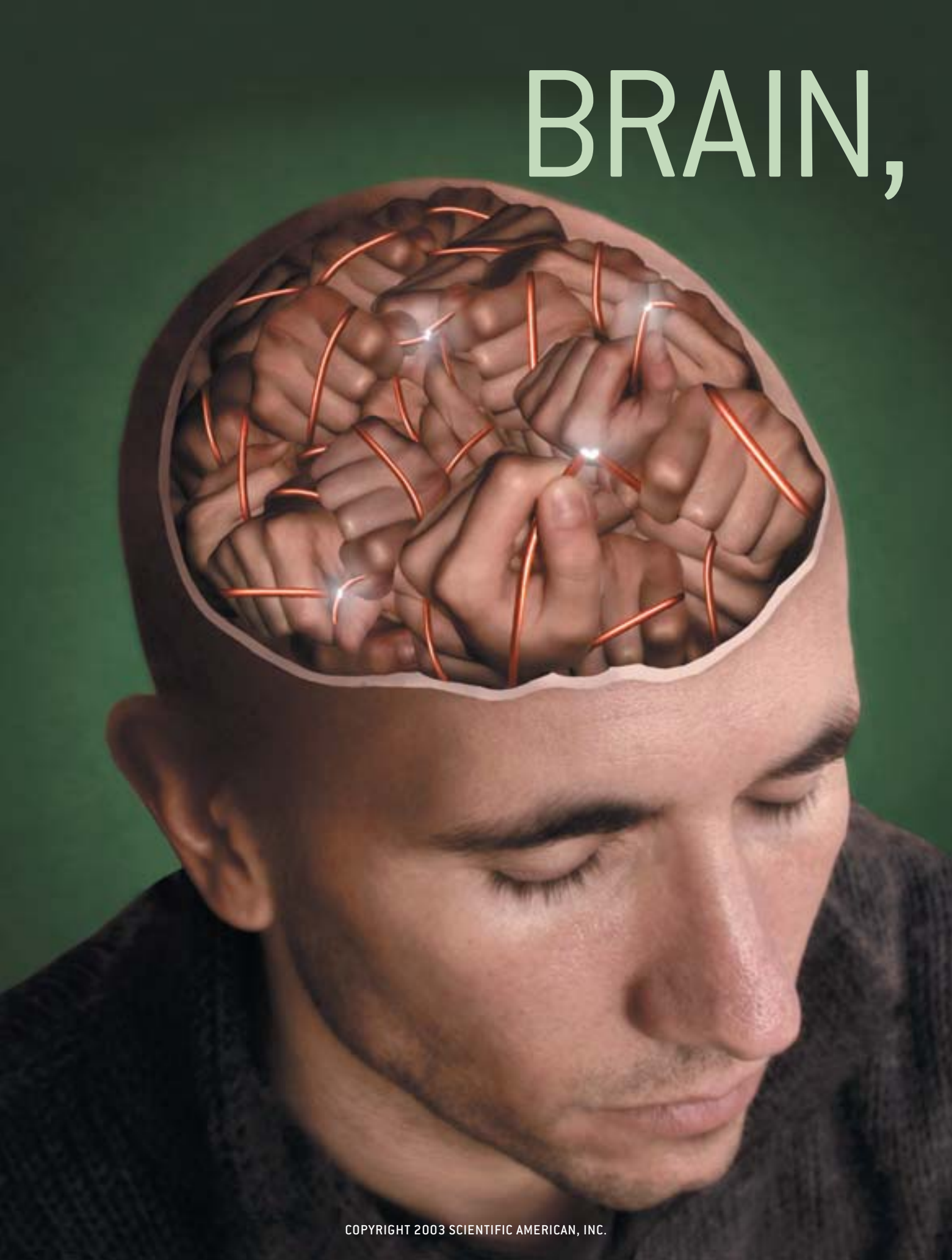
Gary Stix is special projects editor at Scientific American.

NATIONAL GEOGRAPHIC CHANNEL

A segment based on articles in this issue will air August 28 on *National Geographic Today*, a program on the National Geographic Channel. Please check your local listings.

MELISSA SZALKOWSKI

BRAIN,



REPAIR YOURSELF

HOW DO YOU FIX A BROKEN BRAIN? THE ANSWERS MAY LITERALLY LIE WITHIN OUR HEADS. THE SAME APPROACHES MIGHT ALSO BOOST THE POWER OF AN ALREADY HEALTHY BRAIN **BY FRED H. GAGE**

MELISSA SZALKOWSKI

The human brain has the capability to rewire itself to some extent.

FOR MOST OF ITS 100-YEAR HISTORY, NEUROSCIENCE has embraced a central dogma: a mature adult's brain remains a stable, unchanging, computerlike machine with fixed memory and processing power. You can lose brain cells, the story has gone, but you certainly cannot gain new ones. How could it be otherwise? If the brain were capable of structural change, how could we remember anything? For that matter, how could we maintain a constant self-identity?

Although the skin, liver, heart, kidneys, lungs and blood can all generate new cells to replace damaged ones, at least to a limited extent, until recently scientists thought that such regenerative capacity did not extend to the central nervous system, which consists of the brain and spinal cord. Accordingly, neurologists had only one counsel for patients: "Try not to damage your brain, because there is no way to fix it."

Within the past five years, however, neuroscientists have discovered that the brain does indeed change throughout life—and that such revision is a good thing. The new cells and connections that we and others have documented may provide the extra capacity the brain requires for the variety of challenges that individuals face throughout life. Such plasticity offers a possible mechanism through which the brain might be induced to repair itself after injury or disease. It might even open the prospect of enhancing an already healthy brain's power to think and ability to feel.

Neuroscientists, of course, have tried to come up with fixes for brain injury or brain disorders for decades. Such treatment strategies have primarily involved replacing diminished neurotransmitters, the chemicals that convey messages between nerve cells (neurons). In Parkinson's disease, for instance, a patient's brain loses the ability

to make the neurotransmitter dopamine because the cells that manufacture it die. A chemical relative of dopamine, L-dopa, can temporarily ameliorate the symptoms of the disease, but it is not a cure. Neuroscientists have also attempted to implant brain tissue from aborted fetuses to replace the neurons that perish in Parkinson's disease—and in other neurological disorders such as Huntington's and spinal cord injury—with modest success. Lately, some have turned to neurons derived from embryonic stem cells, which under the right conditions can be coaxed in laboratory dishes to give rise to all the cell types of the brain [*see box on page 50*].

The ULTIMATE VISION is that physicians would be able to DELIVER DRUGS that would stimulate the brain to REPLACE ITS OWN cells.

Although stem cell transplants have many advantages, switching on the innate capacity of the adult nervous system to repair itself would be much more straightforward. The ultimate vision is that physicians would be able to deliver drugs that would stimulate the brain to replace its own cells—and thereby rebuild its damaged circuits.

Newborn Nerve Cells

MANY INVESTIGATORS are now pursuing exactly that vision. The hope that repair might be feasible stems from a series of exciting discoveries made starting about 40 years ago. Researchers first demonstrated that the central nervous systems of mammals contain some innate regenerative properties in the 1960s and 1970s, when several groups showed that the axons, or main branches, of neurons in the adult brain and spinal cord can regrow to some extent after injury. Others (including my colleagues and me) subsequently revealed the birth of new neurons, a phenomenon called neurogenesis, in the brains of adult birds, nonhuman primates and humans [see "New Nerve Cells for the Adult Brain," by Gerd Kempermann and Fred H. Gage; SCIENTIFIC AMERICAN, May 1999].

Shortly thereafter scientists began to wonder why, if it can produce new neurons, the central nervous system fails to repair itself more reliably and completely in the wake of disease or injury. The answer lies in understanding how—and perhaps to what end—adult neurogenesis normally occurs and how the brain's natural inclination to fix itself might be amplified.

We now know that the birth of new brain cells is not a single-step process. So-called multipotent neural stem cells divide periodically in the brain, giving rise to other stem cells and to progeny that can grow up to be either neurons or support cells named glia. But to mature, these newborn cells must migrate away from the influence of the multipotent stem cells. On average, only half of them make the trip; the rest die. This seemingly wasteful process mirrors that which takes place before birth and during early childhood, when more brain cells arise than are needed to form the developing brain. During that period, only those cells that form active connections with other neurons survive.

Whether the young cells that persist become neurons or glia depends on where in the brain they end up and what type of activity is occurring in that brain region at the time. It takes more than one month from when a new neuron is formed from a stem cell until it becomes fully functional and able to send and receive information. Thus, neurogenesis is a process, not an event, and one that is tightly controlled.

Neurogenesis is regulated by a variety of naturally occurring molecules called growth factors that are currently under intense investigation. A factor dubbed sonic hedgehog that was first discovered in insects, for example, has been shown to regulate the ability of immature neurons to proliferate. In contrast, another factor named notch and a class of molecules called the bone morphogenetic proteins appear to influence whether newborn cells in the brain become glial cells or neurons. Once young cells are committed to becoming either neurons or glial cells, other growth factors—such as brain-derived neurotrophic factor, the neurotrophins and insulinlike growth factor—play important roles in keeping the cells alive and encouraging them to mature and become functional [*see table on page 53*].

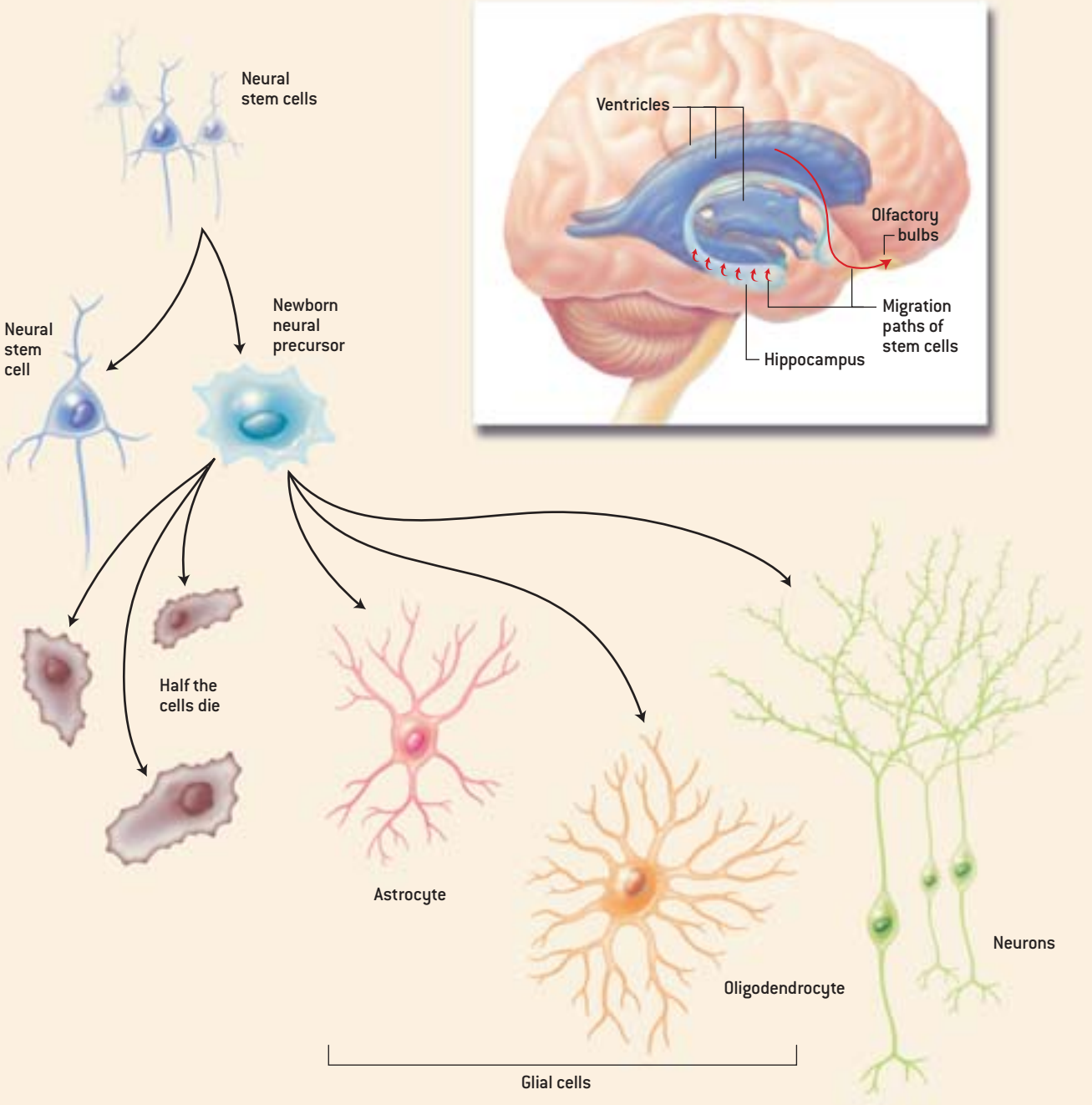
OVERVIEW/*New Adult Nerve Cells*

- Naturally occurring growth factors in the adult human brain can spur the production of new nerve cells in some instances.
- The growth factors—or more easily administered drugs that prompt their production—might be useful as therapies for various brain disorders and for brain or spinal cord injuries.
- The factors could potentially be tested to enhance normal brain function, but questions remain about whether the strategy would work.

HOW THE BRAIN MAKES NEW NEURONS

NEURAL STEM CELLS are the fount of new cells in the brain. They divide periodically in two main areas: the ventricles (*purple, inset*), which contain cerebrospinal fluid to nourish the central nervous system, and the hippocampus (*light blue, inset*), a structure crucial for learning and memory. As the neural stem cells proliferate (*cell pathways below*), they give rise to other neural stem cells and to neural precursors that can grow up to be either neurons or support cells, which are collectively termed glial cells (astrocytes or oligodendrocytes).

But these newborn neural stem cells need to move (*red arrows, inset*) away from their progenitors before they can differentiate. Only 50 percent, on average, migrate successfully (the others perish). In the adult brain, newborn neurons have been found in the hippocampus and in the olfactory bulbs, which process smells. Researchers hope to be able to induce the adult brain to repair itself by coaxing neural stem cells or neural precursors to divide and develop when and where they are needed. *—F.H.G.*



ALICE Y. CHEN

STEM CELLS AS THERAPIES

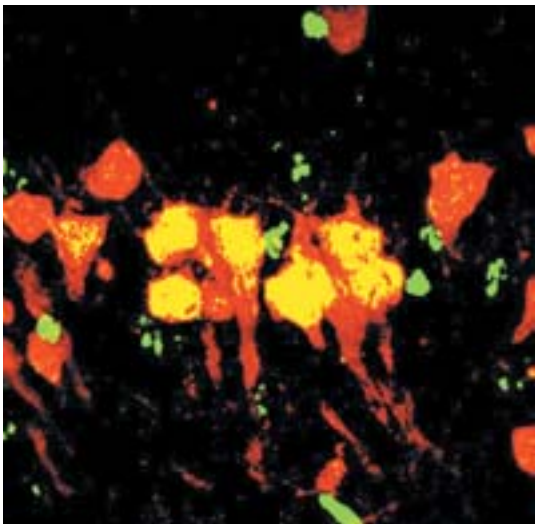
SCIENTISTS ARE INVESTIGATING two types of stem cells for possible use in brain-repair strategies. The first are adult neural stem cells: rare, primordial cells left over from early embryonic development that are known to occur in at least two areas of the brain and that can divide throughout life to yield new neurons as well as support cells called glia. The second are human embryonic stem cells that have been isolated from very early human embryos, at the stage in which the embryos consist of only 100 or so cells. Such embryonic stem cells have the potential to make any cell type in the body.

Most studies have involved observing neural stem cells while they are growing in laboratory culture dishes. Such cultured cells can multiply and be genetically marked in culture and then be transplanted back into the nervous system of an adult. In these experiments, which have so far only been performed using animals, the cells survive well and can differentiate into mature neurons in the two areas of the brain where the formation of new neurons normally occurs, the hippocampus and the olfactory bulbs. Adult neural stem cells do not readily differentiate into neurons when transplanted into any other brain areas, although they can become glia.

The problem with adult neural stem cells is that they are still immature. Unless the adult brain into which they are transplanted is making the necessary signals to direct the stem cells to become a particular neural cell type, such as a hippocampal neuron, they will either die, become glial cells or merely persist as undifferentiated stem cells. The solution would be for scientists to determine which biochemical signals normally prompt adult neural stem cells to become a particular neuronal type and then induce the cells toward that lineage in a culture dish. Once transplanted into a particular part of the brain, the cells would be expected to continue becoming that cell type, form connections with other brain cells and begin to function. —*F.H.G.*

Where the Action Is

NEW NEURONS DO NOT arise spontaneously in every part of the adult mammalian brain but appear so far to form only in fluid-filled cavities called ventricles in the forebrain and in a seahorse-shaped structure called the hippocampus that is buried deep in the brain. Researchers have shown that cells destined to become neurons travel from the ventricles to the olfactory bulbs, a pair of structures that receives input from odor-sensing cells in the nose. Although no one is sure why the olfactory bulb requires so many new neurons, we can more easily speculate why the hippocampus needs them: this structure is crucial for learning new information, so adding neurons there would presumably spur the formation of connections between new and existing neurons, increasing the brain's capacity to process and store novel information.



One month after treatment with neural growth factors, the brain of a rat that had experienced a stroke generated new neurons (*yellow*).

A handful of reports have purported to find new neurons in areas outside the hippocampus and olfactory bulb, but those results have not yet been substantiated. One reason is that the methods used to prove the existence of neurogenesis are complex and difficult to carry out. Newer, more sensitive techniques may detect neurogenesis elsewhere in the adult brain and spinal cord as well. As we learn additional details about the molecular mechanisms that control neurogenesis and the environmental stimuli that regulate it, we anticipate that we will be able to direct neurogenesis anywhere in the brain. By understanding how growth factors and different cellular environments control neurogenesis in the normal brain, for instance, we hope to be able to develop therapies that can prompt a diseased or damaged brain to fix itself.

Several neurological diseases might be ameliorated by stimulating neurogenesis. A stroke, for instance, occurs when a clot restricts blood flow to part of the brain, cutting off the oxygen supply and killing neurons. After a stroke, neurogenesis commences in the hippocampus in an apparent attempt to produce new neurons to heal such damaged brain tissue. Most of the newborn cells die, but some successfully migrate to the damaged area and have been reported to become adult neurons. Although such microrepair is not sufficient to reverse the damage of a major stroke, it is probably adequate to help the brain recover from small, often unrecognized strokes. Epidermal growth factor (EGF) and fibroblast growth factor (FGF) are now being used to try to enhance this intrinsic repair process, with encouraging results.

Unfortunately, EGF and FGF are large molecules

HIROFUMI NAKATOMI ET AL. IN *CELL*, VOL. 110; AUGUST 23, 2002

that have difficulty crossing the blood-brain barrier, the meshlike network of tightly woven cells that lines the blood vessels of the brain. Wyeth-Ayerst Laboratories and Scios, a biotechnology company based in Sunnyvale, Calif., halted clinical trials of FGF to treat stroke in 1999, in part because the molecule was not reaching the brain. Several research groups have tried to overcome this obstacle for FGF by linking it to another molecule that tricks the cells into taking it up and transferring it into brain tissue or by genetically engineering cells to make FGF and then transplanting those cells into the brain. So far such approaches have been tested only in studies involving animals, however.

Stimulating neurogenesis could also lead to a new type of treatment for depression. Chronic stress is believed to be the most important causal factor in depression aside from a genetic predisposition to the disorder, and stress is known to restrict the number of newly generated neurons in the hippocampus [see "Taming Stress," by Robert Sapolsky, on page 86]. Many currently available drugs for treating depression, such as Prozac, augment neurogenesis in experimental animals. Interestingly, most of these drugs take up to one month to elevate mood—the same time required for neurogenesis. This finding has led to the hypothesis that depression is in part caused by a decrease in neurogenesis in the hippocampus. Recent clinical imaging studies have confirmed that the hippocampus is shrunken in chronically depressed patients. But long-term administration of antidepressants appears to spur neurogenesis: rodents that were administered such drugs for months had new neurons sprouting in their hippocampus.

Do-It-Yourself Brain

ANOTHER DISORDER in which prompting neurogenesis might be beneficial is Alzheimer's disease. Several recent studies have demonstrated that mice genetically engineered to contain human genes that predispose to Alzheimer's display various abnormalities in neurogenesis. Those engineered to overproduce a mutant form of the human amyloid precursor protein, for instance, have fewer than normal neurons in the hippocampus. And the hippocampus of other mice carrying the mutant human gene for a protein named presenilin has a decreased number of dividing cells, resulting in a reduced number of surviving neurons. If growth factors such as FGF can reduce the trend, they might be useful therapies for this devastating disease.

The challenge now is to learn more about the specific growth factors that govern the various steps of neurogenesis—the birth of new cells, the migration of newborn cells to the correct spots, and the maturation of those cells into neurons—as well as the factors that inhibit each step. In diseases such as depression, where cell division is reduced and cell loss results, the goal is to find drugs or specific therapies that increase cell proliferation. In epilepsy, where it appears that new cells are born but then migrate to the wrong locations, finding ways to redirect errant neurons could be the key. In the brain cancer glioma, glial cells proliferate and form deadly, rapidly growing tumors. Although the origin of gliomas is still unclear, some speculate that they arise from neural stem cells. Natural substances that regulate the division of such stem cells might hold promise as a treatment.

Several neurological DISEASES might be AMELIORATED by stimulating NEUROGENESIS.

In stroke, where cells die or fail to mature, it will be important to identify growth factors that support neuronal survival and teach immature cells to become healthy, well-connected neurons. Disorders such as Huntington's, amyotrophic lateral sclerosis (ALS) and Parkinson's—in which very specific cell types die and cause particular cognitive or motor symptoms—might be the easiest initial targets because the cells that are responsible for the disease are in discrete areas of the brain that can be pinpointed.

An important concern will be how to control the amount of neurogenesis a particular treatment prompts, because the overproduction of new neurons can also be dangerous. In some forms of epilepsy, for example, neural stem cells continue to divide past the point at which new neurons can form useful connections. Neuroscientists speculate that these aberrant cells not only end up in the wrong place but

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MAKING CRUCIAL CONNECTIONS

BECAUSE IT TAKES roughly one month from the time neural stem cells divide until their offspring become integrated into the functional circuits of the brain, the role that the new neurons play in behavior probably has less to do with the birth of the cells and more to do with how new or existing cells connect to one another (form synapses) and to existing neurons to form circuits. In the process of synaptogenesis, so-called spines on the arms, or dendrites, of one neuron make connections with points on the main branch, or axon, of another neuron. According to recent studies, dendritic spines (*below*) can change their shapes in a matter of minutes, suggesting that synaptogenesis might underpin learning and memory. The solid-color micrographs (*red, yellow, green* and *blue*) were taken one day apart in the brain of a living mouse. The multicolor image (*far right*) shows the color photographs superimposed on one another. Areas where no change occurred appear white. —*F.H.G.*

also remain immature, contributing to the miswiring of the brain that causes seizures. Growth factor treatments for stroke, Parkinson's and other disorders might prompt neural stem cells to divide inappropriately and cause similar symptoms, so researchers must first better understand how to use the growth factors to trigger growth, the migration of new cells to specific places, or their maturation into adult cells.

In treating spinal cord injury, ALS or multiple sclerosis, the strategy may be to induce stem cells to yield a subset of glial cells called oligodendrocytes. These cells are essential for neurons to communicate with one another because they insulate the long axons between neurons, preventing the electrical signal carried by the axons from dissipating. Stem cells in the spinal cord have already been shown to have the capacity to make oligodendrocytes at low frequency. My colleagues and I—as well as other groups—have also used growth factors to induce the proliferation of oligodendrocytes in animals with spinal cord injury, with beneficial results.

A Brain Workout

ONE OF THE MOST STRIKING aspects of neurogenesis in the hippocampus is that experience can regulate the rate of cell division, the survival of newborn neurons and their ability to integrate into the existing neural circuitry. Adult mice that are moved from a rather sterile, simple cage to a larger one that has running wheels and toys, for instance, will experience a significant increase in neurogenesis. Henriette van Praag in my laboratory has found that exercising mice in a running wheel is sufficient to nearly double the number of dividing cells in the hippocampus, resulting in a robust increase in new neurons. Intriguingly, regular physical activity such as running can also lift depression in humans, perhaps by activating neurogenesis.

Once neurogenesis can be induced on demand in a controlled fashion, it could change our very conception of brain disease and injury. I imagine a time when selective drugs will be available to stimulate the appropriate steps of neurogenesis to ameliorate specific disorders. Such pharmacological therapies will be teamed with physical therapies that enhance neurogenesis and prompt particular brain regions to integrate the newly developed cells. These potential treatments offer great promise for millions of people suffering from neural diseases and spinal cord injury. The links between neurogenesis and increased mental activity and exercise also suggest that people might be able to reduce their risk of neural disease and enhance the natural repair processes in their brains by choosing a mentally challenging and physically active life.

Just as exciting is the possibility that healthy individuals might become "better than well" by stimulating their brains to grow new neurons. It is unlikely, however, that people seeking to boost their brainpower would want to have regular shots of growth factors, which cannot be taken orally and have difficulty crossing the blood-brain barrier once injected into the bloodstream. Scientists are now seeking small molecules that can be made into pills that would switch on growth factor genes in a person's brain so that the individual's brain cells make more of the factors than usual. For instance, a company named Curis, based in Cambridge, Mass., has devised small molecules that regulate the production of sonic hedgehog, a factor that plays a role in neural development. Other companies have generated similar molecules that might be made into drugs.

Another strategy that could conceivably be used to improve brain performance involves gene therapy and cell transplantation. Under such a scenario, researchers would genetically engineer cells in the

KAREL SVOBODA *Cold Spring Harbor Laboratory*

SELECTED NEURAL GROWTH FACTORS UNDER DEVELOPMENT

These factors might be used as drugs on their own, or scientists might design other drugs to stimulate or block the factors.

NAME	FUNCTION	POTENTIAL DISEASE TARGETS	SOME COMPANIES INVOLVED IN RESEARCH
Brain-derived neurotrophic factor (BDNF)	Keeps newborn neurons alive	Depression (abandoned for amyotrophic lateral sclerosis)	Amgen, Thousand Oaks, Calif.
Ciliary neurotrophic factor (CNTF)	Protects neurons from death	Huntington's disease (now testing against obesity)	Regeneron Pharmaceuticals, Tarrytown, N.Y.
Epidermal growth factor (EGF)	Spurs stem cells in brain to divide	Brain tumors and stroke	ImClone Systems, New York City
Fibroblast growth factor (FGF)	In low doses, supports survival of various cell types; at high doses, induces cells to proliferate	Brain tumors and stroke	ViaCell, Boston
Glial cell line–derived neurotrophic factor (GDNF)	Prompts motor neurons to sprout new branches; prevents cells that perish in Parkinson's disease from dying	Parkinson's disease and ALS	Amgen
Glial growth factor-2 (GGF-2)	Favors production of glial (support) cells	Spinal cord injury, multiple sclerosis and schizophrenia	Acorda Therapeutics, Hawthorne, N.Y.
Insulinlike growth factor (IGF)	Fosters the birth of both neurons and glial cells	Multiple sclerosis, spinal cord injury, ALS and age-related dementia	Cephalon, West Chester, Pa.
Neurotrophin-3 (NT-3)	Promotes formation of oligodendrocytes (type of glial cell)	Multiple sclerosis, spinal cord injury and ALS	Amgen and Regeneron Pharmaceuticals

laboratory to overproduce specific growth factors and then implant the cells into particular regions of a person's brain. Alternatively, scientists could insert the genes that encode the production of various growth factors into viruses that would ferry the genes into existing brain cells.

But it is not at all clear whether any of these approaches would necessarily enhance the capabilities of a normal, healthy brain. A handful of animal studies using nerve growth factor suggests that adding growth factors can actually disrupt normal brain function. It is possible that the brain requires a delicate balance and that too much of a good thing can lead to just as many problems as too little. Growth factors could induce tumors to form, and transplanted cells could potentially grow out of control, causing cancer. Such risks might be acceptable for people with diseases as dire as Huntington's, Alzheimer's or Parkinson's but might not be palatable for healthy individuals.

The best ways to augment brain function might not involve drugs or cell implants but lifestyle changes. Like many other organs, the brain responds positively to exercise, a good diet and adequate sleep, which are already known to enhance normal brain function with fewer side effects and potential problems than most of the other strategies described above. I predict that if more people knew that a proper diet, enough sleep and exercise can increase the number of neural connections in specific regions of the brain, thereby improving memory and reasoning ability, they would take better care of themselves.

A final consideration is the environment in which we live and work. More and more experimental evidence indicates that environment can affect the wiring of the brain. This opens up vistas of possibility for architecture and suggests that future homes and offices might be designed with an eye toward how they might provide an enriched environment for enhancing brain function.

More immediately, however, if science can better understand the self-healing abilities of the brain and spinal cord, that insight could constitute one of the major achievements of our time. Neurologists of the future might be able to expand their capabilities by strategically activating the brain's own toolkit for self-repair and enhancement. SA

MORE TO EXPLORE

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THE QUEST FOR A SMART PILL

NEW DRUGS TO IMPROVE MEMORY AND COGNITIVE PERFORMANCE IN IMPAIRED INDIVIDUALS ARE UNDER INTENSIVE STUDY. THEIR POSSIBLE USE IN HEALTHY PEOPLE ALREADY TRIGGERS DEBATE

BY STEPHEN S. HALL
PHOTOGRAPHS BY JAMES SALZANO

ON A WINTRY AFTERNOON IN APRIL, TIM TULLY AND I stood in a laboratory at Helicon Therapeutics, watching the future of human memory and cognition—or at least a plausible version of that future—take shape. Outside, a freak spring snowstorm lashed at the Long Island landscape. I mention the weather because it reminded both Tully and me of winters from our childhoods in the Midwest many years ago. The enduring power of those memories—and the biological processes that record and preserve them in the brain—lie at the heart of an incipient revolution in neuropharmacology that is unfolding in small, relatively unknown labs like this one in Farmingdale, N.Y.

Tully, a neuroscientist at Cold Spring Harbor Laboratory and founder of Helicon, has been one of the leading protagonists in the race to develop a new class of drugs that might improve memory in the memory impaired—drugs that grow out of an increasingly sophisticated molecular and mechanistic understanding of how we can remember everything from snowstorms more than 30 years ago to where we put our car keys 30 minutes ago.

It is, alas, the nature of contemporary science (and commerce and bioethics, for that matter) that we often have to conjure up the future of human cognition, and its pharmacological manipulation, while staring at the behavior of a drugged mouse

meandering in a jury-rigged box. So there we stood, gazing at a video playing on Tully's laptop computer, watching a small brown rodent enter an enclosed environment and begin its scurrying explorations in an experimental scenario known as Object Recognition Training. One day earlier, Tully explained, this same mouse had been placed in this same box, which contained two odd, knoblike objects, each with its distinct olfactory, tactile and other sensory tags. A mouse that is allowed to explore this environment for 15 minutes, Tully continued, will remember it so well that the animal will immediately notice any changes the next day; a mouse allowed to explore for only three and a half minutes, however, typically does not have enough time to commit the scene to long-term memory.

The mouse we were watching had had only three and a half minutes of training. But it did have a pharmaceutical assist, and that is what Tully wanted to show me. Narrating the action like a play-by-play announcer at a sports event, he described the scene as the little creature immediately paid an inordinate amount of murine attention to a new object in the room. "See, there he goes," Tully said in his earnest Midwestern locution. "He's walking around it.... Now he's climbing on top of it. He's not even paying attention to the other object." Indeed, the mouse sniffed at and circled and eventually clambered all over the novel object while ignoring the second object—the one encountered the day before.

To display this degree of curiosity, the mouse needed to *remember* what had been in the box the day before. That requires the formation of a long-term memory. And although years of behavioral experiments have established that mice ordinarily do not recall any changes in their environment after so brief a previous exposure, this one did, because of a drug—a memory drug known as a CREB enhancer that Helicon hopes to begin testing in humans, perhaps as soon as the end of the year. "We've shown that several compounds will enhance the ability of a normal mouse to remember this task," Tully said. "And yet to make it a fact rather than a belief, we have to show it works in humans."

These days smart mice and erudite rats are the stalking-horses for a new pharmacology: drugs that might enhance human cognition, improving memory in those whose memories have faltered because of neurodegenerative disease or aging, perhaps even reengineering memory-forming circuitry in stroke victims or people with mental retardation. The potential market for such medicines is staggeringly large. As Tully and every other biotech and big-pharma executive know by heart, there are four million Americans with Alzheimer's disease, another 12 million with a condition called mild cognitive impairment (which often presages Alzheimer's), and approximately 76 million Americans older than 50, many of whom may soon satisfy a recent definition by the U.S. Food and Drug Administration for age-associated memory impairment (or AAMI), a form of mild forgetfulness. And judging by the sales of the herbal medicine ginkgo biloba, consumers are not waiting for an FDA-approved memory drug. Sales of ginkgo exceed $1 billion a year in the U.S., even though the scientific evidence that it improves memory is marginal at best; sales in Germany outstrip all acetylcholinesterase-inhibiting drugs used to slow memory loss in Alzheimer's patients, including donepezil (Aricept, marketed by Pfizer), rivastigmine (Exelon, marketed by Novartis) and galantamine (Reminyl, marketed by Janssen).

Despite an incessant media drumbeat about the coming revolution in what one magazine has dubbed "Viagra for the brain," smart pills are not around the corner. Cortex Pharmaceuticals in Irvine, Calif., has developed a class of memory-enhancing drugs called ampakines, which the company believes will increase the power of the neurotransmitter glutamate; the drugs have passed Phase I safety testing and are currently in Phase II tests

These days SMART MICE AND ERUDITE RATS are the stalking-horses for novel pharmaceuticals that MIGHT IMPROVE HUMAN COGNITION.

OVERVIEW/*A Brave New Pharmacology*

- An incipient revolution in neuropharmacology would offer drugs that could improve memory in those whose memories have faltered because of disease or aging and increase cognitive acuteness in fatigued individuals.
- Off-label use of some of these cognitive enhancers could allow normal individuals to sleep less, work harder and play more.
- Although most of these drugs are years away from government approval and clinical use, their possible social impact already has bioethicists contemplating the potential dangers.

(small-scale trials for efficacy) against Alzheimer's, mild cognitive impairment and schizophrenia. But those preliminary tests come at the end of a research odyssey that began in the mid-1980s, with no definitive end in sight.

Nevertheless, the action is beginning to heat up. Memory Pharmaceuticals in Montvale, N.J., which is commercializing the Nobel Prize–winning research of Columbia University professor Eric R. Kandel [see "The Biological Basis of Learning and Individuality," by Eric R. Kandel and Robert D. Hawkins; SCIENTIFIC AMERICAN, September 1992], began initial safety testing of its first memory-enhancing drug in humans at the beginning of 2003, and Tully estimates that Helicon's lead drug candidate should enter trials no later than early 2004. Axonyx in New York City has been looking at phenserine (a potent acetylcholinesterase inhibitor) to treat Alzheimer's; the company began advanced testing in June. Princeton University neuroscientist Joe Z. Tsien, who caused an enormous stir in 1999 with the creation of a genetically enhanced smart mouse called Doogie, has advised a San Francisco–based biotech company, Eureka! Pharmaceuticals, which is collaborating with scientists in Shanghai to look for drugs that would merge modern genetics with ancient Chinese herbal medicine. Still, Tsien has his doubts about how soon the much-ballyhooed revolution will begin. "I'd be surprised to see any of these get to the clinic and become a drug anytime soon," he predicted, "especially a drug without side effects."

Although most of these new-generation drugs are years away from government approval and clinical use, their social impact has already been profound. Bioethicists have been working overtime contemplating the social dangers of memory enhancement, especially their potential use as "lifestyle" drugs. Moral philosopher Leon R. Kass, head of the President's Council on Bioethics, recently wrote that "in those areas of human life in which excellence has until now been achieved only by discipline and effort, the attainment of those achievements by means of drugs, genetic engineering, or implanted devices looks to be 'cheating' or 'cheap.'"

In another sense, however, the use of potent drugs as cognitive enhancers has been a feature of human life ever since people began drinking coffee. About 50 years ago the practice gained a more pharmaceutical aura when normal, healthy adults discovered that amphetamines could improve alertness. If, as some predict, the new cognitive enhancers are destined to replicate the pattern of Viagra and become lifestyle drugs, how might that happen, and how widespread might their use become? One possible answer may lie in an earlier generation of cognition-enhancing drugs that have already been approved—methylphenidate (Ritalin) for attentional focus, donepezil for Alzheimer's and modafinil for narcolepsy. These drugs are already taken by normal adults who seek to enhance mental acuity and performance. Users clearly believe that the drugs improve cognitive performance in normal people, although almost no research attests to this—and some research hints that they may be no better than a drug found on most breakfast tables.

Tim Tully of Cold Spring Harbor Laboratory and Helicon Therapeutics shows off a mouse used for testing drugs to improve memory.

The Caffeine Caveat

COGNITIVE ENHANCEMENT has been a feature of military research for a numbers of years. At Walter Reed Army Institute of Research, Nancy Jo Wesensten works on pharmaceutical agents that might improve the alertness (and therefore battlefield performance) of soldiers suffering severe sleep deprivation. In June 1998, while attending a meeting of sleep researchers, Wesensten stopped by the booth of Cephalon, a biotechnology company based in West Chester, Pa., and began chatting with one of its marketing representatives.

At the time, Cephalon was close to gaining FDA approval of a drug with the generic name of modafinil. Marketed as Provigil, this medicine is used to treat narcolepsy, the profound daytime drowsiness that afflicts an estimated 125,000 Americans. Modafinil, it became clear, would be an obvious candidate for the U.S. Army to test as a treatment for sleep deprivation—so much so that Wesensten was whisked up to the company's hospitality suite to discuss the work further. Eventually Cephalon agreed to provide modafinil for the army's research.

That was more than five years ago. In December 1998 the FDA approved the sale of modafinil in the U.S. to treat narcolepsy, and Cephalon is now selling about $200 million worth of the drug each year. That's a lot of narcolepsy medication—more, many observers suspect, than the U.S. population of narcoleptics can support. "There's a huge amount of off-label use by psychiatrists to augment mood," said Helene Emsellem, who runs the Center for Sleep and Wake Disorders in Chevy Chase, Md. In fact, modafinil is used to treat depression, multiple sclerosis and several other clinical conditions associated with fatigue. More to the point, there have been reports that doctors "are getting barraged" (as the online magazine *Slate* recently put it) by healthy people requesting prescriptions for modafinil as a cognitive enhancer that allows them to sleep less, stay up longer, work harder and play more. One well-known academic sleep researcher told me off the record, "People are telling me that they focus better on it, including some of my colleagues." Cephalon has been conducting clinical trials to test Provigil as a treatment for additional disorders of excessive sleepiness—resulting, for example, from disrupted sleep (caused by sleep apnea) or the "circadian misalignment" suffered by night-shift workers such as factory employees and truck drivers.

Which brings us back to Wesensten's study at Walter Reed's sleep center. "We were specifically interested in whether modafinil has any advantages over caffeine, which we find very good for reversing the effects of sleep deprivation on cognitive performance. Plus it's widely available, nonprescription and has a low side-effect profile," she said. "So was there any benefit to modafinil over caffeine?" Wesensten and her colleagues organized a randomized, double-blind, placebo study in which 50 volunteers were kept awake for 54 continuous hours. After about 40 hours, the subjects received either a placebo, 600 milligrams of caffeine (a stiff dose equal to about six cups of coffee) or one of three doses of modafinil (100 milligrams, 200 milligrams or 400 milligrams). Then they were subjected to a battery of tests to assess cognitive function and side effects.

The bottom line? The highest dose of modafinil, 400 milligrams, cut through fatigue and restored cognitive performance to normal levels—but so did caffeine. The reported side effects of modafinil were quite low—but so were those of caffeine. "What we concluded," Wesensten said, "was that there didn't appear to be any benefit to using modafinil over caffeine. It just wasn't there. Both drugs looked very similar."

The U.S. Air Force has also conducted extensive experimentation with drugs that increase alertness in fatigued military personnel, a particular concern for pilots in an operational setting. The air force allowed use of amphetamines as "go pills" by pilots as early as World War II, according to John A. Caldwell, a sleep disorders expert with the air force who has conducted such experiments over the past 10 years. "My primary objective is not to enhance cognitive performance," he said in an interview, "but to maintain the already excellent performance levels of our military."

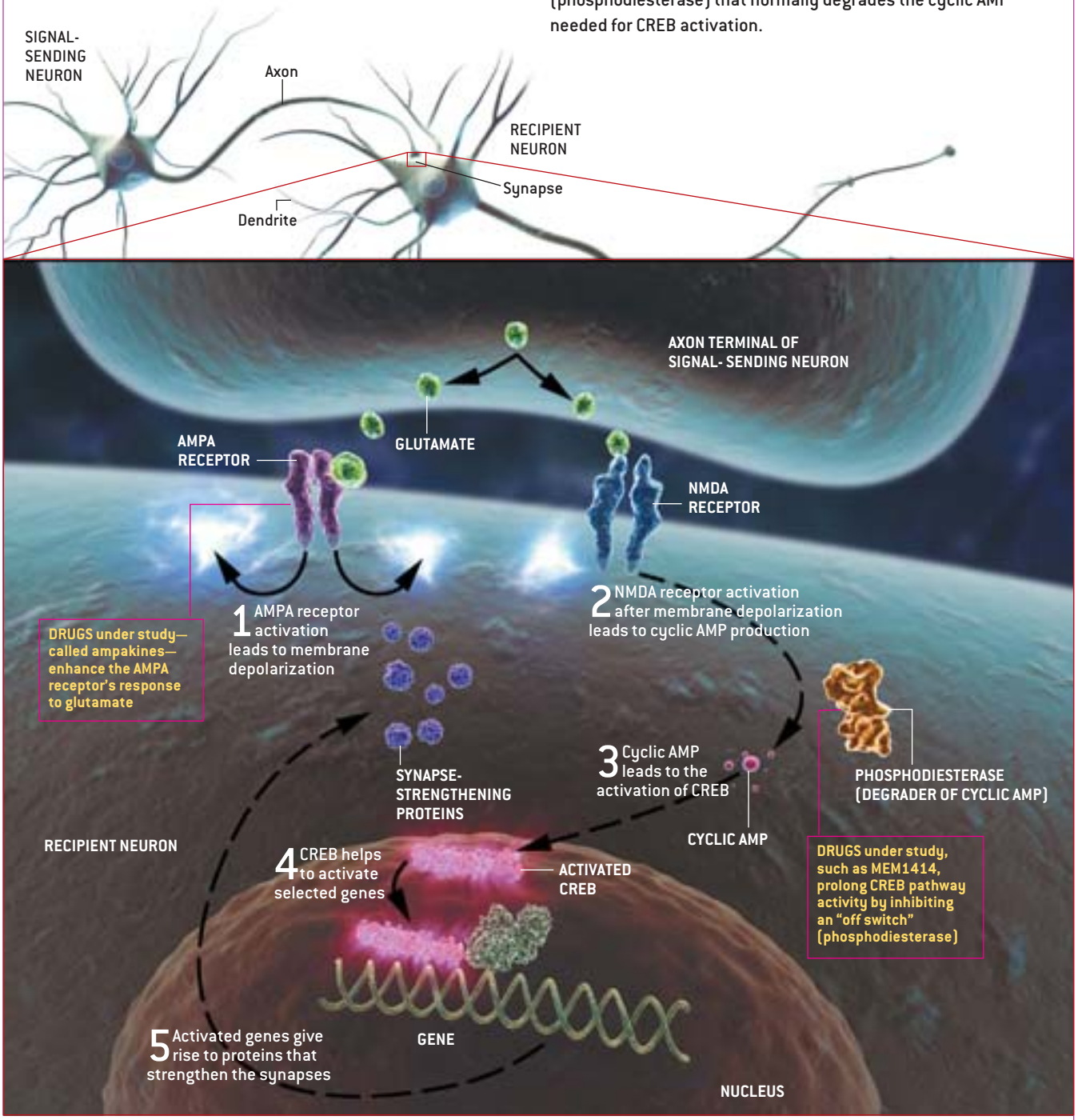
Beginning in 1993, Caldwell carried out randomized, double-blind experiments showing that dextroamphetamine eliminates virtually all the decrements of performance in both male and female pilots who have not slept for 40 hours. Some of the studies took place in a helicopter flight simulator but have been replicated in real aircraft. More recently, he tested modafinil head-to-head against dextroamphetamine in sleep-deprived pilots, showing that the narcolepsy drug overcame fatigue and maintained cognitive performance, although some of the subjects developed nausea akin to motion sickness inside the simulator. "Ultimately, I think there will be a place for modafinil," Caldwell said. "It wouldn't surprise me if it would be approved for use within a year. But I don't think it will be a replacement for our current 'go pill.' We have 50 years of operational experience, and tons of laboratory research,

Some research hints that COGNITIVE ENHANCERS currently on the market may be no better than a drug FOUND ON MOST BREAKFAST TABLES.

HOW SOME MEMORY DRUGS WOULD WORK

CERTAIN MEMORY DRUGS under study influence two processes that operate when neurons encode long-term memories: membrane depolarization and activation of the CREB protein. Depolarization can occur after release of the excitatory neurotransmitter glutamate at synapses (contact points between two nerve cells) stimulates AMPA receptors on recipient cells. Depolarization, however it happens, helps another surface protein, the NMDA receptor, to respond to glutamate. The receptor reacts by activating the CREB pathway inside cells—a series of molecular interactions that includes production of a molecule called cyclic AMP, which leads to activation of CREB. (Broken arrows indicate that steps in the pathway have been omitted for simplicity.) This last event is key: activated CREB helps to switch on genes whose protein products strengthen specific synapses.

Some drugs under investigation aim to speed memory storage by amplifying the AMPA receptor's response to glutamate and thus facilitating depolarization. Other compounds aim to increase a cell's supply of active CREB—such as by inhibiting an enzyme (phosphodiesterase) that normally degrades the cyclic AMP needed for CREB activation.



MIKE MEDICINE HORSE *Hybrid Medical Animation*

with dextroamphetamine. We're not there yet with modafinil."

A Halo of Powder

RESEARCH ON MODAFINIL, nonetheless, highlights a paradox in the ethical debate about cognitive enhancement. The Defense Advanced Research Projects Agency (DARPA) has funded considerable basic and clinical research looking at ways for its personnel to increase cognitive performance. Its Continuous Assisted Performance (CAP) program has funded preclinical research with Cortex's ampakine drugs, for example. So whereas members of one government body, President George W. Bush's bioethics panel, have characterized the use of drugs by healthy people to enhance cognitive performance as a form of cheating, another branch of the government, the military, has aggressively explored the capacity of new pharmaceutical agents to increase cognitive alertness and performance in fatigued but essentially normal individuals—a short hop, skip and a jump to cognitive enhancement for civilians.

Modafinil is merely the latest cognitive enhancer to develop a following among healthy individuals. There is a mini literature (not to say mythology) surrounding the use of Ritalin as a study aid by high school and college students. Ritalin, marketed by Novartis, is typically prescribed for children with attention-deficit hyperactivity disorder (ADHD) but has reportedly found favor with students and even business executives. Several students at a prestigious East Coast preparatory school told me that Ritalin use as a study aid was so common that students occasionally sported a halo of powder around their nostrils after snorting the drug. The practice has spread to college campuses. "It's here," confirmed Eric Heiligenstein, clinical director of psychiatry at the University of Wisconsin Health Services. "It's fairly well established, if you want to use it." Although the amount of Ritalin consumed by college students is almost impossible to quantify, Heiligenstein said that the number of hard-core users is "very small" yet more extensive than those who take modafinil because Ritalin is "available, relatively cheap and has a pretty good safety profile."

Among the sparse findings about the effects of these drugs on healthy individuals, at least one study suggests that a long-standing dementia treatment improves cognitive functioning in normal people. In July 2002 Jerome A. Yesavage of Stanford University, Peter J. Whitehouse of Case Western Reserve University and their colleagues published a study in *Neu-*

STATE OF THE ART FOR SMART

COGNITIVE ENHANCEMENT drugs, some of which are still under development, focus so far on treating dementia and other disorders. Some compounds on the market are also being used or tested to improve normal functioning, such as to increase wakefulness in shift workers or to help pilots perform under stress.

TYPE OF DRUG	COMPANY	PURPOSE	STATUS*
CREB suppressor	Helicon Therapeutics	Suppression of disturbing memories	Early stages of development
CREB enhancer	Helicon Therapeutics	Memory enhancement	Early stages of development
CREB enhancer (MEM 1414)	Memory Pharmaceuticals in partnership with Roche	Memory enhancement	Will enter Phase I trials in late 2003
Calcium flow regulator (MEM 1003)	Memory Pharmaceuticals	Memory enhancement	In Phase I trials
Ampakines	Cortex Pharmaceuticals	Memory enhancement	In Phase II trials
Phenserine	Axonyx	Treatment of mild to moderate Alzheimer's	Phase II trials completed
Modafinil (Provigil)	Cephalon	Treatment of narcolepsy	On the market
Methylphenidate (Ritalin)	Novartis	Attention enhancement	On the market
Donepezil (Aricept)	Eisai/Pfizer	Treatment of mild to moderate Alzheimer's	On the market
Rivastigmine (Exelon)	Novartis	Treatment of mild to moderate Alzheimer's	On the market
Galantamine (Reminyl)	Janssen	Treatment of mild to moderate Alzheimer's	On the market

**Phase I trials study the safety of a new drug in small, healthy human populations. Phase II trials examine safety and efficacy in individuals afflicted with the disorder in question. To gain approval, drugs must also pass through large, Phase III, trials of safety and efficacy.*

rology assessing the impact of donepezil on the performance of pilots. Donepezil, marketed as Aricept, is one of many drugs approved by the FDA to slow the progressive memory loss experienced by patients with Alzheimer's disease. The researchers trained two groups of pilots in a Cessna 172 flight simulator; one group then received a placebo while the other group took five milligrams of donepezil, less than the routine dose for Alzheimer's, for 30 days. Then they tested both groups again in the simulator.

Yesavage and his colleagues threw several curves at the pilots—they were asked to perform some complicated air-traffic maneuvers and had to react to in-flight emergencies, including a drop in oil pressure as indicated by cockpit instrumentation. A month after their initial training, the pilots on donepezil performed significantly better than the control group, with especially enhanced performance on the landing approach and in handling emergencies. Yesavage, who hopes to conduct an expanded study sometime soon, noted in the *Neurology* article that "if cognitive enhancement becomes possible in intellectually intact individuals, significant legal, regulatory, and ethical questions will emerge."

If those questions are true of donepezil, modafinil and other existing drugs, they will be especially true for the new generation of smart drugs, precisely because they are based on a mechanistic approach to memory that could be particularly powerful—unlike the accidental discoveries we have often had up to now. And although every biotech executive decries the notion of a lifestyle drug, everyone is aware of the precedent. "Typically industry wanted to avoid enhancement drugs in the 1990s," said one neuroscientist. "But I think Viagra changed a lot of people's opinion."

Improving Memory

AS HE GUIDED ME through some 32,000 square feet of drug-discovery real estate at Memory Pharmaceuticals in northern New Jersey, Axel Unterbeck punctuated every stop on the tour with the phrase "very sophisticated." Unterbeck, the company's tall, charming, elegantly dressed president and chief scientific officer, invoked the words again and again—in the electrophysiology lab where half a dozen biologists record the effect of potential memory-enhancing drugs on individual neurons and slices of animal brain, in the vivarium where the company tests those candidate drugs in elderly rodents, and in the pharmacokinetics room, where the disembodied whines and clicks of robotic machinery accompany the analysis of blood samples from animals and humans. "They're doing the job as we speak," Unterbeck said, proudly pointing out a $250,000 machine that speedily determines the concentration of drug metabolites in blood. "*Very* sophisticated."

Ritalin, ordinarily prescribed for children with attention-deficit hyperactivity disorder (ADHD), is reportedly used by some high school and college students to increase mental acuity.

Everything about Memory Pharmaceuticals bespeaks state-of-the-art science and high-end ambition—its intellectual godfathers and founders (Columbia Nobel laureate Eric R. Kandel and Harvard Nobel laureate Walter Gilbert), its beautifully landscaped headquarters with birch trees and daffodils flanking the entryway, even its tony neighbors (the North American headquarters of Mercedes-Benz is just up the road). Founded in 1998, the company is betting a lot of money—$41.5 million from a recent round of financing, plus a co-development deal potentially worth $150 million with the Swiss drug giant Roche—that it can navigate the shoals of drug discovery more efficiently by identifying toxicological and pharmacokinetic (drug metabolism) problems in cognition-enhancing drugs early in the process. "That's the future," Unterbeck said, "and we are very well positioned for translating the science into smart drugs."

Axel Unterbeck pauses in the electrophysiology lab at Memory Pharmaceuticals, where potential memory-enhancing drugs are tested on individual neurons and slices of animal brain.

Early in 2003 Memory Pharmaceuticals began initial safety testing of its first smart drug, a compound called MEM 1003, in healthy volunteers in London. The compound regulates the flow of calcium ions into neurons and is designed to restore the equilibrium of calcium in brains cells that have been disrupted by Alzheimer's, mild cognitive impairment or a condition called vascular dementia. "So far this program looks exceptionally good in terms of pharmacokinetics and toxicology," Unterbeck said. "The compound looks exceptionally safe." But perhaps the most closely watched of Memory's potential smart drugs is a compound called MEM 1414, because this drug would tweak a molecular pathway identified by Kandel's and Tully's labs as crucial to converting short-term experience and learning into long-term memory. It involves a powerful protein known as CREB [*see box on page 61*].

In the mid-1990s Tully and Jerry Yin of Cold Spring Harbor Laboratory genetically engineered a fruit fly that displayed the insect equivalent of a photographic memory—these flies learned and memorized a task after one training exercise, whereas normal flies took 10 practice sessions. They managed this stunning enhancement of memory by goosing the output of a single gene called CREB. Both Tully's and Kandel's labs have shown that when simple animals learn a task and commit it to memory, the synapses used to form the memory are remodeled and strengthened in a process that requires the activation of genes. As it turns out, memory formation unleashes a messenger molecule inside the cell known as cyclic AMP. This molecule in turn triggers the formation of a protein that binds to the DNA of a nerve cell, thus activating an entire suite of genes that add the mortar and brick at synapses to consolidate memory formation. This instigating protein is called cyclic AMP response element binding protein, or CREB. The more CREB swimming around in a neuron, the faster long-term memory is consolidated. That at least has been the case with sea mollusks, fruit flies and mice. Now the question is: Will it be true of humans, too?

Normally, another chemical—phosphodiesterase (PDE)—breaks down cyclic AMP in the cell. Pharmacologically inhibiting phosphodiesterase makes more CREB available for a longer period—thus, in theory, strengthening and speeding the process of memory formation. Phosphodiesterase inhibitors have a spotty reputation in pharmaceutical circles, however; one version was approved in Japan to treat depression, but the molecules have a history of causing nausea. Nevertheless, PDE inhibitors have performed exceedingly well as memory enhancers in preclinical testing, according to researchers in the field, because they allow more CREB to hang around in the cell during learning, which promotes memory consolidation. Hence, both Memory Pharmaceuticals and Helicon Therapeutics are developing drugs based on a class of molecules known as PDE-4. Helicon is also working on a drug that suppresses memories, something that might be used to block or erase disturbing memories of a traumatic event. "We have preclinical evidence that suggests that they might selectively block traumatic memories that have formed before," Tully said.

Memory Pharmaceuticals is especially high on its MEM 1414 molecule—a fascination ratified in July 2002 when Roche agreed to be a partner in its development. "What is really interesting, you see the same kind of age-associated memory impairment in nonhuman primates and rodents as you see in humans," Unterbeck explained. About 50 percent of aged animals, he continued, are unable to form new memories, yet MEM 1414 restored age-related

deficits in the animals' recall to close to normal. The company launched Phase I tests (for safety) of the compound earlier this year.

Even an ideal progression through clinical testing and federal drug approval, however, adverts to a slow and perilous timeline. "MEM 1003 could—and it's a big could—be on the market in 2008," said Tony Scullion, Memory's CEO, "and 1414 wouldn't be too far behind." But as Unterbeck knows from his previous tenure at Bayer, the promise of a new drug often doesn't unravel until late in the game, when the large number of patients typically enrolled in Phase III trials can reveal not only less-than-optimal efficacy but more-than-expected side effects. "Drug companies put $500 million down," he said, "and you get failure in Phase III." Larry Squire, an elder statesman of memory research at the University of California at San Diego, added, "In fact, you could say the whole history of the field has been to deal with side effects."

got our hands full just showing that these drugs will work," admitted Tully, who has a long history of being keenly attentive to the social implications of scientific research. "Having said that, do I think there will be off-label use if it works clinically? Yes, I do. In principle, these compounds could improve the motor skills required to play the piano or second-language acquisition. The off-label use of drugs happened with Viagra, and it didn't stop Viagra, it didn't stop Ritalin, and it didn't stop amphetamines. But the fact is, off-label use of prescription drugs is dangerous because of unanticipated side effects. You may create unknown psychological problems. But it's not worth even talking about at all except as science fiction. We simply have to wait until we put these drugs into people and see what happens."

Given that we are most likely five or 10 years away from "seeing what happens," we're probably destined to read a lot more about smart drugs before we actually have any pills in hand. But there may be

Although every biotech executive decries the notion of a LIFESTYLE DRUG, everyone is aware of the PRECEDENT SET BY VIAGRA.

Moreover, there is hardly unanimity that CREB is the best or only route to a blockbuster memory drug. "There's not very strong biology in the CREB pathway, especially in mammalian systems," one neuroscientist who requested anonymity pointed out. "The targets are not well validated, and CREB is expressed everywhere, very early on." Another prominent neuroscientist told me that even a scientific adviser to Memory Pharmaceuticals has privately expressed the view that the new drugs may prove no more effective than caffeine. Nor is CREB the only portal to memory manipulation. Tsien, creator of the smart mouse at Princeton [see "Building a Brainier Mouse," by Joe Z. Tsien; Scientific American, April 2000], is pursuing a different memory pathway involving a receptor of the neurotransmitter NMDA that is limited to the forebrain; and Cortex's ampakine technology is focused on a different neurotransmitter system. "Frankly speaking, we still know so little," Tsien said. "We know no principles, no operating code for memory. We know a lot of genes, but we don't have a coherent picture, and I think that is the problem with the whole area of therapeutic research and development."

Researchers are resigned to the continuing bioethical debate on the drugs, no matter how premature the science or how fuzzy the future. "We've

a cautionary warning in a little episode that happened when I visited Tsien at Princeton. He was walking me through the animal facility, which houses his genetically engineered "smart" mice, when one of the lab technicians walked by holding a mouse trap with two unhappy occupants. Tsien looked down at the two cognitively enhanced rodents in the trap, shook his head and said simply, "Not so smart." SA

Stephen S. Hall is a writer based in New York City. He has written four books chronicling the contemporary history of science, including most recently an account of stem cell and cloning research, Merchants of Immortality *(Houghton Mifflin, 2003).*

MORE TO EXPLORE

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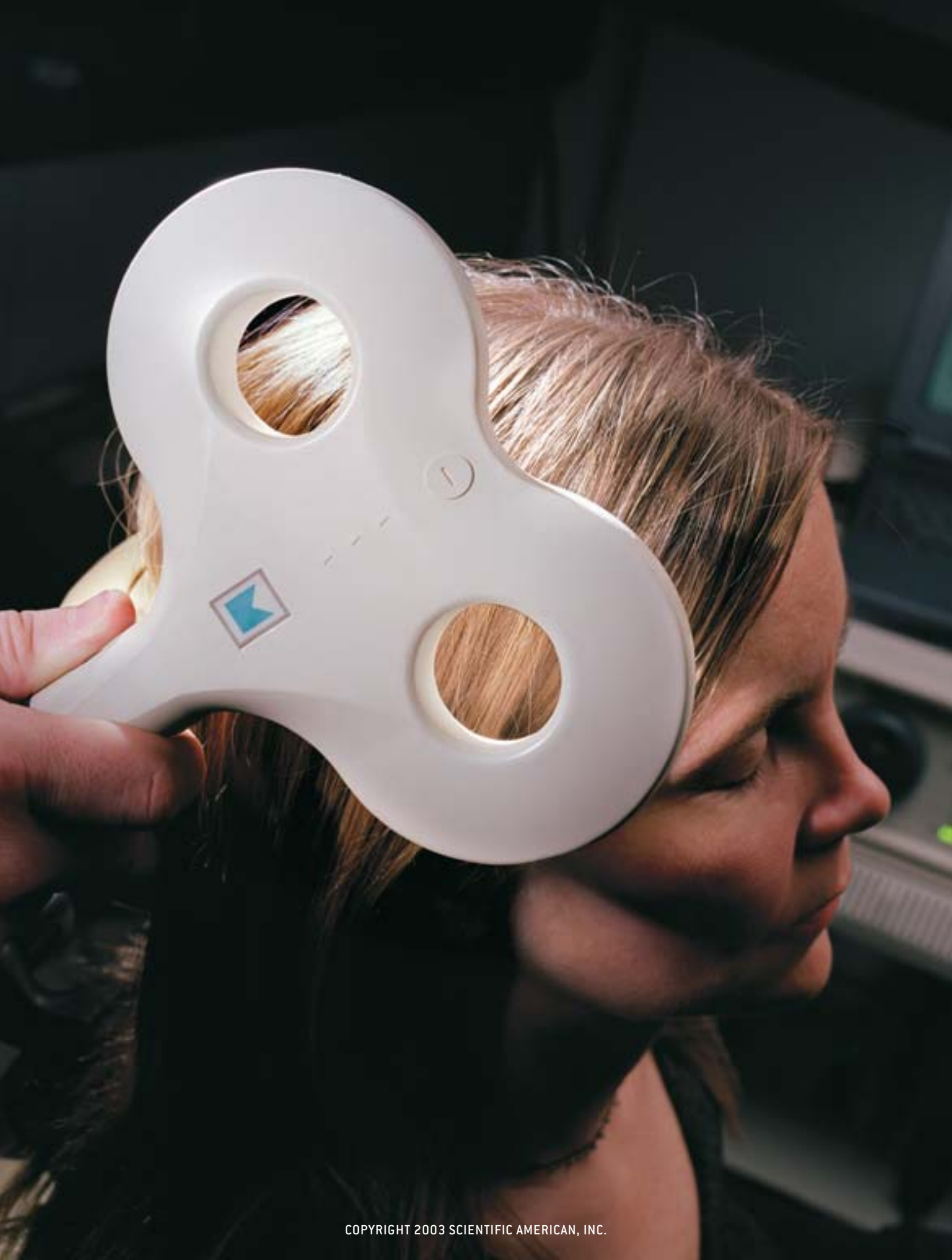


STIMULATING THE BRAIN

ACTIVATING THE BRAIN'S CIRCUITRY WITH PULSED MAGNETIC FIELDS MAY HELP EASE DEPRESSION, ENHANCE COGNITION, EVEN FIGHT FATIGUE

BY MARK S. GEORGE

BLEARY-EYED, THE PILOT STARES AT THE INSTRUMENTS while sipping stale coffee. The cup is nearly empty, as is the radar screen. So, he realizes, are the airplane's fuel tanks, not to mention his own energy reserves. Another cup certainly won't help much. His co-pilot dozes beside him, having already flown several legs of their long mission to deliver sorely needed humanitarian aid to the other side of the world. The pilot considers, then rejects popping a pep pill. Uppers make him jumpy, a bad feeling to have during the tricky nighttime aerial-refueling maneuver he will soon have to execute. Suddenly the radar shows a blip orbiting up ahead. Scanning the cloudy sky for the tanker's navigation lights, the pilot knows he has to get focused fast. He flips a switch. A "rat-a-tat-tat" sound, like that of a staple gun, echoes through his helmet, and fatigue abruptly flees his mind. Clear-headed for the first time in what seems days, the pilot almost immediately spies lights flashing in the murky distance. He nudges the co-pilot, who absently toggles his own switch as he stifles a yawn. Muffled snapping noises follow. Fully awake, the aviators steer for the flying gas station circling overhead.

In the scenario above, sharp sounds emerge when electromagnets inside the helmets generate magnetic fields to excite particular parts of the pilots' brains—areas that govern tiredness and wakefulness. Neuroscientists developing this novel noninvasive technique call it transcranial magnetic stimulation (TMS). TMS employs head-mounted wire coils that send strong but very short magnetic pulses directly into specific brain regions, thus safely and painlessly inducing tiny electric currents in a person's neural circuitry.

This scenario is still speculative, but research to make this promising technology a reality is advancing steadily. The Defense Advanced Research Projects Agency (DARPA) is funding several studies to investigate the use of TMS to improve the performance of U.S. service personnel exhausted by protracted field operations. And DARPA is not alone in its interest in TMS, because the procedure offers one of the most promising technological (nonpharmaceutical) methods to literally turn particular parts of the human brain on and off.

Some TMS researchers, for example, are inducing temporary brain "lesions" in healthy subjects to gain insight into fundamental neuronal mechanisms such as speech and spatial perception: they inhibit a basic brain function with a magnetic pulse stream and then compare the "before"

Wire coil containing time-varying electric currents generates brief magnetic pulses that cause brain cells to fire. Transcranial magnetic stimulation is being evaluated at Columbia University's College of Physicians and Surgeons.

JAMES SALZANO/IMAGING BY TRILOBYTE

condition with the "after." Other investigators are trying to determine whether the hyperactive brain regions that create epileptic seizures might be quieted with magnetic fields. Still other neuroscientists are attempting to employ TMS to alter the operation of specialized nerve cell networks to enhance people's memory and learning. Many of my colleagues are looking for ways to use the technology as an alternative to seizure-causing electroconvulsive therapy (ECT) to ease depression. Whatever the goals, TMS holds great potential as a tool for understanding how the brain works, correcting its dysfunctions and even augmenting its abilities.

The Electric Brain

TMS TAKES ADVANTAGE of the fact that the brain is fundamentally an electrical organ that transmits electrical signals from one nerve cell to the next. When a TMS coil is activated near the scalp, an extremely powerful and rapidly changing magnetic field travels unimpeded through skin and bone. Although the field reaches a strength of nearly 1.5 tesla—tens of thousands of times that of the earth's magnetic field—each pulse lasts for less than a millisecond. The popping sound it generates when it is operating arises from the passing of current through the insulated coil [*see illustration on opposite page*].

TMS offers a PROMISING METHOD to turn particular parts of the BRAIN ON AND OFF without drugs.

OVERVIEW/*Electromagnetic Excitation*

- Neuroscientists utilize a variety of electromagnetic stimuli to directly activate neurons in the brain. Electroconvulsive therapy (ECT), a procedure in which electrodes are attached to the scalp, is the best known of these techniques. Its use, however, remains somewhat problematic for various reasons.
- For a decade, researchers have been experimenting with pulsed magnetic fields that induce electrical activity in specific areas of the brain safely and painlessly. The ability of transcranial magnetic stimulation (TMS) to target specific brain regions is key to many new applications.
- TMS offers potential treatments for depression and other neurophysiological disorders. The technology may also provide a nonpharmaceutical method to rouse people from the effects of severe fatigue or to teach them a new skill.

In the brain, the magnetic field encounters resting nerve cells and induces small electric currents to flow in them. Thus, electrical energy in the copper-wire coil (typically encased in a paddlelike wand) is converted into magnetic energy, which is then changed back into electric current in the neurons of the brain. The $30,000 to $40,000 TMS machines are manufactured by the Magstim Company Limited in Whitland, Wales, by Dantec/Medtronic in Denmark and in Shoreview, Minn., and by Neuronetics in Malvern, Pa.

Unlike purely electrical techniques—such as ECT and others [*see box on page 73*], which involve attaching electrodes to the scalp or even to brain or nerve tissue—TMS creates a magnetic field that enters the brain without any interference or direct contact. The technique can be thought of as electrodeless electrical stimulation. Although magnetism does interact with biological tissue to some degree, the majority of TMS effects most likely derive not from the magnetic fields directly but from the electric currents they produce in neurons.

Magnetic Excitation

THE IDEA OF USING electromagnetic fields to alter neural function goes back to at least the early 1900s. Psychiatrists Adrian Pollacsek and Berthold Beer, who worked down the street from Sigmund Freud in Vienna, filed a patent to treat depression and neuroses with an electromagnetic device that looked surprisingly like a modern TMS apparatus.

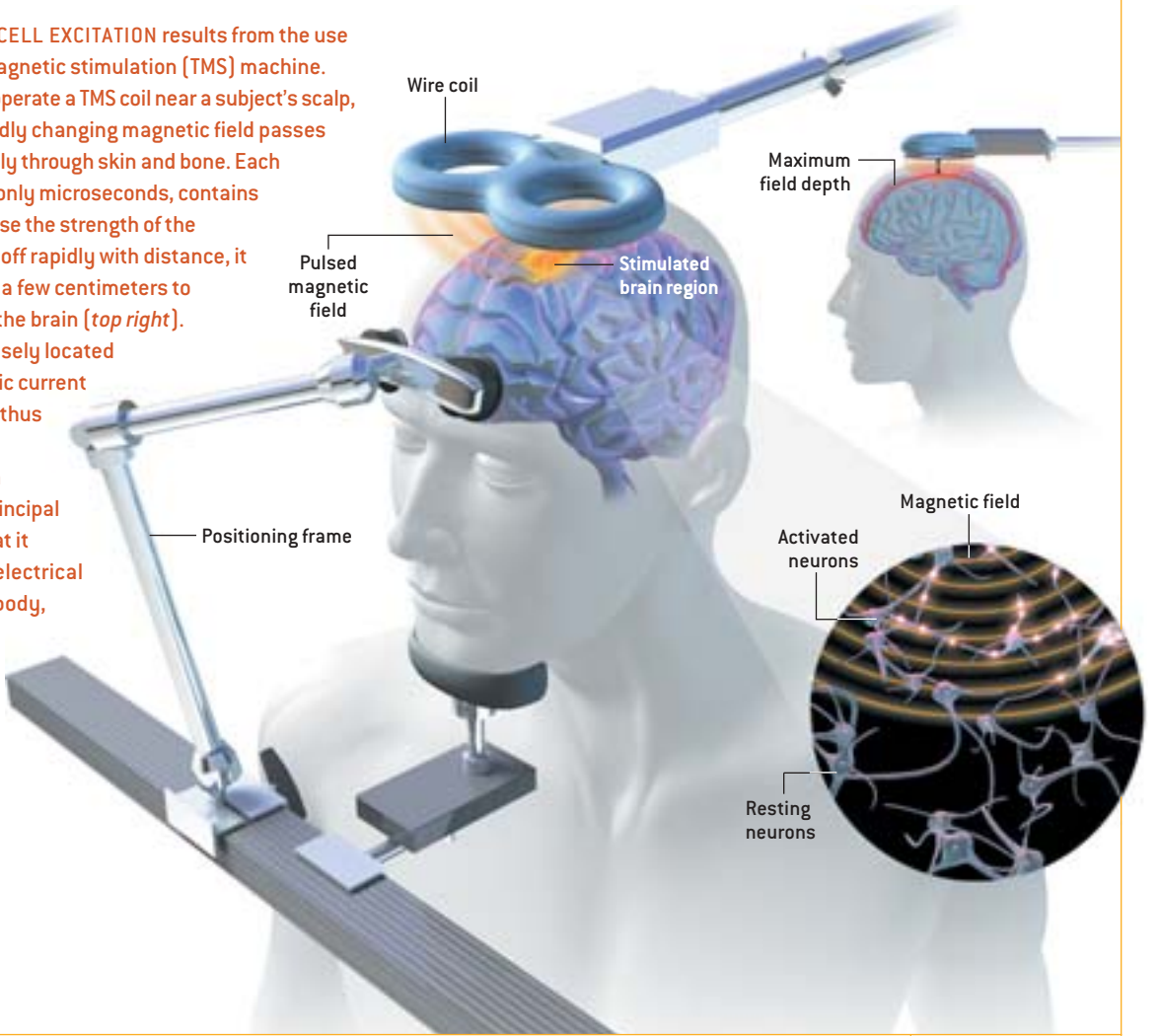
Today's TMS technology took shape in 1985, when medical physicist Anthony T. Barker and his colleagues at the University of Sheffield in England created a focused electromagnetic device with enough power to create currents in the spinal cord. They quickly realized that their equipment could also directly and noninvasively stimulate the brain itself. Since then, the field of TMS research has exploded.

Unfortunately, TMS devices can excite only the surface cortex of the brain because magnetic field strength falls off sharply with distance from the coil (maximum range: two to three centimeters). A magnetic field that can safely penetrate and activate the brain's central structures continues to be the Holy Grail of TMS research because it offers the possibility of treating difficult conditions such as Parkinson's disease [*see box on page 72*].

When researchers send a single magnetic pulse into the motor cortex of a subject's brain, it produces a jerk in the hand, arm, face or leg, depending on where the coil is placed. One pulse directed to the back of the brain can generate a flash of light in the eyes. That is the extent of the immediate effects of single-pulse TMS, however. Magnetic field pulses

TRANSCRANIAL MAGNETIC STIMULATION

LOCALIZED BRAIN-CELL EXCITATION results from the use of a transcranial magnetic stimulation (TMS) machine. When researchers operate a TMS coil near a subject's scalp, a powerful and rapidly changing magnetic field passes safely and painlessly through skin and bone. Each brief pulse, lasting only microseconds, contains little energy. Because the strength of the magnetic field falls off rapidly with distance, it can penetrate only a few centimeters to the outer cortex of the brain (*top right*). On arrival, the precisely located field induces electric current in nearby neurons, thus activating targeted regions of the brain (*bottom right*). A principal benefit of TMS is that it requires no direct electrical connection to the body, as is required for electroconvulsive therapy.



emitted in rhythmic succession, which neuroscientists call repetitive TMS, or rTMS, though, can induce behaviors not seen with the use of single pulses. These results are now the subject of intense study.

For brief periods during stimulation, rTMS can block or inhibit a brain function. Repetitive TMS application over the speech-control motor area, for instance, can leave the subject temporarily unable to speak. Cognitive neuroscientists have employed this so-called functional knockout capability to re-explore and confirm our knowledge about which part of the brain controls which part of the body, insights that have been gleaned from decades of studying stroke patients.

Field Learning

WHEN SINGLE NERVE CELLS are made to discharge repeatedly, they can form themselves into functioning circuits. Researchers have found that stimulating a neuron with a low-frequency electrical signal can produce what they call long-term depression (LTD), which diminishes the efficiency of the intercellular links. High-frequency excitation over time can generate the opposite effect, which is known as long-term potentiation (LTP). Scientists believe that these cell-level behaviors are involved in learning, memory and dynamic brain changes associated with neural networks. The chance that one could use magnetic brain stimulation to alter brain circuitry in a manner analogous to LTD or LTP fascinates many researchers. Although this controversial notion remains unresolved, several studies have

THE AUTHOR

MARK S. GEORGE is a practicing psychiatrist and neurologist as well as a research neuroscientist. George first studied the relation between mind and brain as an undergraduate philosophy student at Davidson College. His fascination with the human brain continued throughout medical school and dual residencies at the Medical University of South Carolina (MUSC). George investigated and developed new brain-imaging and brain-stimulation techniques during fellowships at the Institute of Neurology in London and the National Institutes of Health. He returned to MUSC eight years ago to run laboratories devoted to brain-imaging and brain-stimulation research.

BRYAN CHRISTIE DESIGN

shown nerve cell network inhibition or excitation lasting for up to a few hours after rTMS application. The implications of these results could be enormous. If one could employ rTMS techniques to change learning and memory by resculpting brain circuits, the possibilities are nearly endless. TMS might be used on a stroke patient to teach the remaining, intact parts of the brain to pick up the functions formerly conducted by the damaged region. Or overactive brain circuits that drive epilepsy might be toned down, resulting in fewer seizures.

Recent experiments in our laboratory at the Medical University of South Carolina (MUSC) and elsewhere hint that rTMS might temporarily enhance cognitive performance, either during application or for short periods afterward. Investigators at the National Institute of Neurological Disorders and Stroke, for example, found that TMS applied to the prefrontal cortex can enable subjects to solve geometric puzzles more rapidly.

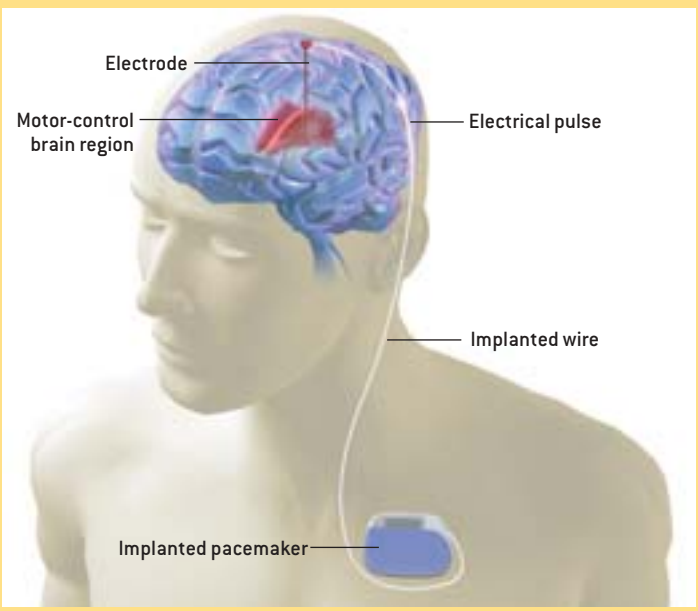
Most researchers working in this area stimulate subjects' brains over the prefrontal cortex or pari-

ZAPPING THE BRAIN

WHEREAS TRANSCRANIAL MAGNETIC STIMULATION of the human brain came into modern use in the 1980s, electrical excitation has been around for at least a century. David Ferrier and others in the 1880s showed that direct electrical brain stimulation could change behavior and that activation of specific regions correlated with certain behavioral changes. For the past 100 years, neurosurgeons have stimulated the brain electrically during brain surgery, cataloguing the resulting effects along the way.

Physicians have long known that electrical stimulation could be therapeutic as well. During electroconvulsive therapy (ECT), a doctor applies electrodes directly to the scalp of an anesthetized subject with the goal of inducing a generalized seizure. For reasons that are still unclear, repeated ECT sessions over the course of several weeks is an effective treatment for depression, mania and catatonia. The technique is, however, associated with memory loss and requires repeated general anesthesia. Because the skull acts as a large resistor that spreads direct electric current, ECT cannot be focused on or directed to specific targets within the brain.

Persistent shaking (*dyskinesia*) caused by Parkinson's disease can be lessened by *electrical* deep brain stimulation, imparted by implanted electrodes.



BRYAN CHRISTIE DESIGN

Of late, neuroscientists have explored other methods to electrically stimulate the brain. These new techniques tend to be either more focused or less invasive, or both, than the older ones. Employed in conjunction with the advanced brain-imaging technologies developed over the past two decades, these approaches are being used to build on our recently assembled understanding of how the brain works (*see table on page 73*).

Two direct electrical brain-stimulation techniques have been approved for therapeutic use. In deep brain stimulation (DBS), a neurosurgeon guides a small electrode into the brain through a small hole in the skull with the help of three-dimensional images (*left*). The surgeon then connects the electrode to a pacemaker (signal generator) implanted in the chest. The pacemaker sends high-frequency electrical pulses directly into the brain tissue. DBS is approved by the U.S. Food and Drug Administration for the treatment of Parkinson's disease, typically in patients who no longer respond to medication.

Within the motor-control circuitry of the brain, several regions (including the internal globus pallidus, thalamus and subthalamic nucleus) are inhibitory in function and so act as brakes on movement. In current practice, neurosurgeons place DBS electrodes in those regions and then stimulate them at high frequencies to arrest the shaking (dyskinesia) that characterizes Parkinson's. The technique is being explored as a treatment for depression as well. Little information exists concerning what happens when DBS is applied to other brain regions or when low-frequency pulses are used.

Theoretically, DBS electrodes can be removed with no lasting damage. Thus, the procedure represents an advance over traditional ablative brain surgery in which neural tissue is lost forever. In rare cases, DBS can, however, lead to infections, strokes and even death, so it is largely restricted to patients who have failed to respond to other therapies.

Another electrical brain-excitation technique now in use is vagus nerve stimulation (VNS). The vagus nerve is an important cranial nerve that connects the brain with the body's viscera. Eighty years of research has shown that stimulation of the vagus nerve in the chest or neck can alter the operation of brain regions involved in the control of bodily functions. In the 1980s Jake Zabara of Temple University discovered that excitation of the

etal cortex while they perform a task. To control for testing bias, neuroscientists also use deactivated ("sham") rTMS coils. Our lab is funded by DARPA to study whether rTMS might temporarily energize sleep-deprived individuals so they can perform better over the short term. Early results are promising. Another DARPA-supported group at Columbia University, led by Yaakov Stern and Sarah H. Lisanby, is exploring whether rTMS might be used to retrain subjects to accomplish a task in a different manner by shifting neural activity to an alternative cellular network that might be more resilient to stress or sleep deprivation.

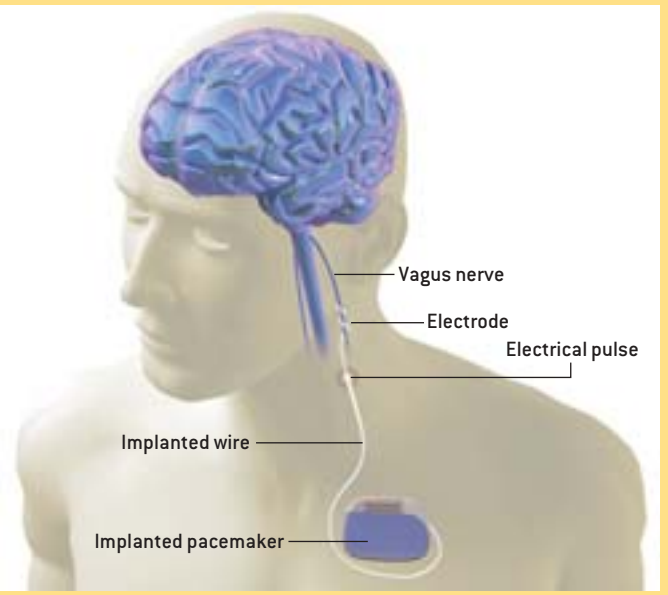
Recent media reports have made public Australian claims that TMS might be used to unleash nascent savant skills (mastery of difficult tasks without training) in healthy subjects by temporarily disabling one brain hemisphere. This work has not yet been published in the scientific press. In fact, most neuroscientists believe that the reported effects are unlikely to be true. Researchers have supervised TMS sessions involving thousands of subjects and have yet to witness any so-called savant skill changes. Although existing artistic talents occasionally improve with the onset of dementia, we have not seen savant abilities emerge after TMS-like stimuli such as focal brain disability caused by trauma, stroke or surgery or after brain areas are injected with anesthetics.

What Excites What

INTRIGUING AS THESE POTENTIAL applications might be, they raise difficult questions. Scientists would like to ascertain exactly which neurons rTMS affects as well as the detailed neurobiological events that follow stimulation. In addition to figuring out which electromagnetic frequencies, intensities and dose regimens might produce different behaviors, researchers must decide (for each individual) exactly where to place the rTMS coil and whether to activate it when someone engages in a task. Scientists also need more knowledge about what rTMS is doing at both the cellular level—the effects on neurotransmitters, gene expression, synaptic changes—as well as at the circuit level.

Further complication occurs because each person's brain is wired differently, so the location for behaviors varies. If one's motor area is close to one's skull, TMS might have a large effect. In someone else, whose motor area lies deeper in, TMS may have little or no effect on movement.

To better understand the effects of rTMS on brain circuits, physicist Daryl E. Bohning and others in our group at MUSC developed the ability to perform rTMS testing in combination with a functional magnetic resonance imaging (fMRI) scanner. Many researchers had thought that generating the powerful TMS magnetic fields within an fMRI machine was impossible or unwise. By applying rTMS within the scanner as subjects perform a task, however, one can know exactly where the stimulation is occurring and can image alterations to the neural circuit taking place because of the stimulus. Our group has shown that the brain changes that TMS causes when it makes your thumb move are very much the same as when you move your thumb in a



Direct electrical excitation of the vagus nerve in the neck can suppress the onset of brain seizures.

vagus nerve could abort a seizure occurring in a dog. This finding led to clinical trials of the technique and eventual FDA approval of VNS for suppressing seizures.

Surgeons typically wrap the VNS electrode around the left vagus nerve in the neck and connect it to a pacemaker they have implanted in the patient's chest wall (*above*). The VNS apparatus can be programmed to produce electrical stimuli in various intermittent patterns.

Researchers are now conducting studies to determine if VNS has therapeutic value for other disorders such as depression and anxiety. As with the other stimulation approaches, we do not know if changing how the VNS electrical signals are delivered would produce different brain effects. Our group at the Medical University of South Carolina has investigated VNS within a functional magnetic resonance imaging scanner to determine whether altering VNS parameters achieves different results. If it is confirmed, one might modulate brain regions by varying the VNS pulse pattern at the neck. No brain surgery would be needed. —*M.S.G.*

DEEP BRAIN MAGNETIC STIMULATION

TRANSCRANIAL MAGNETIC STIMULATION fields extend only a few centimeters to the surface of the cortex. Although TMS is promising for certain applications, the procedure could find much wider use if it could reach to the central structures of the brain.

High-intensity TMS fields could penetrate farther into the brain, but they can cause seizures, tissue damage or discomfort. Thus, a magnetic field that can safely penetrate and activate the brain's inner regions has remained the Holy Grail of TMS research for some time. Creation of such a field offers the possibility of treating difficult conditions such as Parkinson's disease. Though unlikely, it might even make it possible to energize the brain's "pleasure center" directly (think "Orgasmatron," from Woody Allen's film *Sleeper*).

An interdisciplinary team at the U.S. National Institutes of Health has invented a new TMS coil configuration that is designed to generate sufficient magnetic field strength to stimulate neurons deep inside the brain mass without posing a hazard. The research group included Abraham Zangen, Roy A. Wise, Mark Hallett, Pedro C. Miranda and Yiftach Roth.

According to Zangen, now a neurobiologist at the Weizmann Institute of Science in Israel, the prototype device is designed to maximize the electric field deep in the brain by summing separate fields projected into the skull from several points around its periphery. The device also minimizes the accumulation of electrical charge on the surface of the brain, which would give rise to an electrostatic field that reduces the magnitude of the induced electric field both at the surface and inside. The unique, form-fitting shape of the base of the new stimulator positions wire coils containing several wire strips that is set tangentially to the scalp's surface. Each set of strips is connected in series and contains current flowing in the same direction. Therefore, each set generates a field that extends into the brain in a specified orientation from each location along the scalp.

The prototype apparatus underwent an initial round of clinical evaluations this summer. Investors have recently established a company called Brainsway in Delaware to carry on the research and development effort and to commercialize the deep brain magnetic stimulator. *—The Editors*

similar pattern of your own accord. Two research groups in Germany have also succeeded in conducting rTMS studies within an fMRI scanner.

Magnet Therapy

IN THEORY, TMS could be a useful therapy for any brain disorder involving dysfunctional behavior in a neural circuit. Researchers have tried employing the technique as a treatment for obsessive-compulsive disorder, schizophrenia, Parkinson's, dystonia (involuntary muscle contractions), chronic pain and epilepsy. For most of these conditions, only a few inconclusive or contradictory studies currently exist, so the jury is still out regarding the effectiveness of TMS as therapy for them.

Most of these inquiries have concentrated on relieving depression. In the mid-1990s I was among the first researchers (along with several European groups) to investigate the use of daily rTMS sessions to treat depression. Perhaps, we thought, one could accomplish what ECT does for depressed individuals with TMS while avoiding seizures. My studies (at the National Institute of Mental Health) focused on stimulating the prefrontal cortex because that region appears abnormal in many internal images of depressed patients and because it governs deeper limbic regions involved in mood and emotion regulation. Double-blind studies soon indicated a small but significant antidepressant effect. A few patients at the NIH who had not responded to any other treatments had emerged from their depression and returned home.

Since then, more than 20 randomized and controlled trials of prefrontal rTMS as a treatment for depression have been published. Most of these studies show antidepressant effects significantly greater than sham electrode application, a conclusion that has been further confirmed by subsequent meta-analyses of the results. Whereas current consensus holds that rTMS offers a statistically significant antidepressant effect, controversy continues over whether these effects are sufficient to be clinically useful.

Because no commercial industry yet exists to promote TMS as an antidepressant therapy and because most of the studies have been relatively small (with considerable variation in rTMS methods and patient selection), the use of rTMS as a treatment for depression is still considered experimental by the U.S. Food and Drug Administration. The technique has, however, already been sanctioned for use in Canada, where it is now available. A large industry-sponsored trial designed to garner FDA acceptance is being planned. Even if the approach is approved, much additional research remains to refine it.

Repetitive TMS can, it should be noted, cause seizures or epileptic convulsions in healthy subjects, depending on the intensity, frequency, duration and interval of magnetic stimuli. In the history of the technique's use, TMS has led to eight unintended seizures, but since the publication of safety guidelines several years ago, no new seizures have been reported. Some scientists are investigating the potential positive application of this result. Harold A. Sackeim and Sarah H. Lisanby of Columbia have shown that a supercharged version of TMS, which they call magnetic seizure therapy (MST), can produce beneficial seizures in depressed patients (who are first anesthetized). Unlike ECT, MST allows users to focus on the site where the seizure is triggered. Better control over the seizure should block its spread to the regions of the brain responsible for

MELISSA SZALKOWSKI

ELECTROMAGNETIC BRAIN-STIMULATION TECHNIQUES

Neuroscientists employ electricity and magnetism to treat brain disorders. Each method offers different degrees of targeting accuracy.

	TREATMENT USE	PULSE DELIVERY	TARGETING ABILITY	ADVANTAGES	DISADVANTAGES
Electroconvulsive therapy (ECT)	Depression, mania, catatonia	Skin electrodes	Fair	Effective for depression; side effects reduced with newer systems	Nonfocal; can lead to memory side effects; requires repeated general anesthesia
Transcutaneous electrical nerve stimulation (TENS)	Pain, spasticity	Skin electrodes (attached to peripheral nerves)	Good	Does not require surgery	Limited access to brain
Vagus nerve stimulation (VNS)	Approved for epilepsy; FDA trials under way for depression and anxiety	Electrodes (attached to vagus nerve)	Fair	Does not involve brain surgery	Effects modest (to date); unclear how to tune pulses to alter brain function
Deep brain stimulation (DBS)	Approved for Parkinson's disease; under investigation for pain and obsessive-compulsive disorder	Electrodes (embedded in brain regions)	Excellent	Discrete targeting; marked effects	Potential side effects if incorrectly positioned; invasive brain surgery
Transcranial direct current stimulation (tDCS)	Under investigation for Parkinson's disease	Electric field	Unfocused	Noninvasive	Scalp irritation; nonfocal
Transcranial magnetic stimulation (TMS)	Under investigation for depression; FDA trials under way	Magnetic field	Excellent	Noninvasive and safe; potential for many applications	Limited to surface brain stimulation; effect on neural function still unclear
Magnetic seizure therapy (MST)	Under investigation for depression	Magnetic field	Fair	May offer better targeting and might avoid side effects of ECT	No efficacy data yet; requires repeated general anesthesia

the memory loss seen with ECT. Preliminary data indicate that MST has fewer cognitive side effects than traditional ECT techniques. More needs to be done to determine whether the MST really works and for which disorders it might be beneficial.

The technology of TMS is evolving as well. Our group at MUSC, for instance, has recently developed a portable TMS machine—an advance that may someday translate into the fatigue-fighting flight helmets depicted earlier. Extensive development is also proceeding on new designs and prototypes for coils that can stimulate more deeply inside the brain, that can be focused more finely or that operate in coordinated arrays. Most of our actions and thoughts arise not from activity in a single brain region but rather through the coordinated firing of many brain regions. If one could make several TMS coils, distributed over various key regions and fired in a coordinated way, new vistas might open up for TMS as a neuroscience tool and treatment.

After more than a decade of experimentation, TMS is still not FDA-approved to alleviate any disorder. Nevertheless, interest remains high among researchers who continue to believe in the intuitive aptness of using safe magnetic fields to turn specific brain regions on and off. If TMS proves itself, it could even lend some credence to the folk wisdom that humans use only a small portion of their brains. SA

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For more information on transcranial magnetic stimulation, visit **pni.unibe.ch/TMS.htm**

MIND READERS

BRAIN-SCANNING MACHINES MAY SOON BE CAPABLE OF DISCERNING RUDIMENTARY THOUGHTS AND SEPARATING FACT FROM FICTION

BY PHILIP ROSS

IMAGINE A WORLD YOU COULD TRUST—REALLY TRUST— where truth was transparent and juries, police, locksmiths and gossip columnists were largely overthrown. Human society would be orderly, boring and as alien as an anthill.

This is the promise and the threat of a machine that could read minds. The hoary polygraph has never filled the bill. It measures not thoughts but only the indirect physiological consequences of thoughts—blood pressure and respiration, among others—that hint that a subject may be lying. The result, critics charge, is false positives—an honest answer misjudged as a lie—and false negatives—a lie misjudged as the truth. The courts have long ruled polygraph findings inadmissible as evidence. Just last October the National Research Council damned the device as a "blunt instrument," of little use in ferreting out criminals, spies and terrorists.

Greek philosopher Diogenes walked with a lamp, in search of an honest man. Yet why shine your lamp into someone's face when you can look at the very brain? There you might do better than merely tell truth from lies. You might also converse with minds trapped inside paralyzed bodies, expose to analysis the suppressed fears and desires of the stormy unconscious, even observe the insights and errors by which a student moves toward the solution of a math problem.

The idea of looking directly at brain activity to tell truth from falsehood dates back roughly 20 years, to when J. Peter Rosenfeld of Northwestern University observed an interesting feature in the electroencephalograph, or EEG, a chart of the brain's electrical signals as detected on the surface of the skull. The P300 wave had already been known to be evoked by oddball cues, such as hearing one's name mentioned in a list of other words. Rosenfeld found that lying elicited it, too. He is now mapping the P300 wave across the scalp to get enough spatial resolution to improve the sensitivity of the test.

The next step appears to have been articulated for the first time by the often prophetic science columnist David Jones, a.k.a. Daedalus, who wrote in 1996 that "a modern magnetic-resonance brain scanner should be a perfect lie detector....

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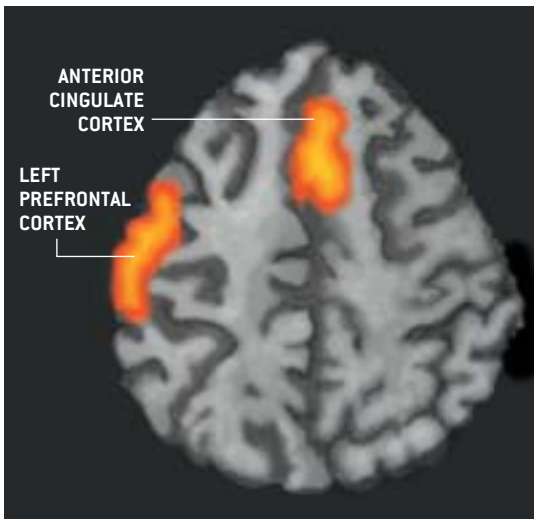
Telling the truth should activate just one site in the brain.... Telling a lie should activate two sites: one holding the lie and the other holding the truth that it is masking."

Five years later Daniel Langleben of the University of Pennsylvania and his colleagues used functional magnetic resonance imaging (fMRI) to scrutinize the brains of subjects acting out a question-and-answer series. Under certain conditions, the subject would tell a string of falsehoods in such a manner as to mimic lying; in other conditions, the subject would utter a string of truthful statements. The two brain images from each category were averaged and compared.

It turned out that all areas activated during truth telling were also triggered during lying but that a number of areas were active particularly during lying. "That suggests that the default position is truth, and deception is some sort of process you perform on truth," Langleben remarks. He notes that several areas activated more during lying—including the anterior cingulate cortex and part of the left prefrontal cortex—are associated with suppression of response, as when the brain decides to go with one of



A graphical rendition of a brain slice highlights two areas that are more active when a subject falsely denies possessing the five of clubs than when the person tells the truth.

two conflicting responses and must therefore inhibit the other one [*see illustration above*].

According to this theory of "cognitive load," actor Sean Connery, when asked his name during the filming of a movie, cannot help but flash to the words "Sean Connery"; it is only with a modicum of effort that he chokes off that response to say instead, "Bond. James Bond." So far two other fMRI groups have published similar research; more have written papers now wending their way to publication.

None of these groups have yet claimed much power in catching a particular hostile witness in a particular lie. "As a practical method, this thing is not even in the proof-of-concept stage," Langleben admits. "In April [2004] we will take the next step and try to determine the size of the truth-versus-lie effect at a given spot in the brain." He expects to use a larger sample, 60 to 90 subjects, and to create situations closer to real-life deception—perhaps a poker game. (It might be a little hard to simulate, though, inside a churning, claustrophobia-inducing MRI machine.)

BRAIN IMAGING follows processes that are MUCH CLOSER TO THOUGHT than the pulse, skin conductance and respiratory rate measured by A POLYGRAPH.

In principle, brain imaging is better than a polygraph, he argues, for two reasons. First, it seems to have nothing to do with general anxiety, whereas polygraphs have almost everything to do with it. Indeed, polygraphs are often used to instill fear as much as to detect it (like the "fear-o-sensor" that a dog waves over a stranger in one of Gary Larson's cartoons). Second, brain imaging follows a phenomenon that is much closer to thought, in the train of events, than are the pulse, skin conductance, respiratory rate and so on—"output that is 10 times removed from what's happening in the brain," Langleben says.

Even fMRI does not sample the neurons themselves, though, but just the oxygen in the nearby bloodstream. More precisely, it measures the ratio of oxygenated to deoxygenated blood. The machine can pinpoint metabolic activity at good resolution, of about four millimeters in diameter, yet it is relatively slow, tracking activity occurring for two seconds or so. That's not really fast enough to catch a thought.

To capture that level of complexity would require recording a signal lasting for mere milliseconds, providing a snapshot of, say, calcium ions in the neurons themselves. To detect it, however, would require magnets several times as powerful as even Langleben's four-tesla unit. No such magnets big enough for humans exist, and, for safety reasons, none are likely be approved for that purpose. "I can tell you there won't be human studies in 20-tesla machines," asserts Marcus E. Raichle, an fMRI researcher at Washington University. "It can stimulate the vestibular system, making you feel dizzy; it can heat up the brain, manipulating the very thing you're supposed to study."

Another approach to get good resolution in both space and time might come by combining fMRI with EEG. One might measure both things at the same time, or correlate a lie-detecting component of fMRI with a given aspect of EEG. "If we did that, we could

LUCY READING (*left*); JAMES SALZANO (*right*)

discard fMRI and use the EEG signal, and it would be 10 times cheaper," Langleben says.

Although it may be too hard for today's brain scanners to trap a hostile witness or a cheating spouse, they may well suffice to divine certain, simple thoughts of a willing communicant, leading to a more general form of mind reading. Unlike lie detection, the task, of course, is made simpler when the subject cooperates with the testing. Already monkeys with electrodes implanted in motor-control areas of their brains have been taught, through biofeedback techniques, to convey neural impulses over an Internet connection to manipulate a robotic arm [see "Controlling Robots with the Mind," by Miguel A. L. Nicolelis and John K. Chapin; SCIENTIFIC AMERICAN, October 2002]. Niels Birbaumer of the University of Tübingen in Germany has reported a degree of success in using biofeedback to train patients immobilized by nerve damage to vary their brain waves and so to spell out sentences on a computer screen.

But true mind reading must do better, by catching a word or concept exactly as it forms itself in the brain. Marcel A. Just of Carnegie Mellon University claims he has done just that with fMRI, by limiting the concepts to a small number and keeping them very simple—carpentry tools, for instance, or kinds of dwellings. "We have 12 categories and can determine which of the 12 the subjects are thinking of with 80 to 90 percent accuracy," he explains. He is even better at distinguishing brains reading a clear sentence from those reading an ambiguous one or imagining a verb as opposed to a noun.

Just's colleague Tom Mitchell, a computer scientist, has devised a means to classify the complex brain images that their experiments produce. He analyzes them with neural networks, a type of software that can tune itself to improve its ability to distinguish patterns. "If isolated words can be identified with some degree of accuracy, it ought to be possible to do even better with entire sentences," Mitchell says. That is because sentence structure constrains the possibilities that the neural network must consider. "If you know that a sentence has two words, then one must be a verb, the other a noun.

"One experiment I would love to do is to find words that produce the most distinguishable brain activity," he adds. Such words might serve as the building blocks for a neural interface, much as particularly discriminable English words were favored in the early, limited-vocabulary protocols of voice-processing software.

Should this concept-recognition system work with even minimal reliability, it might be coupled with lie-detecting fMRI software to produce a much more sophisticated tool. In principle, law-enforcement officers might use the combination technology to tell not only that a bank robber is lying but that the loot is stashed in the garage.

A brain decoder that worked on all brains still might not allow for telepathy on the order of a Vulcan mind meld in the *Star Trek* series, which enabled universal translation. An English sentence, beamed into the mind of a non-English speaker, might seem gibberish. Even if the receiving (or eavesdropping) person spoke the same language, he might be puzzled by the idiomatic dialect in which a mind converses with itself, with all its coded entries, abbreviations and emotional associations.

Concocting near-perfect lie detection may, nonetheless, be much easier than making a sophisticated thought reader—and almost as dangerous to mental privacy. Indeed, it would not be necessary to employ such a machine—the threat of its use would exercise a powerful deterrent force.

fMRI can determine which of 12 SIMPLE CATEGORIES a subject is contemplating with 80 TO 90 PERCENT accuracy.

As Daedalus concluded, "Like the atom bomb, it is best reserved as a sort of ultimate social weapon. If widely deployed outside the courtroom, it would make social life quite impossible." SA

Philip Ross writes on science and technology from New York City. His work has also appeared in Acumen Journal of Sciences, IEEE Spectrum, Forbes, *and the* New York Times.

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THE MUTABLE BRAIN

SCORE ONE FOR BELIEVERS IN THE ADAGE "USE IT OR LOSE IT." TARGETED MENTAL AND PHYSICAL EXERCISES SEEM TO IMPROVE THE BRAIN IN UNEXPECTED WAYS

BY MARGUERITE HOLLOWAY

"THE BRAIN WAS CONSTRUCTED TO CHANGE," ASSERTS Michael M. Merzenich as he sits in a small conference room at the University of California at San Francisco Medical Center. The large windows to his left look out onto a hill thick with eucalyptus trees, their branches moving now this way, now that, in the morning's wind. Merzenich's observation—no longer so radical as it was when he and a handful of others put it forth in the 1980s—is that the brain does the same: it moves this way, then that, depending on how experience pushes it. This may seem an obvious idea: of course our brains revise themselves—we learn, after all. But Merzenich is talking about something bigger: this ability of the brain to reconfigure itself has more dramatic implications.

It is as if the brain is a vast floodplain. One year the water might run eastward in a series of small channels; the next it might cut a river deep through the center. A year later, and a map of the floodplain looks completely different: streams are meandering to the west. It is the same with a brain, the argument goes. Change the input—be it a behavior, a mental exercise, such as calculating a tip or playing a new board game, or a physical skill—and the brain changes accordingly. Magnetic resonance imaging machines reveal the new map: different regions light up. And Merzenich and others who work in this field of neuroplasticity are not just talking about young brains, about the still developing infant or child brain, able to learn a first language and then a second in a single bound. These researchers are describing old brains, adult brains, your brain.

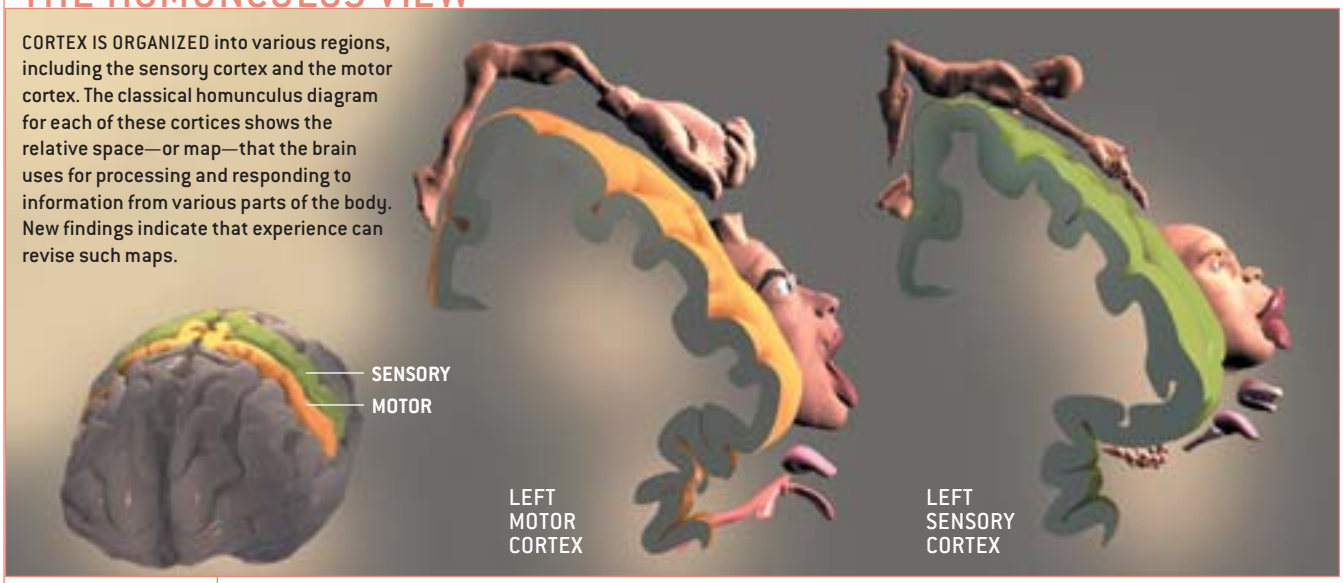
They are saying that the brain can be extensively remodeled throughout the course of one's life, without drugs, without surgery. Regions of the brain can be taught to do different tasks if need be. If one area has dysfunction or damage, another can step in like an understudy and play the role. Such task shifting has been reported in stroke patients who have lost speech or motor ability, cerebral palsy patients, musicians or workers who can no longer move one finger at a time, and those with obsessive-compulsive disorder or reading disorders. A series of intense mental and physical exercises have undone the effects of injury.

The next step, Merzenich and colleagues say, is to expand and refine these treatments and to investigate exercise-based tasks that can ameliorate

MELISSA SZALKOWSKI

THE HOMUNCULUS VIEW

CORTEX IS ORGANIZED into various regions, including the sensory cortex and the motor cortex. The classical homunculus diagram for each of these cortices shows the relative space—or map—that the brain uses for processing and responding to information from various parts of the body. New findings indicate that experience can revise such maps.



schizophrenia, Parkinson's disease, the memory loss of aging, autism and a host of other problems. "One of my dreams is to find all the ways that you can use the plasticity processes of the brain to drive correction," Merzenich muses. "My belief is that this sort of thing will be part of a normal future life. It will be understood that you have to exercise your brain and that there are specific things that you have to do."

To many people—those who meditate or practice biofeedback or undergo psychotherapy—this idea may seem intuitive: focus your effort in certain ways, and your brain, as glimpsed through your behavior, will alter. Within the neuroscience and medical communities, however, this idea and its potential clinical uses are new. "If you go back to the late 1970s and the1980s, people thought of the brain as a hardwired black box," notes Thomas P. Sutula, director of the center for neuroscience at the University of Wisconsin–Madison. "This whole area is as close to a revolution in concept as you can imagine."

Yet it is a nascent revolution and one that is hard to get a handle on, perhaps in part because one of its leading figures is so difficult to pin down. Mention Merzenich's name to a neuroscientist, and he or she will most likely celebrate his brilliance and the importance of talking with him in one breath and in the next add "if you can find him." People talk of being mesmerized by his vision during a presentation, only to wonder a few days later what the data were: "Where's the beef?" asks one scientist. "He is a phantom," jokes another. Some scientists are chary of Merzenich because he started a for-profit company to develop plasticity-based therapies and feel that he has rushed to market without adequate testing.

Beyond the controversy surrounding Merzenich lie the fundamental questions of this new field. Although researchers have laid the foundation for appreciating skill-based or experience-driven neuroplasticity, there are many unknowns. The limits of it, for one. No one knows just how plastic the adult brain is as opposed to the child's—except that it is less so. No one fully understands how plasticity operates at all its various levels, from electrical pulses and neurotransmitters on up to the synapses, networks and specialized regions of the brain. And no one knows how much one part of the brain may lose when it shoulders another's burden—what the "dark side," as some researchers put it, might entail.

OVERVIEW/*Remolding the Brain*

- Contrary to long-held belief, the structure of the adult brain is not set in stone. More readily than was once thought, one region can step in and take over the function of another.
- Researchers are harnessing this neuroplasticity to treat people with reading disorders, stroke and forms of repetitive stress injury, among other conditions.
- Some scientists hope to use physical exercises and computer-based games to help individuals retrain their brains to overcome memory problems and various mental disorders.

Of Synapses and Sections

"'PLASTICITY' IS THE MOST abused word in neuroscience," declares Roger Nicoll, whose U.C.S.F. laboratory is just across town from Merzenich's. The term has come to describe virtually any change in the brain, from the chemical level to the formation of new neurons (a process called neurogenesis) to the remapping of larger regions. At its most basic, however, it is what Nicoll studies: the plasticity of the synapse, which is the place where neurons

ALFRED T. KAMAJIAN

communicate with one another by way of chemical signals, or neurotransmitters. Learning entails strengthening connections between neurons—by creating more connections between neurons as well as by enhancing their ability to communicate chemically. These changes link neurons in a chain that can be retraced to evoke a certain movement or feeling or thought, a phenomenon captured in the oft-quoted phrase "Neurons that fire together, wire together." It is at the level of the synapse that neuroplasticity lives or dies.

Until the mid-1960s it was thought that adults could not form new synapses, that the connections between neurons were frozen into position once brain development stopped. Then studies began to suggest that this was not so. For instance, researchers Geoffrey Raisman and Pauline M. Field, then at Oxford University, demonstrated that there was synaptic plasticity in adults. Others, including Mark R. Rosenzweig of the University of California at Berkeley and William T. Greenough of the University of Illinois and their colleagues, made dramatic discoveries about how environment and experience affect the brain. Greenough, for example, demonstrated that both young and mature rats could establish new synapses if they were given challenging tasks or placed in "complex environments"—which, he points out, are simply very nice cages with nice toys, "certainly not as challenging intellectually as the environment in which they are normally found." These synapses gave rise to enhanced memory and motor coordination.

These studies of exercise and what has come to be called enrichment (providing stimulation through toys or tasks) continue to flower and are being mined for their clinical applications. Stimulation and exercise speed recovery from brain injury in rats, and recent research has suggested that if mice carrying a Huntington's gene are placed in a complex setting, the development of the disease is delayed. Greenough and other investigators have connected these effects not only to the creation of synapses but to the creation of blood vessels and of brain cells called astrocytes—which are important in mopping up excess materials, such as potassium, and in maintaining an optimal environment for neurons. The formation of myelin, a lipid sheath that covers nerve axons and is crucial for their survival and effectiveness, is also enhanced in these situations.

Appreciation for plasticity at a larger scale—at the level of an entire network of neurons or a region of the brain—came well after the recognition of synaptic plasticity. It was, however, an old suggestion. In the late 1800s and early 1900s several scientists had proposed that the brain was plastic, shaped by experience. William James, for example, had posited that the brain is constantly changed by experience, and in the 1920s Karl Lashley found that the motor cortex of monkeys seemed to change every week. Similar work continued through the 1970s, but the findings of scientists who felt the adult brain was fixed and unchanging predominated: the brain changed massively only during infant development and early childhood, so-called critical stages. "The religion developed from the mainstream," Merzenich notes, "and the mainstream thought that the brain was like a computer that established its critical functionality in critical periods."

People THOUGHT of THE BRAIN as a hardwired BLACK BOX.

In the 1980s a series of experiments by Merzenich and his collaborators, including Jon Kaas of Vanderbilt University, revealed that an adult monkey's motor cortex could undergo change. The cortex—the outer part of the brain where, in humans, regions for language and reasoning reside—is organized into areas for sensory, motor, auditory and other information. In one study the researchers am-

REMAPPING OF THE HAND

IN A NOW CLASSIC monkey experiment, Michael M. Merzenich demonstrated the plasticity of the brain's cortical maps. After he cut a nerve conveying information from a part of a finger or hand (*shaded areas on left*) to a specific patch of cortex, he found that the same cortical patch began responding to regions of the hand that it did not serve before (*shaded areas on right*). What is more, the areas represented in that cortex expanded as time went by.

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putated a monkey's finger and saw that the place in the motor cortex that had been activated by that finger was soon showing responses from neurons conveying information from an adjacent finger, indicating that the brain area originally devoted to the lost finger was now monitoring and processing information from the next one. Squatters had immediately laid claim to the abandoned site. "That was an awakening to me," Merzenich reflects.

It was a revelation to the neuroscientific community at large as well. "He was one of the first to do work showing that these [neural] maps moved, and I was stunned," recalls Bryan Kolb, a leading neuroplasticity researcher at the University of Lethbridge in Canada. "People thought there was a genetic blueprint of the brain and how things were organized. No one suspected that changes could have been detected at that gross a level."

The squatters had come from right next door, though, mere millimeters away. Then, in 1991, invaders were found to travel whole centimeters. The foundations for this discovery had been laid many years earlier when Edward Taub, now at the University of Alabama at Birmingham, severed some of the nerves of one arm in a few monkeys to see what happened to their brains as a result. Taub was forced to abandon his research on the Silver Spring monkeys, as they came to be known, because of a lawsuit by animal-rights activists. For a while, his investigations came to a halt.

Years later those same monkeys were examined by Tim P. Pons of the Wake Forest University School of Medicine, Taub and other scientists, who found something remarkable. The area of the brain that had originally received information from the now useless arm was receiving information from the face. The changes extended across great distances. "There was huge reorganization in the cortex that no one thought possible," explains Ford Ebner of Vanderbilt University. "It was another milestone." The adult brain was clearly a dynamic and efficient landlord: no empty space went unused.

Constraint-induced movement therapy works on the principle that a person can be taught to use another part of his or her brain to take over the function of a damaged or dysfunctional area. By restraining his unimpaired arm, this patient forces his brain to relearn how to use the arm affected by stroke.

ELIZABETH DERAMUS

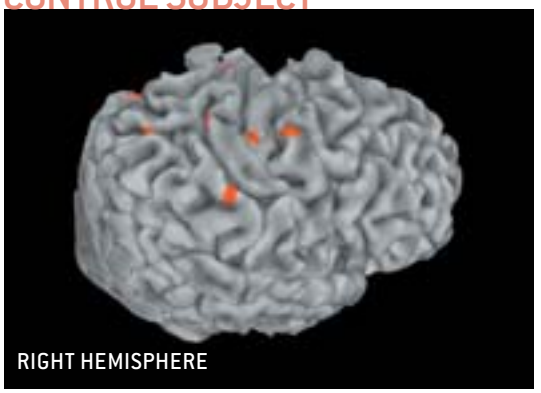
Musical Maps

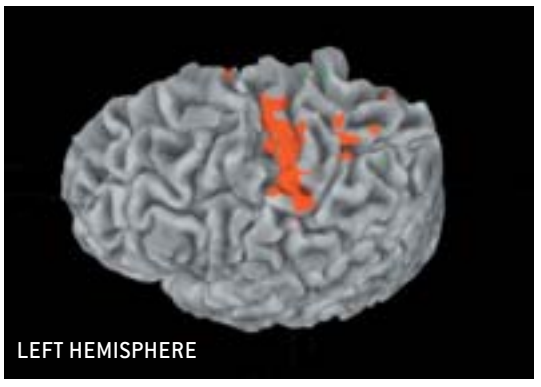
OVER THE PAST TWO DECADES, the research in monkeys has converged with evidence in humans, and cortical plasticity has become an accepted characteristic of the adult brain. In people who have lost a limb, studies show that the space that formerly deciphered information from that limb can serve the stump or the face. In string musicians, the area of the cortex governing the fingering hand is larger than that of the nonfingering hand, and the most-used fingers take the largest space. In Braille readers, the visual cortex becomes active as they touch their fingers to the bumps.

As all these data converged, Merzenich, Taub and others tried to figure out how to use them to benefit those with various injuries or disabilities. "We knew that the brains of children and adults are plastic throughout life," Merzenich says. "And that led us to a simple question: Can we drive changes in the brain at an older age that would be corrective?"

The strongest evidence so far that the brain can be healed by its own plasticity comes from work with stroke patients that Taub and his colleagues began in the 1980s. During earlier experiments, Taub had discovered that monkeys whose arm nerves had been severed could still move their arm if they were forced into doing so by an electric shock. It turns out that people who have lost motor function because of stroke can also learn to use their limb again. By restraining the good arm and having patients perform intensive motor tasks and training with the weak arm for many hours a day for two weeks, Taub and his co-workers—including Wolfgang Mitner of the University of Jena and Thomas Elbert of the University of Konstanz, both in Germany—forced patients to get their seemingly dead limb to move again. Such treatment is called constraint-induced (CI) movement therapy. "The traditional wisdom in the field was that after one year, there was no recovery of function," Taub explains. Yet some patients—even those whose strokes occurred 20 or more years earlier—have been able to use their arms effectively again.

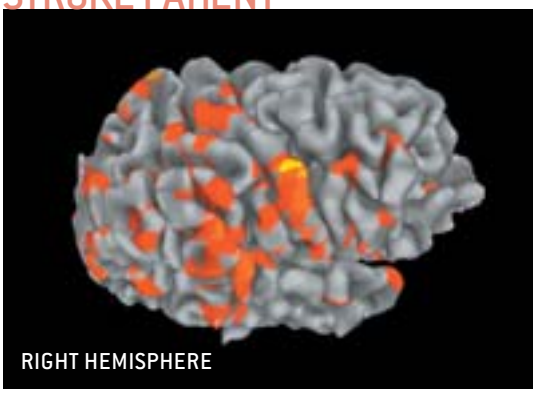
CONTROL SUBJECT

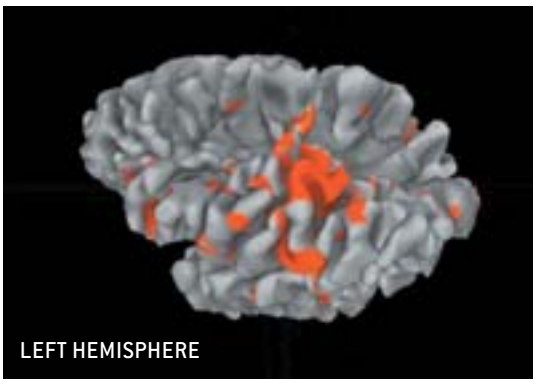




Active brain regions (*red* and *yellow*) can be seen in these fMRI images of a control subject's two hemispheres (*left*) and those of a stroke patient (*right*). When the control subject opens and closes his right hand, the left motor cortex lights up. After rehabilitation, a stroke patient with severe left hemisphere damage uses many areas of the cortex in both the right and left hemispheres to do the same, suggesting that the brain has reorganized to allow for this movement.

STROKE PATIENT





DANIEL B. HIER AND JUN WANG *University of Illinois at Chicago*

The recovery is reflected in the shifting maps of the subjects' brains. "The CI therapy had recruited large new areas of the cortex adjacent to the damaged area," Taub points out. Other groups have seen this as well, and CI therapy is now practiced in various institutions. A recent study by Daniel B. Hier of the University of Illinois at Chicago determined that cortical patterns in stroke patients also shift after another form of rehabiliation.

Although the practice is widespread in various forms, many experts are awaiting further study before they embrace it. To this end, the National Institutes of Health has funded a six-site clinical trial of CI therapy. It will be important to get replication, notes Jordan Grafman of the National Institute of Neurological Disorders and Stroke. Investigators need to know, he says, "whether CI therapy works for some kinds of patients and not others and when after injury it should be done. You need a lot of studies."

Taub, Elbert and their colleagues have begun to use CI therapy to treat children with cerebral palsy. They have also successfully rehabilitated stroke victims who have lost their ability to speak well. These aphasic patients have repeated certain sounds for hours a day. The "constraint" in this method does not entail any "restraint," as the motor therapy does. It is essentially just intensive practice of words and sounds.

Taub and others, including Merzenich and Nancy Byl of U.C.S.F., have used similar therapy to help musicians and workers recover the use of individual fingers. Sometimes when people use a series of fingers over and over again in quick succession, the distinctions between regions in the cortex begin to blur. One finger's zone melds into another's. The result is focal-hand dystonia: try to raise one finger, and another or several inevitably come along, too. By using repetitive tasks that are very distinct for each finger, the researchers say they have been able to restore the original boundaries of the map.

Merzenich has also turned his attention to language disorders and dyslexia in children—as well as some adults—and it is this research that has earned him a degree of enmity and skepticism. In the mid-1990s he joined forces with Paula Tallal of Rutgers University to form Scientific Learning, a company that produces and sells a computer-based program called Fast ForWord. The idea the two had, based on insights from their independent research, was that by slowing down certain sounds—such as "ba" and "da"—children who were having trouble processing language could quickly begin to hear the distinct sounds, the "b" separated from the "ah." Over hundreds of repetitions—training during games that can last for 20 hours a week for months—these sounds could gradually be sped up and, in time, the child would learn to hear and process the sounds at normal speed. According to a recent paper in *Proceedings of the National Acade-*

my of Sciences by Merzenich, Tallal and a group of researchers, dyslexic children participating in Fast ForWord not only improved their reading skills, but their brains changed—different regions were processing language.

Although some researchers believe that this technique might well prove itself, they await independent reviews and replication before they are convinced. Guinevere F. Eden of Georgetown University Medical Center notes that there have been no controlled studies of reading improvements: the kids with reading problems who received the intervention have not been compared with another set of dyslexics who did not. "You would expect kids to be better on the second round of a task because they are always better on the second test—even if nontrained," Eden observes, adding that computer-based games often increase players' attention, so improvement might have more to do with attentiveness as opposed to language processing. And she worries that parents will develop hopes that won't be realized or will spend too much money purchasing the software: "It is a very vulnerable group, and it is a pity that the system isn't in place to protect them more."

Merzenich dismisses these criticisms, scoffing at the idea that the studies he is a party to—such as the recent one in *PNAS*—could be biased. And he says he has no regrets about forming Scientific Learning, except that the programs have not yet reached as many kids as he would have hoped. For some in the field, this business interest has tarnished Merzenich's accomplishments; his research will always be colored by commercial interest. But others applaud it. "It is great to go sit in your lab, but better for people to act," Sutula says. "You can make people's lives better."

And the company offered a practical solution for one of the principal problems of the field of applied neuroplasticity: the gulf between the neuroscience and the rehabilitation communities. "There is a lot of interesting knowledge about how to improve function in people," Grafman notes. "But translating that into rehabilitation has been painful and slow."

"It is very important that the research get carried out, and it is almost impossible to get funding to do this," Taub agrees. To the rehabilitation community, several of these ideas "seem out of left

Reading program designed by Michael M. Merzenich and Paula Tallal seeks to rewire the brains of children with dyslexia or other problems. The controversial computer-based strategy, called Fast ForWord, has not been independently assessed so far, but the researchers say they have found significant improvement in children's reading comprehension.

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field," he says. "Although from the point of view of neuroscience, it is absolutely straightforward."

Limits of Plasticity

MERZENICH'S CURRENT preoccupation may seem even further afield. He is investigating whether training and games can reverse or ameliorate schizophrenia, autism and the memory loss that can accompany aging. As yet, there are no published data to turn to. And Merzenich is not forthcoming about his collaborators either. Although he granted a long interview and opened up his lab, Merzenich never responded to my requests for further information—despite his promises to provide names and despite myriad follow-up phone calls and e-mail messages.

But if his idea bears fruit, it will be stunning. Merzenich believes that the neurotransmitters that underlie memory can be bolstered during tasks performed while sitting at a computer. "Just as in kids that are having problems with learning and memory and whatever," he argues, "the machinery is plastic. And you can almost certainly drive positive changes in the brains of elderly individuals by engaging that machine." He says he can discuss results soon and that the same principle will apply—and is already working—for autistic patients and people with Parkinson's disease. "We are overwhelmingly dominated by thinking that we are going to fix everything in the brain by drug manipulation or by some change in the status of the physical structure of the brain, because it is deteriorating," he asserts. "But a computer-directed exercise can be very efficient. Because it can pound your brain in a highly controlled way." For example, patients could play a computer game in which they won money or overcame obstacles; the positive reward could trigger the release of, say, dopamine—a neurotransmitter associated with the experience of pleasure and one that is also progressively lost in certain illnesses, such as Parkinson's.

Researchers are waiting to see the beef. And to understand what the limits of plasticity are. "My fundamental concern about Mike's view is that he doesn't take the role of genes as seriously as the data suggest," says Steven E. Hyman of Harvard University. "He is a brilliant zealot for plasticity—we need his voice. But ultimately I fear our brain may not turn out to be as plastic." Others wonder what the costs might be—for instance, could triggering plasticity at some point diminish the brain's ability to flourish later on?—and how drugs could be combined with an understanding of neuroplasticity to get fuller recovery. "The sky's the limit, and we are trying to figure out the rules," Kolb states.

In the meantime, evidence from other quarters seems to bolster Merzenich's fundamental belief that healing plasticity can be driven by behavior. Jeffrey Schwartz of the University of California at Irvine has reported brain remapping in people with obsessive compulsive disorder who have undergone behavioral training. They have apparently remolded their brain to avoid certain patterns of thinking. Researchers at Laval University's Geriatric Research Unit in Quebec have suggested that exercise is protective against the development of Alzheimer's disease. A study last year in the *Journal of the American Medical Association* indicated that mental activity, such as reading the newspaper every day, could keep Alzheimer's at bay; a large-scale federal study came to the same conclusion.

THE SKY'S THE LIMIT, and we are trying to figure out the rules.

And during the eight years after his riding accident, actor Christopher Reeve has apparently exercised himself out of paraplegia into a state where he can move his fingers and toes and push with his legs. His recovery marks the first time such extensive reconnection of the spinal cord to the brain has been recorded after such a long period. His brain lights up in unexpected places. "The nervous system is capable of doing all sorts of things," declares Reeve's physician, John W. McDonald of the Washington University School of Medicine. As for fixing the brain, he says, "We just don't know yet which kinds of mental tasks can correct which problems." Merzenich would probably say he knows—if you could get him on the phone. SA

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MORE TO EXPLORE

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TAMING STRESS

AN EMERGING UNDERSTANDING OF THE BRAIN'S STRESS PATHWAYS POINTS TOWARD TREATMENTS FOR ANXIETY AND DEPRESSION BEYOND VALIUM AND PROZAC

BY ROBERT SAPOLSKY

PHOTOGRAPHS BY JAMES SALZANO

OVER THE CENTURIES, SOCIETY'S APPROACHES TO TREATing the mentally ill have shifted dramatically. At present, drugs that manipulate neurochemistry count as cutting-edge therapeutics. A few decades ago the heights of efficacy and compassion were lobotomies and insulin-induced comas. Before that, restraints and ice baths sufficed. Even earlier, and we've entered the realm of exorcisms.

Society has also shifted its view of the causes of mental illness. Once we got past invoking demonic possession, we put enormous energy into the debate over whether these diseases are more about nature or nurture. Such arguments are quite pointless given the vast intertwining of the two in psychiatric disease. Environment, in the form of trauma, can most certainly break the minds of its victims. Yet there is an undeniable biology that makes some individuals more vulnerable than others. Conversely, genes are most certainly important factors in understanding major disorders. Yet being the identical twin of someone who suffers one of those illnesses means a roughly 50 percent chance of *not* succumbing.

Obviously, biological vulnerabilities and environmental precipitants interact, and in this article I explore one arena of that interaction: the relation between external factors that cause stress and the biology of the mind's response. Scientists have recently come to understand a great deal about the role that stress plays in the two most common classes of psychiatric disorders: anxiety and major depression, each of which affects close to 20 million Americans annually, according to the National Institute of Mental Health. And much investigation focuses on developing the next generation of relevant pharmaceuticals, on finding improved versions of Prozac, Wellbutrin, Valium and Librium that would work faster, longer or with fewer side effects.

At the same time, insights about stress are opening the way for novel drug development. These different tacks are needed for the simple fact that despite laudable progress in treating anxiety and depression, currently available medications do not work for vast numbers of people, or they entail side effects that are too severe.

Research in this area has applications well beyond treating and understanding these two illnesses. The diagnostic boundary that separates someone who is formally ill with an anxiety disorder or major depression from everyone else is somewhat arbitrary. Investigations into stress are also teaching us about the everyday anxiety and depression that all of us experience at times.

IMAGING BY TRILOBYTE

Out of Balance

WHEN A BODY is in homeostatic balance, various measures—such as temperature, glucose level and so on—are as close to "ideal" as possible. A stressor is anything in the environment that knocks the body out of homeostasis, and the stress response is the array of physiological adaptations that ultimately reestablishes balance. The response principally includes the secretion of two types of hormones from the adrenal glands: epinephrine, also known as adrenaline, and glucocorticoids. In humans, the relevant glucocorticoid is called cortisol, also known as hydrocortisone.

This suite of hormonal changes is what stress is about for the typical mammal. It is often triggered by an acute physical challenge, such as fleeing from a predator. Epinephrine and glucocorticoids mobilize energy for muscles, increase cardiovascular tone so oxygen can travel more quickly, and turn off nonessential activities like growth. (The hormones work at different speeds. In a fight-or-flight scenario, epinephrine is the one handing out guns; glucocorticoids are the ones drawing up blueprints for new aircraft carriers needed for the war effort.)

EPINEPHRINE IS THE ONE HANDING OUT GUNS. **Glucocorticoids are the ones drawing up blueprints for new aircraft carriers.**

Primates have it tough, however. More so than in other species, the primate stress response can be set in motion not only by a concrete event but by mere *anticipation*. When this assessment is accurate ("This is a dark, abandoned street, so I should prepare to run"), an anticipatory stress response can be highly adaptive. But when primates, human or otherwise, chronically and erroneously believe that a homeostatic challenge is about to come, they have entered the realm of neurosis, anxiety and paranoia.

In the 1950s and 1960s pioneers such as John Mason, Seymour Levine and Jay Weiss—then at the Walter Reed Army Medical Center, Stanford University and the Rockefeller University, respectively—began to identify key facets of psychological stress. They found that such stress is exacerbated if there is no outlet for frustration, no sense of control, no social support and no impression that something better will follow. Thus, a rat will be less likely to develop an ulcer in response to a series of electric shocks if it can gnaw on a bar of wood throughout, because it has an outlet for frustration. A baboon will secrete fewer stress hormones in response to frequent fighting if the aggression results in a rise, rather than a fall, in the dominance hierarchy; he has a perception that life is improving. A person will become less hypertensive when exposed to painfully loud noise if she believes she can press a button at any time to lower the volume; she has a sense of control.

But suppose such buffers are not available and the stress is chronic. Repeated challenges may demand repeated bursts of vigilance. At some point, this vigilance may become overgeneralized, leading an individual to conclude that he must always be on guard—even in the absence of the stress. And thus the realm of anxiety is entered. Alternatively, the chronic stress may be insurmountable, giving rise to feelings of helplessness. Again this response may become overgeneralized: a person may begin to feel she is always at a loss, even in circumstances that she can actually master. Depression is upon her.

Stress and Anxiety

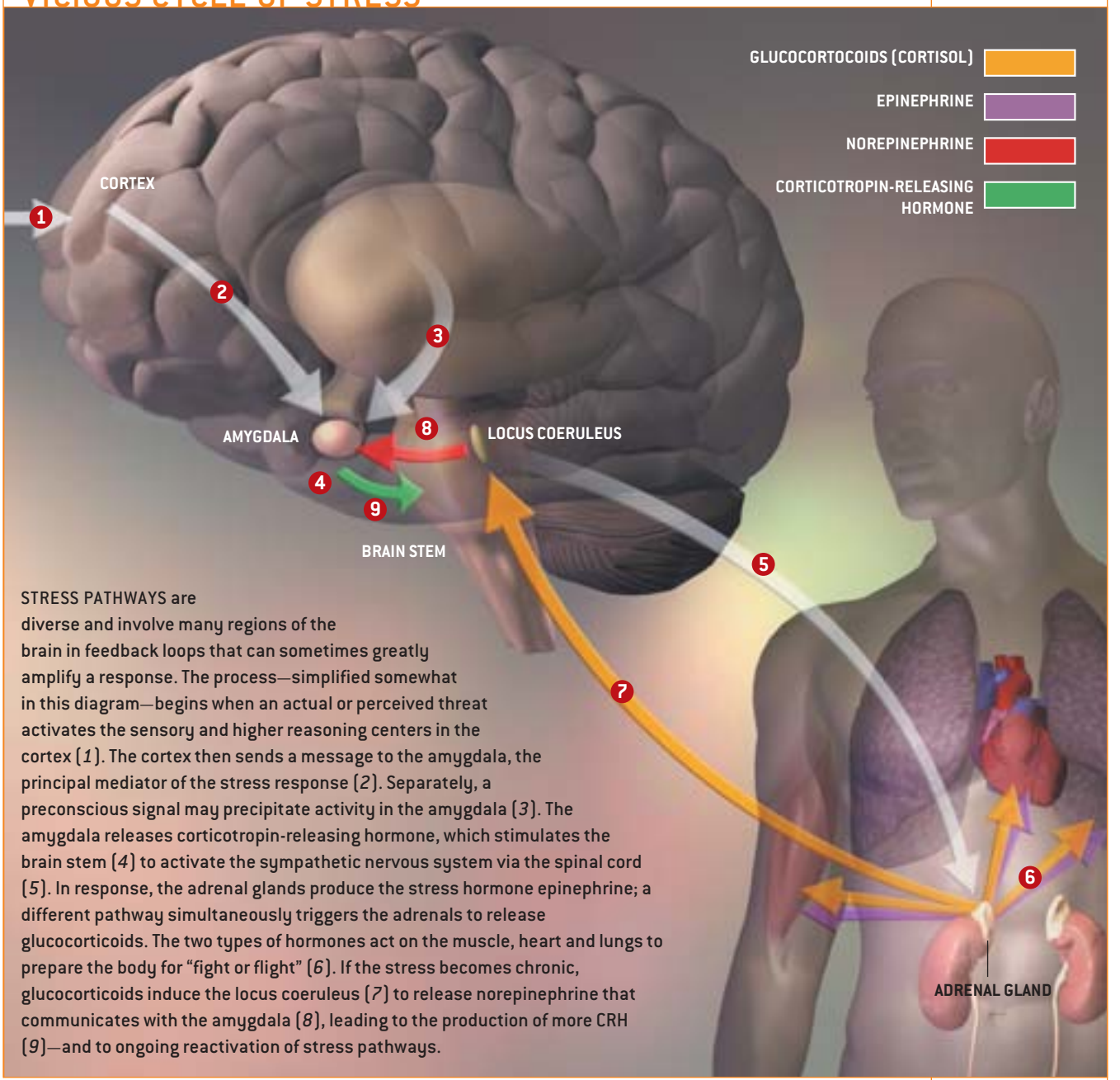
FOR ITS PART, anxiety seems to wreak havoc in the limbic system, the brain region concerned with emotion. One structure is primarily affected: the amygdala, which is involved in the perception of and response to fear-evoking stimuli. (Interestingly, the amygdala is also central to aggression, underlining the fact that aggression can be rooted in fear—an observation that can explain much sociopolitical behavior.)

To carry out its role in sensing threat, the amygdala receives input from neurons in the outermost layer of the brain, the cortex, where much high-level processing takes place. Some of this input comes

OVERVIEW/*Battling Stress*

- Scientists understand a lot about the role stress plays in the development of anxiety disorders and major depression, which may affect as many as 40 million people in the U.S. And they are coming to see the ways in which unremitting stress can transform anxiety into depression.
- Insights into the neurochemistry of stress are allowing researchers to develop new ways of thinking about drug development. In addition to refining drugs that are already on the market, these findings are leading to entirely novel strategies for treatments.
- Finding these alternatives is crucially important because many people are not helped by currently available medications.

VICIOUS CYCLE OF STRESS



STRESS PATHWAYS are diverse and involve many regions of the brain in feedback loops that can sometimes greatly amplify a response. The process—simplified somewhat in this diagram—begins when an actual or perceived threat activates the sensory and higher reasoning centers in the cortex (*1*). The cortex then sends a message to the amygdala, the principal mediator of the stress response (*2*). Separately, a preconscious signal may precipitate activity in the amygdala (*3*). The amygdala releases corticotropin-releasing hormone, which stimulates the brain stem (*4*) to activate the sympathetic nervous system via the spinal cord (*5*). In response, the adrenal glands produce the stress hormone epinephrine; a different pathway simultaneously triggers the adrenals to release glucocorticoids. The two types of hormones act on the muscle, heart and lungs to prepare the body for "fight or flight" (*6*). If the stress becomes chronic, glucocorticoids induce the locus coeruleus (*7*) to release norepinephrine that communicates with the amygdala (*8*), leading to the production of more CRH (*9*)—and to ongoing reactivation of stress pathways.

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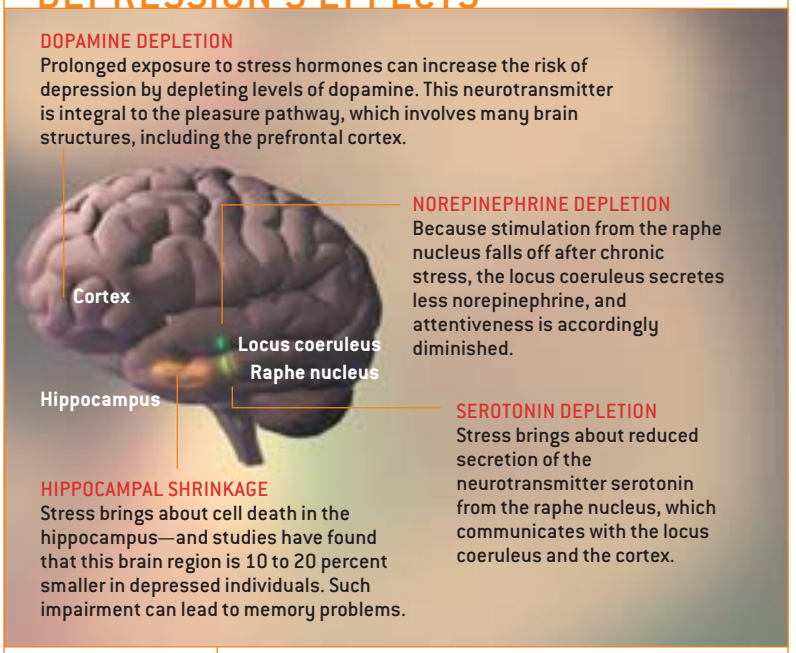
from parts of the cortex that process sensory information, including specialized areas that recognize individual faces, as well as from the frontal cortex, which is involved in abstract associations. In the realm of anxiety, an example of such an association might be grouping a gun, a hijacked plane and an anthrax-tainted envelope in the same category. The sight of a fire or a menacing face can activate the amygdala—as can a purely abstract thought.

The amygdala also takes in sensory information that bypasses the cortex. As a result, a subliminal preconscious menace can activate the amygdala, even before there is conscious awareness of the trigger. Imagine a victim of a traumatic experience who, in a crowd of happy, talking people, suddenly finds herself anxious, her heart racing. It takes her moments to realize that a man conversing behind her has a voice similar to that of the man who once assaulted her.

The amygdala, in turn, contacts an array of brain regions, making heavy use of a neurotransmitter called corticotropin-releasing hormone (CRH). One set of nerve cells projecting from the amygdala reaches evolutionarily ancient parts of the midbrain and brain stem. These structures control the autonomic nervous system, the network of nerve cells projecting to parts of the body over which you

DEPRESSION'S EFFECTS



normally have no conscious control (your heart, for example). One half of the autonomic nervous system is the sympathetic nervous system, which mediates "fight or flight." Activate your amygdala with a threat, and soon the sympathetic nervous system has directed your adrenal glands to secrete epinephrine. Your heart is racing, your breathing is shallow, your senses are sharpened.

The amygdala also sends information back to the frontal cortex. In addition to processing abstract associations, as noted above, the frontal cortex helps to make judgments about incoming information and initiating behaviors based on those assessments. So it is no surprise that the decisions we make can be so readily influenced by our emotions. Moreover, the amygdala sends projections to the sensory cortices as well, which may explain, in part, why sensations seem so vivid when we are in certain emotional states—or perhaps why sensory memories (flashbacks) occur in victims of trauma.

SEVERE STRESS can harm the hippocampus, preventing the consolidation of a conscious, EXPLICIT MEMORY OF THE EVENT.

Whether it orchestrates such powerful reimmersions or not, the amygdala is clearly implicated in certain kinds of memory. There are two general forms of memory. Declarative, or explicit, memory governs the recollection of facts, events or associations. Implicit memory has several roles as well. It includes procedural memory: recalling how to ride a bike or play a passage on the piano. And it is involved in fear. Remember the woman reacting to the similarity between two voices without being aware of it. In that case, the activation of the amygdala and the sympathetic nervous system reflects a form of implicit memory that does not require conscious awareness.

Researchers have begun to understand how these fearful memories are formed and how they can be overgeneralized after repeated stress. The foundation for these insights came from work on declarative memory, which is most likely situated in a part of the brain called the hippocampus. Memory is established when certain sets of nerve cells communicate with one another repeatedly. Such communication entails the release of neurotransmitters—chemical messengers that travel across synapses, the spaces between neurons. Repeated stimulation of sets of neurons causes the communication across synapses to be strengthened, a condition called long-term potentiation (LTP).

Joseph LeDoux of New York University has shown that repeatedly placing rats in a fear-provoking situation can bring about LTP in the amygdala. Work by Sumantra Chattarji of the National Center for Biological Science in Bangalore extends this finding one remarkable step further: the amygdalic neurons of rats in stressful situations sprout new branches, allowing them to make more connections with other neurons. As a result, any part of the fear-inducing situation could end up triggering more firing between neurons in the amygdala. A victim—if he had been robbed several times at night, for instance—might experience anxiety and phobia just by stepping outside his home, even under a blazing sun.

LeDoux has proposed a fascinating model to relate these changes to a feature of some forms of anxiety. As discussed, the hippocampus plays a key role in declarative memory. As will become quite pertinent when we turn to depression, glucocorticoid exposure can impair LTP in the hippocampus and can even cause atrophy of neurons there. This phenomenon constitutes the opposite of the stress response in the amygdala. Severe stress can harm the hippocampus, preventing the consolidation of a conscious, explicit memory of the event; at the same time, new neuronal branches and enhanced LTP facilitate

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the amygdala's implicit memory machinery. In subsequent situations, the amygdala might respond to preconscious information—but conscious awareness or memory may never follow. According to LeDoux, such a mechanism could underlie forms of free-floating anxiety.

It is interesting that these structural changes come about, in part, because of hormones secreted by the adrenal glands, a source well outside the brain. As mentioned, the amygdala's perception of stress ultimately leads to the secretion of epinephrine and glucocorticoids. The glucocorticoids then activate a brain region called the locus coeruleus. This structure, in turn, sends a powerfully activating projection back to the amygdala, making use of a neurotransmitter called norepinephrine (a close relative of epinephrine). The amygdala then sends out more CRH, which leads to the secretion of more glucocorticoids. A vicious circle of mind-body feedback can result.

Assuaging Anxiety

AN UNDERSTANDING of the interactions between stress and anxiety has opened the way for new therapies, some of which hold great promise. These drugs are not presumed better or safer than those available today. Rather, if successful, they will give clinicians more to work with.

The medicines that already exist do target aspects of the stress system. The minor tranquilizers, such as Valium and Librium, are in a class of compounds called benzodiazepines. They work in part by relaxing muscles; they also inhibit the excitatory projection from the locus coeruleus into the amygdala, thereby decreasing the likelihood that the amygdala will mobilize the sympathetic nervous system. The net result is a calm body—and a less anxious body means a less anxious brain. While effective, however, benzodiazepines are also sedating and addictive, and considerable research now focuses on finding less troublesome versions.

In their search for alternatives, researchers have sought to target the stress response upstream of the locus coeruleus and amygdala. Epinephrine activates a nerve called the vagus, which projects into a brain region that subsequently stimulates the amygdala. A new therapy curtails epinephrine's stimulation of the vagus nerve.

Chemical messengers such as epinephrine exert their effects by interacting with specialized receptors on the surface of target cells. A receptor is shaped in such a way that it can receive only a certain messenger—just as a mold will fit only the statue cast in it. But by synthesizing imposter messengers, scientists have been able to block the activity of some of the body's natural couriers.

Drugs called beta blockers fit into some kinds of epinephrine receptors, preventing real epinephrine from transmitting any information. Beta blockers have long been used to reduce high blood pressure driven by an overactive sympathetic nervous system, as well as to reduce stage fright. But Larry Cahill and James McGaugh of the University of California at Irvine have shown that the drugs also blunt the formation of memories of emotionally disturbing events or stories. Based on their findings and others, clinicians such as Roger Pitman of Harvard University have started studies in which beta blockers are given to people who have experienced severe trauma in the hope of heading off the development of post-traumatic stress disorder.

Other therapies are being designed to act in the amygdala itself. As described, the amygdala's shift from merely responding to an arousing event to be-

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SOME NOVEL THERAPEUTIC STRATEGIES

Substance P. This compound is released during painful sensations and stress and acts on neurokinin-1 receptors, which are found throughout the central nervous system but in greater amounts in the amygdala and locus coeruleus (*highlighted*), among other stress-related areas. Current work—including one clinical trial—suggests that blocking the action of Substance P may blunt anxiety and depression. But another clinical trial did not support this finding.

Corticotropin-Releasing Hormone. This hormone is released by the amygdala and initiates the stress cascade. Research efforts now include trying to block receptors for CRH in the brain stem. Without information from CRH, the brain stem will not set the sympathetic nervous system in motion, thus preventing the release of epinephrine by the adrenal glands. This blockade could curb both anxiety and depression.

Brain-Derived Neurotrophic Factor. This substance is important to the creation of new nerve cells. By injecting BDNF into brains, researchers hope to counteract the deleterious effects of glucocorticoids on neurogenesis in the hippocampus, thereby maintaining healthy memory function and preventing the hippocampal atrophy often seen in depressed people.

Gene Therapy. This treatment can introduce novel genes to specific regions of the brain; these genes can then produce proteins that can undo or prevent the effects of stress. Current studies aim to figure out which genes are active in the amygdala during stress. Introducing genes that inhibit unwanted neural branching in the amygdala might then thwart the anxiety-inducing effects of stress. For depression, the goal is different: genes placed in the hippocampus could produce proteins that would break down glucocorticoids, preventing damage to nerve cells—and, accordingly, the memory impairment—that can accompany depression.

coming chronically overaroused probably involves memory formation as well as the growth of new synapses. Work in my laboratory is exploring the molecular biology underlying those changes. Because prolonged stress has opposite effects on synapse formation in the hippocampus and the amygdala, we would like to know how the profiles of genes turned on and off by stress differ in those two structures. Our goal is to then try to block the changes by introducing genes into the amygdala that might give rise to proteins that could inhibit synapse formation during stress. In this work, viruses that have been rendered safe are used to ferry genes to the amygdala [see "Gene Therapy in the Nervous System," by Dora Y. Ho and Robert M. Sapolsky; SCIENTIFIC AMERICAN, July 1997].

Another strategy—for both anxiety and depression—targets CRH, the neurotransmitter used by the amygdala when it sends information elsewhere. Based on insights into the structure of CRH and its receptors, scientists have developed chemical imposters to bind with the receptors and block it. In research by Michael Davis of Emory University, these compounds have proved effective in rat models of anxiety. They have reduced the extent to which a rat anxiously freezes when placed in a cage where it was previously shocked.

Stress and Depression

IN CONTRAST TO ANXIETY, which can feel like desperate hyperactivity, major depression is characterized by helplessness, despair, an exhausted sense of being too overwhelmed to do anything (psychomotor retardation) and a loss of feelings of pleasure. Accordingly, depression has a different biology and requires some different strategies for treatment. But it, too, can be related to stress, and there is ample evidence of this association. First of all, psychological stress entails feeling a loss of control and predictability—an accurate description of depression. Second, major stressful events seem to precede depressive episodes early in the course of the disease. Finally, treating people with glucocorticoid hormones to control conditions such as rheumatoid arthritis can lead to depression.

One way in which stress brings about depression is by acting on the brain's mood and pleasure pathways. To begin, prolonged exposure to glucocorticoid hormones depletes norepinephrine levels in the locus coeruleus neurons. Most plausibly, this means that

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the animal—or person—becomes less attentive, less vigilant, less active: psychomotor retardation sets in.

Continued stress also decreases levels of serotonin—which may be important in the regulation of mood and sleep cycles, among other things—as well as the number of serotonin receptors in the frontal cortex. Serotonin normally arrives in the frontal cortex by way of the raphe nucleus, a structure that also communicates with the locus coeruleus. You can probably see where this is going. Normally, serotonin stimulates the release of norepinephrine from the locus coeruleus. When serotonin becomes scarce, less norepinephrine is released—exacerbating the shortage caused by earlier unremitting glucocorticoid bombardment.

Stress affects dopamine, the main currency of the pleasure pathway, in a way that seems counterintuitive at first. Moderate and transient amounts of stress—and the ensuing presence of glucocorticoids—increase dopamine release in the pleasure pathway, which runs between a region called the ventral tegmentum/nucleus accumbens and the frontal cortex. More dopamine can lead to a feeling of well-being in situations of moderate or transient stress during which a subject is challenged briefly and not too severely. For a human, or a rat, this situation would entail a task that is not trivial, but one in which there is, nonetheless, a reasonably high likelihood of success—in other words, what we generally call "stimulation." But with chronic glucocorticoid exposure, dopamine production is curbed and the feelings of pleasure fade.

Not surprisingly, the amygdala also appears relevant to depression. Wayne Drevets of the National Institute of Mental Health reports that the images of the amygdala of a depressed person light up more in response to sad faces than angry ones. Moreover, the enhanced autonomic arousal seen in anxiety—thought to be driven by the amygdala—is often observed in depression as well. This fact might seem puzzling at first: anxiety is characterized by a skittish torrent of fight-or-flight signals, whereas depression seems to be about torpor. Yet the helplessness of depression is not a quiet, passive state. The dread is active, twitching, energy-consuming, distracting, exhausting—but internalized. A classic conceptualization of depression is that it represents aggression turned inward—an enormous emotional battle fought entirely internally—and the disease's physiology supports this analysis.

Memory and New Cells

STRESS ALSO ACTS ON the hippocampus, and this activity may bring about some of the hallmarks of depression: difficulty learning and remembering. As I explained before, stress and glucocorticoids can disrupt memory formation in the hippocampus and can cause hippocampal neurons to atrophy and lose some of their many branches. In the 1980s several laboratories, including my own, showed that glucocorticoids can kill hippocampal neurons or impair their ability to survive neurological insults such as a seizure or cardiac arrest.

Stress can even prevent the growth of new nerve cells. Contrary to long-held belief, adult brains do make some new nerve cells. This revolution in our understanding has come in the past decade. And although some findings remain controversial, it is clear that new neurons form in the olfactory bulb and the hippocampus of many adult animals, including humans [see "Brain, Repair Yourself," by Fred H. Gage, on page 46]. Many things, including learning, exercise and environmental enrichment, stimulate neurogenesis in the hippocampus. But stress and glucocorticoids inhibit it.

The helplessness of DEPRESSION is not a quiet, passive state. The dread is active, twitching, ENERGY-CONSUMING.

As would be expected, depression is associated with impaired declarative memory. This impairment extends beyond remembering the details of an acute trauma. Instead depression can interfere with declarative memory formation in general—in people going about their everyday routine or working or learning. Recent and startling medical literature shows that in those who have been seriously depressed for years, the volume of the hippocampus is 10 to 20 percent smaller than in well-matched control subjects. There is little evidence that a small hippocampus predisposes someone toward depression; rather the decreased volume appears to be a loss in response to depression.

At present, it is not clear whether this shrinkage is caused by the atrophy or death of neurons or by the failure of neurogenesis. Disturbingly, both the volume loss and at least some features of the cognitive impairments persist even when the depression

resolves. (It is highly controversial whether new neurons are required for learning and memory; thus, it is not clear whether an inhibition of neurogenesis would give rise to cognitive deficits.)

Glucocorticoids may act on the hippocampus by inhibiting levels of a compound called brain-derived neurotrophic factor (BDNF)—which may aid neurogenesis. Several known antidepressants increase amounts of BDNF and stimulate hippocampal neurogenesis in laboratory animals. These findings have led some scientists to speculate that the stress-induced inhibition of neurogenesis and of BDNF are central to the emotional symptoms of depression. I find it to be somewhat of a stretch to connect altered hippocampal function with the many facets of this disease. Nevertheless, these hippocampal changes may play a large part in the substantial memory dysfunction typical of major depression.

New Drugs for Depression

THE CURRENT GENERATION of antidepressants boost levels of serotonin, dopamine and norepinephrine, and there is tremendous ongoing research to develop more effective versions of these drugs. But some novel therapies target steps more intimately related to the interactions between stress and depression.

Not surprisingly, some of that work focuses on the effects of glucocorticoids. For example, a number of pharmaceuticals that are safe and clinically approved for other reasons can transiently block the synthesis of glucocorticoids in the adrenal glands or block access of glucocorticoids to one of their important receptors in the brain. Fascinatingly, the key compound that blocks glucocorticoid receptors is RU486, famous and controversial for its capacity to also block progesterone receptors in the uterus and for its use as the "abortion drug." Beverly Murphy of McGill University, Owen Wolkowitz of the University of California at San Francisco and Alan Schatzberg of Stanford have shown that such antiglucocorticoids can act as antidepressants for a subset of severely depressed people with highly elevated glucocorticoid levels. These findings are made even more promising by the fact that this group of depressed individuals tend to be most resistant to the effects of more traditional antidepressants.

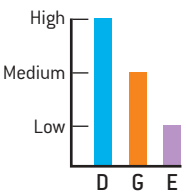
Another strategy targets CRH. Because depression, like anxiety, often involves an overly responsive amygdala and sympathetic nervous system, CRH is a key neurotransmitter in the communication from the former to the latter. Moreover, infusion of CRH into the brain of a monkey can cause some depressionlike symptoms. These findings have prompted studies as to whether CRH-receptor blockers can have an antidepressant action. It appears they can, and such drugs are probably not far off.

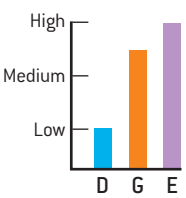
Using the same receptor-blocking strategy, researchers have curbed the action of a neurotransmitter called Substance P, which binds to the neurokinin-1 (NK-1) receptor. In the early 1990s workers discovered that drugs binding with NK-1 prevent some aspects of the stress response. In one trial and several animal studies, Substance P has worked as an antidepressant.

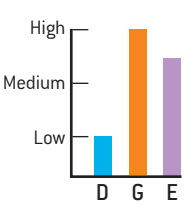
Other approaches center on the hippocampus. Investigators are injecting BDNF into the brains of rats to counteract the inhibitory effects of glucocorticoids on neurogenesis. My own laboratory is using gene therapy to protect the hippocampus of rats from the effects of stress—much as we are doing in the amygdala to prevent anxiety. These genes are triggered by glucocorticoids; once activated, they express an enzyme that degrades glucocorticoids. The net result blocks the deleterious effects of these hormones. We are now exploring whether this treatment can work in animals.

As is now clear, I hope, anxiety and depression

Anxiety becomes depression if stress is chronic and levels of dopamine (*D*), glucocorticoids (*G*) and epinephrine (*E*) change accordingly (*graphs*). If a rat knows how to press a lever to avoid a shock, it can feel pleasure in that mastery (*1*). If the lever no longer works, however, anxiety sets in and the animal desperately tries different strategies to avoid the shock (*2*). As coping proves elusive, hypervigilance is replaced by passivity and depression (*3*).







ALFRED T. KAMAJIAN

are connected. Yet a state of constant vigilance and one of constant helplessness seem quite different. When does stress give rise to one as opposed to the other? The answer seems to lie in how chronic the stress is.

The Stress Continuum

IMAGINE A RAT trained to press a lever to avoid a mild, occasional shock—a task readily mastered. The rat is placed into a cage with the lever, and the anticipatory sense of mastery might well activate the pleasurable dopaminergic projections to the frontal cortex. When the increase in glucocorticoid secretion is moderate and transient—as would likely be the case here—the hormone enhances dopamine release.

Suppose that in this circumstance, however, the lever has been disconnected; pressing it no longer prevents shocks. Initially this alteration produces a wildly hypervigilant state in the rat as it seeks a new coping response to stop the shocks. The animal presses the lever repeatedly, frantically trying to regain control. This is the essence of anxiety and of the multiple, disorganized attempts at coping. Physiologically, this state is characterized by massive activation of the sympathetic nervous system by epinephrine and of the norepinephrine projection from the locus coeruleus, as well as moderately increased glucocorticoid secretion.

And as the shocks continue and the rat finds each attempt at coping useless, a transition occurs. The stress response becomes more dominated by high glucocorticoid levels than by epinephrine and the sympathetic nervous system—which are largely in control of the immediate fight-or-flight reaction. The brain chemistry begins to resemble that of depression as key neurotransmitters become depleted and the animal ceases trying to cope. It has learned to be helpless, passive and involuted. If anxiety is a crackling, menacing brushfire, depression is a suffocating heavy blanket thrown on top of it.

Stress and Genes

I DO NOT WANT to conclude this article having given the impression that anxiety and depression are "all" or "only" about stress. Obviously, they are not. Both illnesses have substantial genetic components as well. Genes code for the receptors for dopamine, serotonin and glucocorticoids. They also code for the enzymes that synthesize and degrade those chemical messengers, for the pumps that remove them from the synapses, for growth factors like BDNF, and so on.

But those genetic influences are not inevitable. Remember, if an individual has one of the major psychiatric disorders, her identical twin has only about a 50 percent chance of having it. Instead the genetic influences seem to be most about vulnerability: how the brain and body react to certain environments, including how readily the brain and body reequilibrate after stress.

Experience, beginning remarkably early in life, also influences how one responds to stressful environments. The amount of stress a female rat is exposed to during pregnancy influences the amount of glucocorticoids that cross the placenta and reach the fetus; that exposure can then alter the structure and function of that fetus's hippocampus in adulthood. Separate a newborn rat from its mother for a sustained period and it will have increased levels of CRH as an adult. Seymour Levine, one of the giants of psychobiology, illustrates this point with a quotation from William Faulkner: "The past is not dead. It's not even the past."

A GENETIC LEGACY of anxiety or depression does not confer a life sentence on sufferers of these TRAGIC DISEASES.

An understanding of the role of stress in psychiatric disorders offers much. It teaches us that a genetic legacy of anxiety or depression does not confer a life sentence on sufferers of these tragic diseases. It is paving the way for some new therapies that may help millions. Given that there is a continuum between the biology of these disorders and that of the "normal" aspects of emotion, these findings are not only pertinent to "them and their diseases" but to all of us in our everyday lives. Perhaps most important, such insight carries with it a social imperative: namely, that we find ways to heal a world in which so many people learn that they must always feel watchful and on guard or that they must always feel helpless. SA

MORE TO EXPLORE

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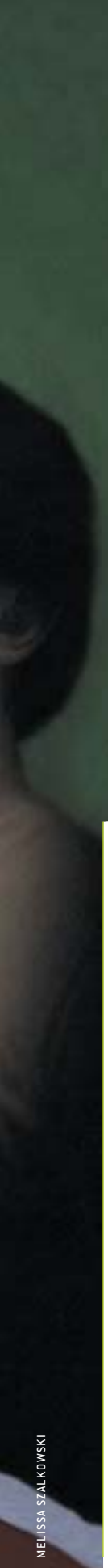
DIAGNOSING DISORDERS

PSYCHIATRIC ILLNESSES ARE OFTEN HARD TO RECOGNIZE, BUT GENETIC TESTING AND NEUROIMAGING COULD SOMEDAY BE USED TO IMPROVE DETECTION

BY STEVEN E. HYMAN



MELISSA SZALKOWSKI

Brain disorders usually have behavioral symptoms that can be observed by a psychiatrist. But the checklist approach to diagnosis is far from perfect.

ACCURATE DIAGNOSIS IS THE CORNERSTONE OF medical care. To plan a successful treatment for a patient, a doctor must first determine the nature of the illness. In most branches of medicine, physicians can base their diagnoses on objective tests: a doctor can examine x-rays to see if a bone is broken, for example, or extract tissue samples to search for cancer cells. But for some common and serious psychiatric disorders, diagnoses are still based entirely on the patient's own report of symptoms and the doctor's observations of the patient's behavior. The human brain is so enormously complex that medical researchers have not yet been able to devise definitive tests to diagnose illnesses such as schizophrenia, autism, bipolar disorder or major depression.

Because psychiatrists must employ subjective evaluations, they face the challenge of reliability: how to ensure that two different doctors arrive at the same diagnosis for the same patient. To address this concern, the American Psychiatric Association in 1980 published the Diagnostic and Statistical Manual of Mental Disorders, Third Edition (widely known by the acronym "DSM-III"). Unlike earlier editions of the manual, DSM-III and its successor volumes (the latest one is referred to as DSM-IV-TR) describe what symptoms must be present—and for how long—to make a diagnosis of a particular brain disorder. Virtually all these criteria, however, are based on the patient's history and the clinical encounter. Without the ability to apply objective tests, physicians may fail to detect disorders and sometimes mistake the symptoms of one illness for another's. Making the task more difficult is the fact that some psychiatric illnesses, such as schizophrenia, may turn out to be clusters of diseases that have similar symptoms but require different treatments.

In recent years, though, advances in genetics, brain imaging and basic neuroscience have promised to change the way that brain disorders are diagnosed. By correlating variations in DNA with disease risks, researchers may someday be able to determine which small differences in a patient's genetic sequence can make that person more vulnerable to schizophrenia, autism or other illnesses. And rapid developments in neuroimaging—the noninvasive observation of a liv-

ing brain—may eventually enable doctors to spot structural features or patterns of brain activity that are characteristic of certain disorders. Better diagnosis will lead to better care: after pinpointing a patient's brain disorder, a physician will be able to prescribe the treatment that is best suited to it. And earlier diagnosis could allow doctors to slow or halt the progress of a disorder before it becomes debilitating.

History of Diagnosis

THE FIRST MODERN ATTEMPT to identify individual psychiatric disorders was made in the 19th century by German scientist Emil Kraepelin, who distinguished two of the most severe mental illnesses: schizophrenia, which he called dementia praecox, and manic-depressive illness, which is now known as bipolar disorder. Much of his careful observational work focused on following the course of the illnesses over the lifetime of his patients. He defined schizophrenia as a disease with psychotic symptoms (such as hallucinations and delusions) that had an insidious onset—in other words, the initial symptoms may be hard to detect—and a chronic, downhill course. In contrast, manic-depressive illness was characterized by discrete episodes of illness alternating with periods of relatively healthy mental function.

Some PSYCHIATRIC ILLNESSES may turn out to be clusters of diseases that have similar symptoms but REQUIRE DIFFERENT TREATMENTS.

In the early 20th century, however, work on psychiatric diagnosis went into eclipse as a result of the influence of the psychoanalytic theories developed by Sigmund Freud and his followers. In their conception of mental illness, symptoms arose from a failure to successfully negotiate stages in psychological development. The symptoms of each illness indicated the point in development at which the trouble arose. The psychoanalytic theory of that period did not allow for the possibility that different psychiatric illnesses might have completely different causes, let alone the modern idea that mental disorders might arise from abnormalities in brain circuits.

Diagnosis returned to a central position in psychiatry in the 1950s, though, with the discovery of drugs for treating psychiatric disorders. Researchers found that chlorpromazine (better known by one of its brand names, Thorazine) could control the psychotic symptoms of schizophrenia and that lithium salts could stabilize the moods of patients with bipolar disorder. By 1960 the first antidepressant and antianxiety drugs were introduced. It quickly became critically important to match the patient with the right treatment. The new antidepressants did not work for schizophrenia and could precipitate an episode of mania in someone with bipolar disorder. Lithium was remarkably effective for bipolar disorder but not for schizophrenia.

In the 1980s the publication of DSM-III and subsequent manuals enabled psychiatrists to use standardized interviews and checklists of symptoms to make their diagnoses. Although the checklist approach is imperfect, it represented an enormous advance in both clinical care and research. For example, before the advent of DSM-III, it appeared that schizophrenia was twice as prevalent in the U.S. as it was in Great Britain. This discrepancy turned out to be an artifact of divergent approaches to diagnosis. In fact, the prevalence of schizophrenia is about 1 percent of people worldwide. The standardization of diagnosis made it clear that mental disorders are common and quite often disabling. According to the World Health Organization's data on the global burden of disease, major depression is the leading cause of disability in the U.S. and other economically advanced nations. In aggregate, mental disorders rank second only to cardiovascular diseases in terms of their economic and social costs in those countries.

Meanwhile advances in neuroscience showed that certain neurological diseases leave unmistakable signatures on the brain. Parkinson's disease,

OVERVIEW/*Improving Diagnosis*

- Because psychiatrists lack objective tests for detecting brain disorders, they sometimes fail to observe mental illness or mistake the symptoms of one disorder for another's.
- Scientists have recently found gene variants that seem to confer susceptibility to disorders such as schizophrenia and autism. Doctors may someday be able to determine a patient's risk of developing these diseases by analyzing his or her DNA.
- In addition, advances in neuroimaging may allow physicians to look for subtle anomalies in the brain caused by mental disorders. As the technology improves, doctors could use neuroimaging to diagnose psychiatric illnesses and to track the success of therapy.

for instance, is characterized by the death of nerve cells in the midbrain that make the neurotransmitter dopamine, a chemical that transmits signals between neurons. The definitive signs of Alzheimer's disease are deposits of an abnormal protein called amyloid and tangles of protein in the cells of the cerebral cortex, the outermost layer of the brain. (Because one needs a microscope to observe these anomalies, a conclusive diagnosis can be made only after the patient's death.) But when it comes to psychiatric illnesses such as schizophrenia and depression, the abnormalities in the brain are much more subtle and difficult to discover. For this reason, many researchers have begun to look for indicators of brain disorders in the human genome.

The Genetics of Disorder

JUST AS NORMAL behavioral traits are often passed from parent to child, certain mental disorders run in families. To determine whether the resemblance is a result of genes or family environment, researchers have conducted studies comparing the risk of illness in identical twins (who share 100 percent of their DNA) to the risk in fraternal twins (who on average share 50 percent of their DNA). Another type of study, which is more cumbersome, focuses on whether an illness in offspring who were adopted early in life is more often shared with their biological relatives or their adoptive families.

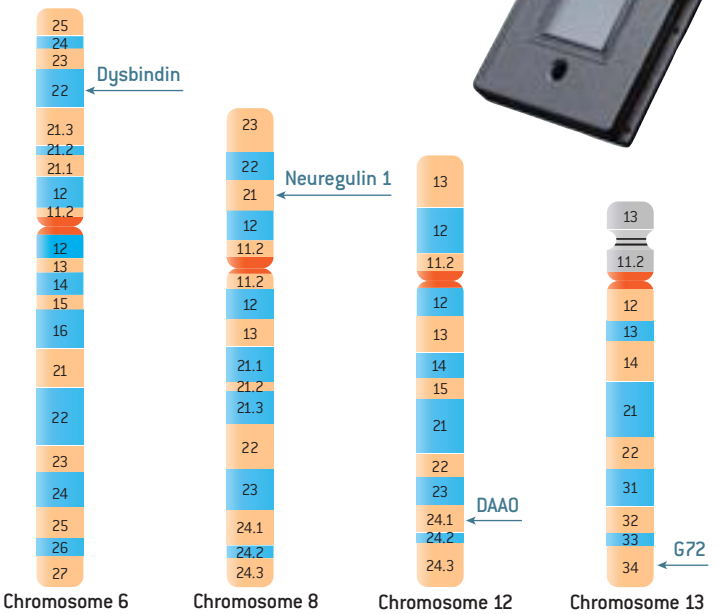
Such studies reveal that genes play a substantial role in the transmission of mental disorders but that other factors must also be at work. For example, if one identical twin has schizophrenia, the risk to the other is 45 percent. If one identical twin has autism—a developmental brain disorder characterized by impairments in communication and social interaction—the other twin has a 60 percent chance of sharing the same diagnosis. These are enormous increases over the risks for the general population (1 percent for schizophrenia, 0.2 percent for autism), but the key point here is that some twins do not develop the disorders even if they carry the same genes as their affected siblings.

Therefore, nongenetic factors must also contribute to the risk of illness. These factors may include environmental influences (such as infections or injuries to the brain early in life) and the random twists and turns of brain development. Even among identical twins growing up in exactly the same environment, it is not possible to wire up a brain with 100 trillion synapses in identical fashion. For all mental disorders—and, indeed, for all normal patterns of behavior that have been studied—genes are important, but they are not equivalent to fate. Our brains, not our genes, directly regulate our behavior, and our brains are the products of genes, environment and chance operating over a lifetime.

What is more, new research indicates that the strong genetic influence on the risk of developing a disorder such as schizophrenia is not the work of a single gene. Rather, the increase in risk seems to be an aggregate effect of many genes interacting with one another and with nongenetic factors. By studying the DNA sequences of people with schizophre-

FIRST STEPS TOWARD A GENETIC TEST?

PEOPLE WHO POSSESS DNA SEQUENCE VARIATIONS in any of the four genes shown below appear to have a slightly increased risk of developing schizophrenia. These genes are involved in the transmission of signals among neurons in the brain, so it is possible that the genetic variations disrupt that process. But possessing the variations is neither necessary nor sufficient to cause schizophrenia, which most likely arises by several pathways. In the future, as researchers learn more about the genetic and nongenetic causes of brain disorders, doctors may be able to estimate a patient's risk of acquiring a psychiatric illness by analyzing his or her DNA with a gene chip (*at right*).



GENE CHIP IMAGE COURTESY OF AFFYMETRIX; SOURCE FOR CHART: NATIONAL ACADEMY OF SCIENCES

THE AUTHOR

From an early age, *STEVEN E. HYMAN* was curious about how our brains underlie thinking, emotion and behavioral control. He studied philosophy as an undergraduate at Yale University and philosophy of science at the University of Cambridge, where he was a Mellon Fellow. After earning his M.D. at Harvard University, he received clinical training in psychiatry and scientific training in molecular neurobiology. He was the founding director of Harvard's Interfaculty Initiative in Mind, Brain and Behavior. From 1996 to 2001 he served as Director of the National Institute of Mental Health, the component of the National Institutes of Health charged with generating the knowledge needed to understand, treat and prevent mental illness. Since 2001 he has been Harvard's provost and a professor of neurobiology at Harvard Medical School.

nia and their family members, researchers have already found several genetic variations that appear to increase susceptibility to the disorder [*see illustration on preceding page*]. These variations occur in genes that code proteins involved in the transmission of signals among neurons in the brain, so it is possible that the variations disrupt that process. Similar studies have identified genetic variations that appear to increase the risk of developing major depression and bipolar disorder. Furthermore, a variation of *HOXA1*, a gene related to early brain development, seems to boost susceptibility to autism. The variant gene is present in about 20 percent of the general population but in about 40 percent of people with autism.

Although possessing the variation of *HOXA1* approximately doubles the risk of developing autism, more than 99.5 percent of people who have the variant gene do not acquire the disorder, and about 60 percent of people with autism do not possess the variant gene. As is the case for many diseases, there is not likely to be a single set of genes that are necessary and sufficient to cause either schizophrenia or autism. Instead these illnesses may arise by several pathways. This situation, called genetic complexity, seems to apply to bipolar disorder and depression as well. Each of these disorders may actually represent a group of closely related mental illnesses that share key aspects of abnormal physiology and symptoms but may differ in details large and small, including severity and responsiveness to treatment.

Genes are not equivalent to fate. Our brains are the PRODUCTS OF GENES, ENVIRONMENT AND CHANCE operating over a lifetime.

What are the implications for diagnosis? Imagine that variations in 10 distinct genes can boost the risk of developing a mental illness but that none of the genetic variations by itself is either necessary or sufficient to bring on the disorder (this is close to a current model for autism). Different combinations of the variant genes may confer risks of similar but not identical forms of the illness. To correlate all the possible genetic combinations with all the clinical outcomes would be an immensely complex task. But the tools for such an undertaking are already available. Thanks to technologies developed for the Human Genome Project, scientists can rapidly determine what variations are present in a person's DNA. Using gene chips—small glass slides holding arrays of thousands of reference DNA samples—researchers can also discover which genes are actively coding proteins in a given cell or tissue.

If the gene-hunting effort is successful, doctors will someday be able to analyze a patient's genetic sequence and see where it fits in the matrix of risks. The accuracy of this matrix would be greatly enhanced if physicians also had more information about environmental risk factors. In all likelihood, none of the environmental influences has an overwhelming effect on illness risk—otherwise, researchers would have probably noticed it by now—so epidemiologists will need to study large numbers of people to tease out all the small contributions. By taking both genetic and environmental factors into account, this method may be able to determine whether a person is at high risk for acquiring a particular brain disorder. High-risk patients could then receive close scrutiny in follow-up observations, and if symptoms of the disorder appear, doctors would be able to begin treatment at the earliest stages of the illness.

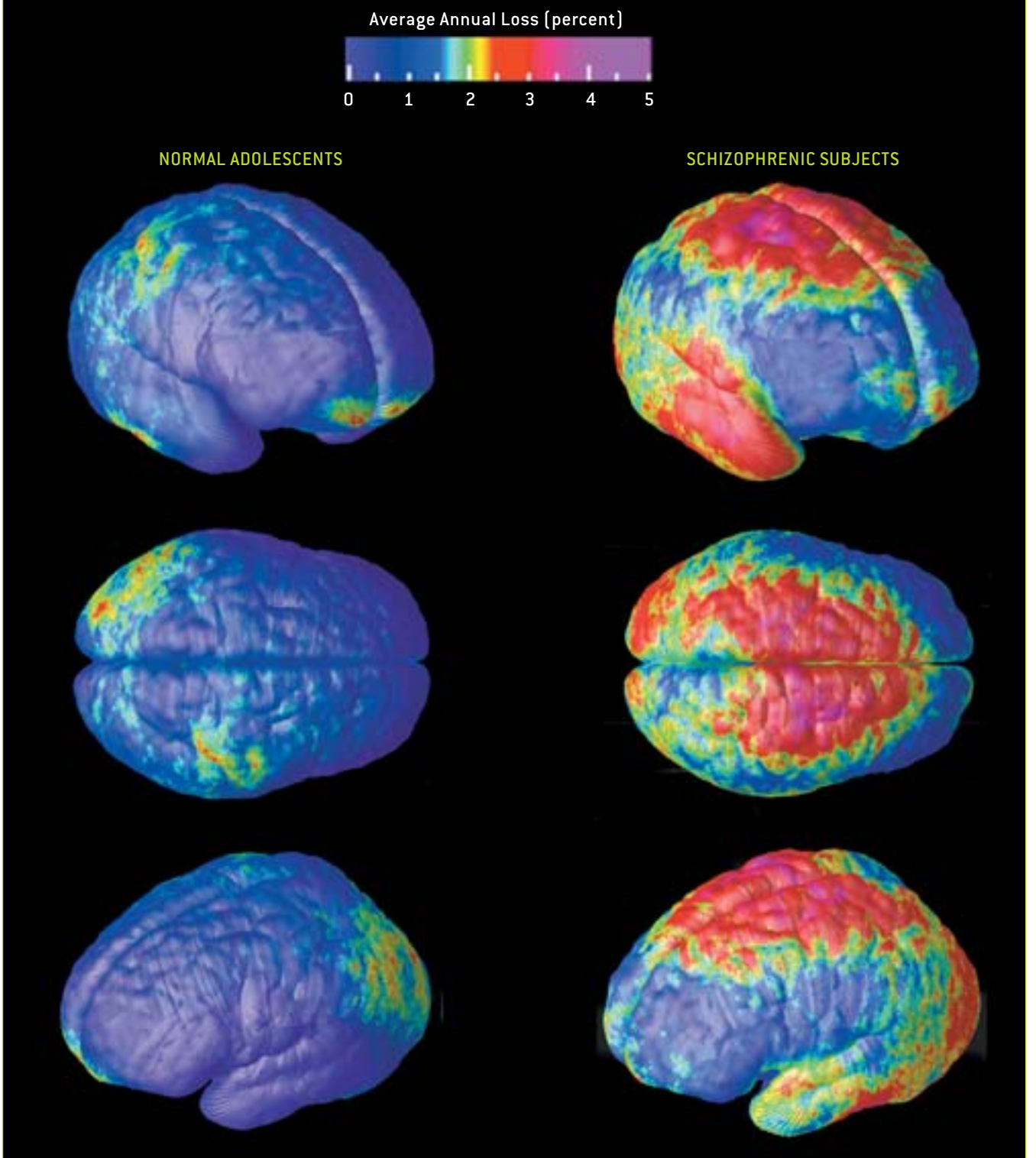
For patients already showing symptoms of a disorder, their genetic information would be quite useful in narrowing down the diagnostic possibilities. And as researchers learn how genetic variations can affect responses to drugs, knowing a patient's genomic profile could help a physician choose the best treatment. But there is a downside to this medical advance: in a society where people can carry their DNA sequences on a memory chip, policymakers would have to grapple with the question of who should have access to this data. Even though a genetic sequence by itself cannot definitively predict whether a person will descend into depression or psychosis, one can readily imagine how employers, educational institutions and insurance companies might use or misuse this information. Society at large will have to become far more sophisticated in its interpretation of the genetic code.

Imaging the Brain

MOVING IN PARALLEL with the genomic revolution, neuroscientists have dramatically improved their ability to image the living brain noninvasively. There are three major types of neuroimaging studies. The first is morphometric analysis, which

TELLTALE SIGNS IN THE BRAIN

THREE-DIMENSIONAL MAPS of the brain derived from magnetic resonance imaging reveal that one type of schizophrenia causes a characteristic pattern of tissue loss in the cerebral cortex. The maps show that the average annual reduction in the cortical gray matter of adolescent patients suffering from childhood-onset schizophrenia (*right*) is much greater than the loss in healthy teenagers (*left*) between the ages of 13 and 18.



COURTESY OF PAUL THOMPSON AND ARTHUR W. TOGA *UCLA Laboratory of Neuro Imaging* AND JUDITH L. RAPOPORT *National Institute of Mental Health*

THE SPECTRUM OF PSYCHIATRIC ILLNESS

MENTAL DISORDERS, which afflict millions of people every year, can be hard to diagnose. As the table shows, some illnesses have overlapping symptoms. Certain mood disorders, such as major depression and dysthymia, have similar symptoms but differ in severity. Among anxiety disorders, the primary distinction is the trigger that initiates fear, panic or avoidance behavior. Psychotic disorders also range from mild to severe. More definitive diagnostic methods are clearly needed.

DISORDER	COMMON SYMPTOMS	PREVALENCE (PERCENT)*
MOOD DISORDERS		
Major Depression	Characterized by episodes during which the patient feels sad or empty nearly every day; loses interest or pleasure in hobbies and activities; experiences changes in appetite, weight, energy levels or sleeping patterns; or harbors thoughts of death or suicide	5.3
Dysthymia	Similar to major depression, but the symptoms are less severe and more chronic. Sad or empty mood on most days for at least two years. Other symptoms include low self-esteem, fatigue and poor concentration.	1.6
Bipolar I	Episodes of abnormally elevated or irritable mood during which the patient feels inflated self-esteem; needs less sleep; talks more than usual; or engages excessively in pleasurable but unwise activities. These manic periods may alternate with depressive episodes	1.1
Bipolar II	Depressive episodes alternate with less severe manic periods that do not markedly impair functioning or require hospitalization	0.6
ANXIETY DISORDERS		
Specific Phobia	Excessive or unreasonable fear of a specific object or situation, such as flying, heights, animals, receiving an injection or seeing blood. Exposure to the stimulus may provoke a panic attack (palpitations, sweating, trembling, shortness of breath, etc.)	8.3
Agoraphobia	Anxiety about being in any place or situation from which escape might be difficult. Typical fears involve being alone outside the home, standing in a crowd, crossing a bridge, or traveling in a bus, train or automobile	4.9
Post-traumatic Stress Disorder	Patient persistently reexperiences a traumatic event through distressing recollections, recurring dreams or intense reactions to anything symbolizing or resembling the event	3.6
PSYCHOTIC DISORDERS		
Schizophrenia	Characterized by delusions, hallucinations, disorganized speech, inappropriate or blunted emotional responses, loss of motivation and cognitive deficits	1.3
Schizophreniform Disorder	Similar to schizophrenia, but the symptoms last for less than six months and may not be severe enough to impair social or occupational functioning	0.1

**Percent of U.S. population between ages 18 and 54 suffering from the disorder in any one-year period.*

SOURCES: NATIONAL INSTITUTE OF MENTAL HEALTH; *DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS*, FOURTH EDITION, 1994

generally relies on high-resolution magnetic resonance imaging (MRI) to produce precise measurements of brain structures. The second is functional neuroimaging, which generates maps of brain activity by detecting signals that correlate with the firing of brain cells. Functional neuroimaging usually involves the application of MRI or positron emission tomography (PET). The third type of neuroimaging, which typically employs PET, uses radioactive tracers to locate and quantify specific molecules in the brain. In research settings, imaging tools can help explain what goes wrong in the brain to produce certain mental illnesses, and these findings in turn can help define the boundaries of brain disorders. In clinical settings, neuroimaging tools may eventually play a role in diagnosis and in monitoring the effectiveness of treatment.

To be useful for psychiatric diagnosis, a test based on neuroimaging must be affordable and feasible to administer. It must also be sensitive enough to detect the inconspicuous features of a particular brain disorder and yet specific enough to rule out other conditions. Some anatomical signs of mental disorders are nonspecific: people with schizophrenia generally have enlarged cerebral ventricles (the fluid-filled spaces deep in the brain), but this abnormality may also occur in people with alcoholism or Alzheimer's. In patients with severe, chronic depression, the hippocampus—a brain structure critically involved in memory—may be atrophied, but

this anomaly has also been observed in post-traumatic stress disorder and is characteristic of the later stages of Alzheimer's. The utility of imaging for diagnosis will depend on finding abnormalities that are specific to a certain disease or perhaps to a symptom complex that may occur as a component of one or more diseases.

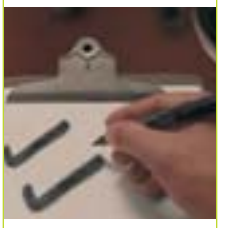
Furthermore, morphometric analysis of the human brain has proved to be challenging. Because the overall sizes and shapes of people's brains differ so much, researchers must employ complex computer algorithms to define normal values for various populations and compare the brains of individuals against those group norms. Moreover, the boundaries between brain structures may be very subtle. MRI atlases showing the anatomy of the normal human brain as it develops over the course of childhood and adolescence are only now becoming available.

Nevertheless, scientists have been able to use neuroimaging to shed some light on psychiatric illnesses. In 2001 teams led by Judith L. Rapoport of the National Institute of Mental Health and Paul Thompson and Arthur W. Toga of the David Geffen School of Medicine at U.C.L.A., produced an impressive study that found striking anatomical changes in the brains of adolescents with schizophrenia. The researchers focused on a relatively rare form of schizophrenia that begins in childhood. (The first signs of schizophrenia usually appear in the late teens or early 20s.) MRI scans of the brains of the affected children showed a remarkable loss of gray matter in the cerebral cortex—the brain structure responsible for higher thought—between the ages of 13 and 18 [*see illustration on page 101*]. As the disease progressed, the loss of gray matter intensified and spread, engulfing cortical regions that support associative thinking, sensory perception and muscle movement. The anatomical abnormalities mirrored the severity of the psychotic symptoms and the impairments caused by the disease.

Such studies point the way toward a diagnostic test. It is possible that some index of measurements of cortical thickness and the size of structures known to be affected in schizophrenia (such as the hippocampus) could be used to discern whether a young person is suffering from the disorder and to chart the progress of the disease. Early detection of schizophrenia could be a great boon to treatment. Researchers are now investigating whether early intervention in schizophrenia with antipsychotic drugs and stress management therapy can delay the onset of symptoms and reduce their severity.

Functional neuroimaging may also find significant uses in diagnosis. In Alzheimer's, loss of brain function may precede the macroscopic atrophy of brain structures. Investigators are already trying to refine the diagnosis for Alzheimer's by linking cognitive testing with functional imaging using MRI or PET. A similar strategy could possibly be applied to schizophrenia, which is characterized by failures in working memory (the ability to keep information in mind and manipulate it). It is conceivable that cognitive tests combined with functional imaging of the prefrontal cortex—a brain region that supports working memory—could contribute to the diagnosis of schizophrenia and, perhaps more important, track the success of therapy.

NEUROIMAGING TOOLS may eventually play a role in diagnosis and in monitoring the EFFECTIVENESS OF TREATMENT.



By combining neuroimaging with genetic studies, physicians may eventually be able to move psychiatric diagnoses out of the realm of symptom checklists and into the domain of objective medical tests. Genetic testing of patients could reveal who is at high risk for developing a disorder such as schizophrenia or depression. Doctors could then use neuroimaging on the high-risk patients to determine whether the disorder has actually set in. I do not want to sound too optimistic—the task is daunting. But the current pace of technological development augurs well for progress. SA

MORE TO EXPLORE

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IS BETTER BEST?

A NOTED ETHICIST ARGUES IN FAVOR OF BRAIN ENHANCEMENT **BY ARTHUR L. CAPLAN**

THE REVOLUTION IN OUR ABILITY TO IDENTIFY AND manipulate genes has spurred all sorts of ethical debates, but an equally profound revolution—in brain science—is attracting amazingly little attention.

Progress in many areas of neuroscience promises not only to reveal how the brain works in general but to provide information about our intentions, thoughts and feelings as well as the mental aberrations that plague so many of us. Right now sophisticated imaging tools are enabling scientists to see which parts of the brain are active at any given time and to observe the effects of drugs, fear or other stimuli. Granted, researchers so far have only a limited understanding of brain function. But that will change. Because the structure and activities of our brain influence our mental health and behavior much more directly than our genes do, it is very likely that advances in the ability to "read" the brain will be exploited as much as, or more than, knowledge of genetics for such purposes as screening job applicants, diagnosing and treating disease, determining who qualifies for disability benefits and, ultimately, enhancing the brain.

Already lawyers are attempting to submit brain scans as evidence of their clients' innocence. Government agencies are considering scanning the heads of prospective military pilots, astronauts and secret agents to see who might be predisposed to do what in response to stress or temptation. Doctors are implanting devices directly into the brain to help patients cope with Parkinson's disease. There is talk of pills to aid soldiers in erasing the memories of war horrors and implants that might repair or even enhance memory. And high school kids who have no obvious learning disabilities are swallowing Ritalin and other psychoactive drugs to get an edge when they take classroom exams or SATs. All this activity ought to get our ethical radar going, prompting considerations of who might be harmed and how to protect those people. At the moment, questions far outnumber answers, but identifying key ethical issues is an essential first step.

It is hard to argue that anything is fundamentally wrong with trying to detect and ameliorate brain disease. But those efforts nonetheless raise serious issues similar to those arising from the ability to perform genetic testing and therapy: Who decides, and on what basis, whether a risky procedure is justified for a given person? And does each of us have the right to insist that no testing or intervention be done, with no results shared with others, unless we give our consent?

Even people comfortable with the idea of fixing obvious brain deficits become much prissier when it comes to mucking with brains to make them better than good. Americans in particular believe that people should earn what they have. Having a brain

THE AUTHOR

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that can do more as a result of a drug or a chip or an implant seems like getting something for nothing.

But is it really so terrible if techniques used to treat Alzheimer's disease or attention-deficit disorder lead to ways to improve normal memory? Would it be bad if some innovation—say, a brain chip implanted in the hippocampus—enabled a person to learn French in minutes or to read novels at a faster pace? Should we shun an implant that enhances brain development in newborns? If altering the brain makes it possible to perform better, achieve more or have greater capacities than one's parents, is such alteration patently immoral?

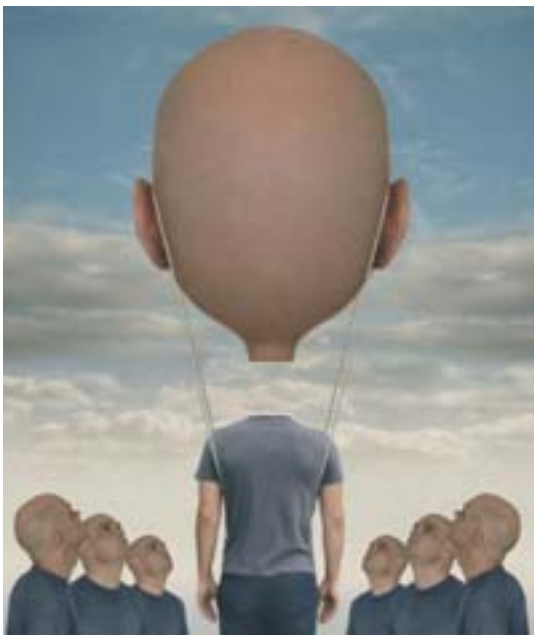
Unfair? Unnatural?

I SEE LITTLE WRONG with trying to enhance and optimize our brains. To clarify why I think this way, let us consider some likely objections.

One is that tweaking neurons to improve brain capabilities might threaten the equality of human beings; by becoming advantaged, recipients would achieve more and command greater respect. But the right to be treated with respect has never depended on biological sameness or on a leveling of behaviors. Just as the disabled and sick should never have a lesser right to fair treatment, happiness and opportunity, neither should those who do not receive brain-enhancing interventions.

Many people believe that enhancement would be unethical because some of us would be able to get an improved brain and some would not, which would be unfair. It is certainly possible—in fact, probable—that if nothing were done to ensure access to brain-enhancing technologies, inequities would arise. But as Kaplan test preparatory courses, music camps and math tutors remind us, access to things that improve the mind is already skewed unfairly. This state of affairs does not make inequity right. The solution, though, is to provide fair access—be it to teachers or implantable chips—not to do away with the idea of improvement. As it happens, my son is privileged; he goes to private school. If I told people in a poor neighborhood about his education, they would not say I should be ashamed of myself for giving him an advantage. Nor would they claim that better education is immoral. They would say, "I wish I could do that for my child."

Equity aside, isn't it true that brain engineering is unnatural? If we started to enhance ourselves, we might be able to do more, but would we still be human when we were done? The main flaw with this argument is that it is made by folks who wear eyeglasses, use insulin, have artificial hips or heart valves, benefit from transplants, ride on planes, dye their hair, talk on phones, sit under electric lights and swallow vitamins. What are they really talking about? Have we become less human because we ride instead of walk to work? We might be less healthy, but does a reliance on technology for transportation make us unrecognizable as humans? Is there a natural limit beyond which our nature is clearly defiled by change? Surely not. It is the essence of humanness to try to improve the world and oneself.



Unequal access to enhancement technology would be unfair. But the solution, the author says, is to improve access, not to bar enhancement.

Last, some may argue that brain enhancement is wrong because it will inevitably involve coercion. Subtly or otherwise, the government or corporate advertisers will convince us that unless we have the best brains possible, we will be letting down our families and communities. People might also feel coerced in that if they did not submit to enhancement, they might be left behind in the hunt for jobs and social success. But the answer is not prohibiting improvement. It is ensuring that enhancement is always done by choice, not dictated by others.

In reality, though, it is unlikely that coercion will be needed to induce people to want to optimize their brains. Market-driven societies encourage improvement. Religious and secular cultures alike reward those who seek betterment; every religion on the planet sees the improvement of oneself and one's children as a moral obligation. If anything, the impending revolution in our knowledge of the brain will require us to build the legal and social institutions that allow fair access to all who choose to do what most will feel is the right thing to do. SA

MORE TO EXPLORE

Neuroethics: Mapping the Field. Edited by S. J. Marcus. Dana Press, 2002. Available at **www.dana.org/books/press/neuroethics/neuroethics.pdf**

Emerging Ethical Issues in Neurology, Psychiatry and the Neurosciences. A. L. Caplan and M. Farah in *The Molecular and Genetic Basis of Neurologic and Psychiatric Disease.* Third edition. Edited by R. N. Rosenberg et al. Butterworth-Heinemann (in press).

MELISSA SZALKOWSKI

BILL VALIDATORS

On the Money

If you have ever stepped up to a vending machine, arcade game or slot machine and inserted a $1, $5, $10 or $20 bill, your money has been scrutinized by a "bill validator." Relatively unchanged since they were first tested in the late 1960s for $1 bills, in the past few years these chunky sensors have gone high tech.

For decades, bill validators simply had a magnetic head—similar to a tape recorder's—that brushed up against the lengthwise center of a bill, drawn by rollers. Magnetic ink in one of the note's seals, and in the middle of the portrait, created characteristic signatures that circuitry compared against a table of reference values to determine the bill's denomination and authenticity. But the magnetic head got grimy as ink flaked off, requiring frequent servicing, and counterfeiters could sometimes fool the machinery with "bills" duplicated on copy machines that used magnetic toner.

Today's validators use optical, inductive and dielectric sensors that assess all kinds of traits. Much harder to fool, they are cropping up at self-checkout counters in stores and in automatic teller machines (ATMs) that accept cash as deposits.

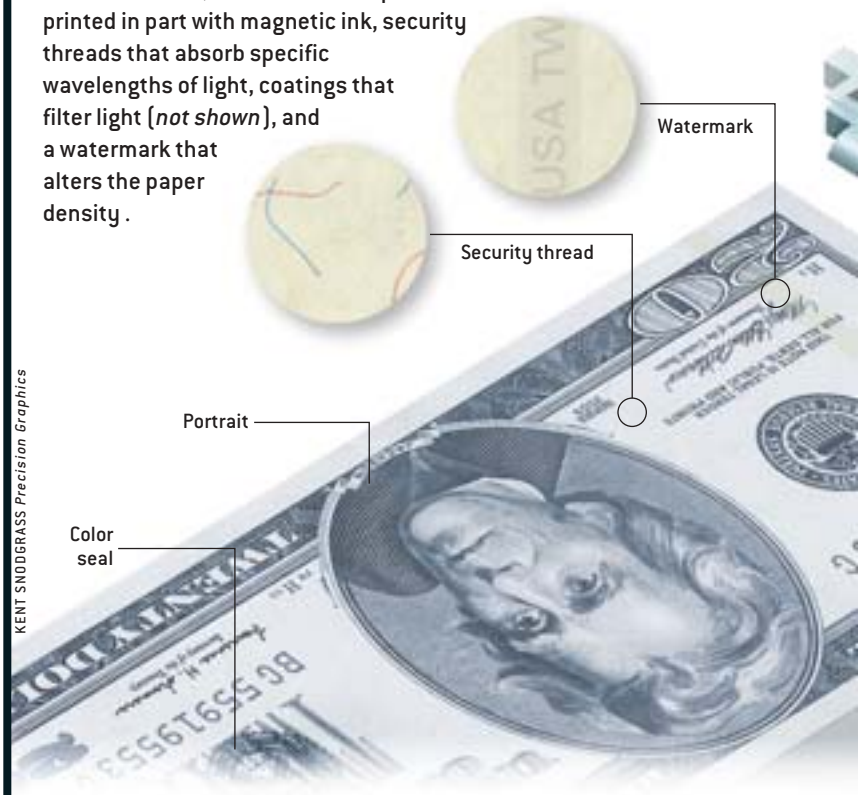
Whenever the U.S. Treasury changed a bill design, however, makers of validators had to scramble to install new integrated circuit chips in hundreds of thousands of machines. In 1998 the treasury made things easier when it decided to introduce a new generation of $5 and $10 notes. "The government for the first time gave the validator industry samples six months in advance so we could reprogram our machines," says Marlon Silver, technical service manager at CashCode in Concord, Ontario, one of the largest of the world's 15 or so suppliers. The newest validators have a port for a flash-memory stick that a technician can insert to update the circuitry, instead of installing a new chip.

This autumn the treasury plans to introduce a new $20 that has a subtle background color. "We have the bills," Silver notes, "but we still don't have a release date." There are now more than 2.5 million vending machines in North America and millions more slot machines. "If we're given short notice to update the validators," Silver says "it'll be a war out there."

—Mark Fischetti

BILL VALIDATOR spins its rollers when a note's leading edge interrupts an activator beam. As the bill heads through the validator, optical sensors go to work. They each contain light-emitting diodes that shine different wavelengths of infrared and visible light and one phototransistor (receiver); they sense the reflectivity, transmittance and fluorescence of various spots on the bill to read its denomination and the position and colors of the seals, portrait and security threads.

CURRENCY has features unique to each denomination that a bill validator can verify, among them a seal printed with colored ink, a black seal and portrait printed in part with magnetic ink, security threads that absorb specific wavelengths of light, coatings that filter light (*not shown*), and a watermark that alters the paper density .



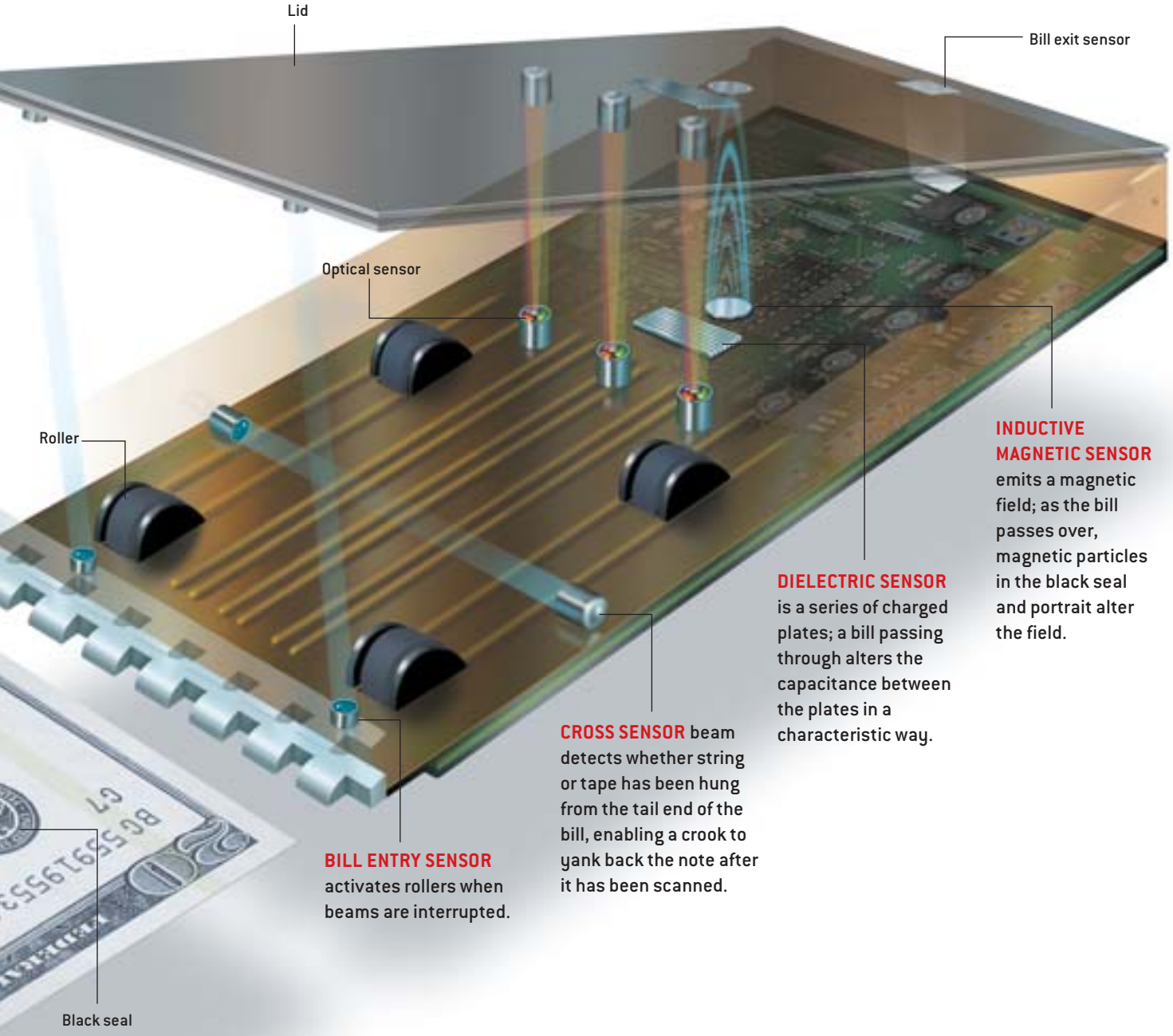
KENT SNODGRASS *Precision Graphics*

DID YOU KNOW . . .

➤ REJECTED: You feed a nice dollar into a vending machine, but the blasted machine spits it back at you. Why? Three leading reasons: Repeated folding across the portrait can break up the magnetic ink, presenting an invalid magnetic signature to sensors. Holding the money too long as you insert it can disrupt the smooth intake speed the validator needs to move the bill accurately over sensors. And if the bill's corners are bent, they can jam the rollers, so the validator gives it back.

➤ LAUNDERING: When programming chips or flash-memory sticks that will update validators for new bill designs, employees at manufacturers artificially age sample greenbacks by manually passing them around, wrinkling them and running them through a washing machine. "Still," says Marlon Silver at CashCode, "they're just not the same as street money." Once bills are in circulation, technicians may need to further update machines to improve the acceptance rate of worn currency.

➤ WIDE WORLD OF MONEY: Many countries issue notes of various widths for different denominations. To handle these variations, some machines have an elliptical wheel just inside the mouth of validators that props the bill above the rollers for a moment. As the bill floats back down, side rails quickly veer in to center it over sensors, then retract out of the way.



INDUCTIVE MAGNETIC SENSOR emits a magnetic field; as the bill passes over, magnetic particles in the black seal and portrait alter the field.

DIELECTRIC SENSOR is a series of charged plates; a bill passing through alters the capacitance between the plates in a characteristic way.

CROSS SENSOR beam detects whether string or tape has been hung from the tail end of the bill, enabling a crook to yank back the note after it has been scanned.

BILL ENTRY SENSOR activates rollers when beams are interrupted.

This month's topic was suggested by reader Tim Silverstein. Send your ideas to workingknowledge@sciam.com

Friable Flowers

GLASS UNDER GLASS: HARVARD UNIVERSITY'S UNUSUAL BOTANICAL COLLECTION

BY MARGUERITE HOLLOWAY

It is easy to get lost in the tall grasses. They stretch out, the matte green of their leaves conveying what it would be like to touch them, to run your finger down the blade and feel the rough resistance of these durable plants' skin: the gama grass, rough hair grass and broom beard grass. Their spindly, delicate roots seem just plucked from the earth.

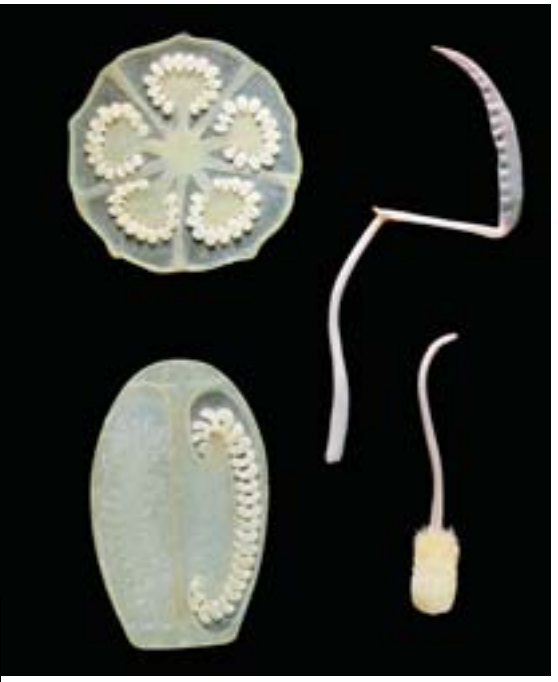
It would be possible to spend a morning with these three alone. But there are at least 3,000 other plants in this cool, gently lit room with its muffling gray-brown rug. And they are just as entrancing. Arranged in shallow wooden cases, this botanical collection at the Harvard Museum of Natural History is unique. No hothouse or herbarium contains anything comparable; no wilted, browned specimens pressed between paper rival it. These plants and flowers are made of glass—down to the tiny, hairlike bristles on some of their roots. They look so real, so exactly like their soil-anchored counterparts the world over, that some people spend hours in the Ware Collection of Glass Models of Plants: seeing flora as if for the first time, trying to spot an inconsistency between a model and a recollection of the real thing, straining to see brittle glass where it seems there is only yielding tissue.

Beginning with grasses—including floating manna-grass, squirrel-tail grass, pigeon grass—on the left side of the small, three-aisled room, and ending with a case containing chicory on the right, the collection holds about 800 species—palm, lily, orchid, cactus, cacao, laurel, sunflower, pitcher plant, goldenrod, zinnia and ivy among them. Many of the displays include not only a plant and its flowers but also enlarged models of various parts: transected ovaries (magnified 50 to 60 times in some instances) like thin, pale slices of cucumber, as well as stamens, stigmas and spikelets. A pollen grain 2,000 times its natural size resembles a koosh ball; another, a soccer ball. Sometimes the light catches a petal and little sugarlike sparkles give away the glass. Such is the case with the tiny purple flowers of the pineapple plant (*Ananas comosus*). In other models, it is impossible to tell: the leaves of the ashy willow (*Salix cinerea*) are uneven in color, lighter green on the tips with a dusting of brown—the imperfec-

FRAGRANT WATER LILY (*Nymphaea odorata*) (*above*) and purple iris (*Iris versicolor*) (*right*) are among the many flowers in the collection.

tions so perfectly rendered that the branch seems just collected from the woods.

The pieces were created entirely by two artisans, Leopold and Rudolf Blaschka, between 1886 and 1936. The father and son lived near Dresden, Germany, and were renowned for their marine invertebrate models, three of which are displayed elsewhere in Harvard's natural history museum: a jellyfish in the Treasures exhibit and a squid and a sea peach



HILLEL BURGER; © PRESIDENT AND FELLOWS OF HARVARD COLLEGE. ON DISPLAY AT THE HARVARD MUSEUM OF NATURAL HISTORY

FLOWERS' CREATORS also made enlarged plant parts for study, including these slices of ovary (*upper* and *lower left*), stamen (*upper right*) and pistil (*lower right*) of the Glory-Bush (*Tibouchina semidecandra*).

in the Modeling Nature show. (A dozen or so of their other marine models are on view at the Corning Museum of Glass in Corning, N.Y., and will ultimately form part of a much larger permanent collection at Cornell University.) In the late 1880s George L. Goodale, the first director of Harvard's Botanical Museum, heard about plant models by the Blaschkas and began commissioning glass flowers from them for educational use. Students could then study readily accessible, crystal-clear specimens.

Little is known about the Blaschkas' formal education, but their work suggests a strong background in natural science. The duo experimented with various kinds and colors of glass, wire armatures, glue, metal and paint to create the models. For instance, according to a study in the *Journal of the American Institute for Conservation,* the Blaschkas often added a gum arabic varnish to give the glossy glass a matte finish. "They are so absolutely exact that it is something of a mystery to us," says curatorial associate and science historian Susan M. Rossi-Wilcox. "They were not stylizing at all, which is something they could have done. They were really obsessive." Rossi-Wilcox, who is going through the Blaschkas' correspondence, says that the two would even discuss whether a specimen growing in the unnaturally favorable conditions of their garden was appropriate to depict because the resulting glass figure might not be entirely accurate or real looking.

Modern teaching tools, including better microscopes and photographs, rendered the models more artistically than educationally relevant: "They evoke a time, just as fantastic botanical illustrations do, before the dissecting scope, before those were available to students," notes author, anthropologist and botanist Wade Davis, who studied in the 1970s with Harvard's famous ethnobotanist Richard Evans Schultes. Although Davis says he did not visit the collection to learn taxonomy, "it added to the allure of the place that the main exhibit would be something as curious and quaint and old-fashioned and transcendent as those glass flowers."

"The glass flowers were almost like a metaphysical presence, part of the mystique and the experience of that whole building," says another former Schultes student, Douglas C. Daly, curator of Amazonian botany at the New York Botanical Gardens. "Something that was precious and protected and also something they worried about a lot."

That worrying continues today. Although the flowers were recently moved away from the main staircase—where the vibrations from visitors' feet were quite intense—they have suffered damage over time. You can see shattered glass under a leaf of a type of wild cucumber called Nimble Kate (*Sicyos angulatus*) and the unsightly glue of early restoration efforts on many other models. Rossi-Wilcox says that there are thousands of cracks and breaks: "All of the models need to be cleaned, and a majority need to have some small repairs."

Because the Blaschkas trained no apprentices and kept poor records of their techniques, Rossi-Wilcox has initiated high-tech analyses of the models to help guide conservators. The museum is now planning a restoration that could take a minimum of 15,000 hours and cost as much as $5 million. Ideally, says museum director Joshua Basseches, the models would sit in vibration-free cases like those used in museums in earthquake zones.

Despite their beauty, the obvious vulnerability of the flowers can make visiting them a disturbing experience at times. No one is stationed in the room to watch over the exhibit, and in my several hours of looking at the plants, I encountered six school groups, some of whose kids used the cases as a hard surface to write notes for their assignments. But visitors of all ages transgressed. Two men leaned against the displays, tapping on the glass casing to show each other some specimen that was most likely flaking glass as they did so. I left the room several times because it was too nerve-wracking to watch.

The Harvard Museum of Natural History is located at 26 Oxford Street in Cambridge, Mass., and is open every day (except on four major holidays) from 9 A.M. until 5 P.M. Admission is $6.50 for adults. For information, call 617-495-3045 or visit www.hmnh.harvard.edu. Additional resources: www.rps.psu.edu/sep99/glass.html; www.hno.harvard.edu/gazette/2000/11.16/12-flowers.html; and *The Glass Flowers at Harvard,* by Richard Evans Schultes and William A. Davis (1992). SA

Biting Us and the Dust

HUMANITY'S TIME SPENT FLEEING FROM PREDATORS IS ALMOST FINISHED, WHICH IN THE LONG RUN MAY BE AS TRAGIC AS BEING EATEN **BY STEVE MIRSKY**

MONSTER OF GOD: THE MAN-EATING PREDATOR IN THE JUNGLES OF HISTORY AND THE MIND
by David Quammen
W. W. Norton, New York, 2003 ($25.95)

Incoming college freshmen often hear an advisory adage: "You don't take courses, you take professors." That is, regardless of the subject, enroll in classes taught by the best instructors. In that spirit, even without a previous interest in man-eating predators, potential readers will very likely find *Monster of God* worthwhile because David Quammen wrote it.

Quammen is probably best known for the years he spent at *Outside* magazine, writing beautiful, witty and informative essays, which live on in the collections *The Boilerplate Rhino* and *The Flight of the Iguana*. His previous sprawling science-cum-travel book was *The Song of the Dodo*, a globe-trotting adventure that took the author to wild places in search of secrets of island biogeography. A chunk of that work dealt with the Komodo dragon, a stealthy hunter that occasionally bags itself a human victim. Man-eating predators must have gotten under Quammen's skin—figuratively, fortunately. The new work is entirely devoted to the contemplation of a few of the remaining species that can stalk, attack, kill and eat a human being. "It's one thing to be dead," Quammen writes. "It's another thing to be meat."

He frames his parameters in the first chapter. Elephants, bison and rhinos trample the odd person; wolves and hyenas may pack-attack the unlucky human; snake venom poisons people; and "malarial mosquitoes could be considered the deadliest form of wildlife on the planet." But those animals do not sit precariously atop the food chain.

Quammen's thesis is that human beings have a special, coevolutionary relationship with top predators, a result of having long been the hunted rather than the hunter. The top predators thus still haunt our dreams, having been incorporated into our mythology, art, epic literature and religion. One could make the same argument, in particular, for snakes—big ones still sometimes consume people, and they are certainly represented in mythology, art, literature and, God knows, religion. But it somehow *feels* right that Quammen has confined his discussion to four large beasts that can defeat, kill and eat any person not carrying significant weaponry: lions, crocodiles, bears and tigers.

Using case studies to illuminate general points, Quammen limits the locales from which he reports. For lions, he visits the Gir forest of westernmost India, where a few hundred individuals, belonging to a subspecies closely related to the more familiar African lion, survive in close quarters with Maldharis, traditional buffalo herders. Next he hangs out with the Yolngu of north-central Australia, who hang out with crocodiles. He then takes us to Romania's Carpathian Mountains, where bears share the woods with shepherds and state forest managers. The bears are conspecific with American grizzlies but as recently as 1988 had a population density 20 times that in Yellowstone National Park and its surroundings. And he finishes in the Russian Far East, where the Udege people hunt and trap small mammals while avoiding being hunted and trapped by Siberian tigers.

Like any good reporter, Quammen bugs people. He sucks information from scientific experts as well as from the people who still live more or less alongside these animals. And he acknowledges his pestering, referring to the graciousness

"THERE'S JUST NO SINGLE ANSWER," the author writes, "to the question of how Yolngu people regard *Crocodylus porosus* [*below*]. One man's monster is another man's god."

MIKE PARRY *Minden Pictures*

of one source for putting up with "my greedy, unfocused curiosity." That self-description is manifest in the finished work. Reading Quammen can be like having a cocktail-party conversation with a man just home from an around-the-world tour but who is, amazingly, not boring. And so, in addition to news from the front, the reader is treated to excursions into taxidermy recipes, mythology based on heroic battles against man-eaters (including an entire synopsis of *Beowulf* and a good piece of *The Epic of Gilgamesh*), a review of the scientific analysis of predator teeth structure and function, and discussions of ecological theories of body size and predator-prey relationships as functions of environmental constraints. He also muses on cave art, with specific attention to paintings rediscovered in 1994 at Chauvet Cave in France, which, based on the subject matter of an artist who toiled about 35,000 years ago, was lousy with lions.

In all Quammen's case studies, the human voraciousness for habitat means increasingly tragic human-predator interactions and probable eventual doom for the predators. After reviewing U.N. population estimates of almost 11 billion humans teeming on earth by 2150, he writes, "Call me a pessimist, but when I look into that future, I don't see any lions, tigers, or bears." Oh my, indeed. The only way to ensure a version of survival may be to allow individuals of these species to be hunted for big bucks, thus making extant beasts economically attractive. "To me it's a tedious paradox," Quammen concludes, "not a liberating insight, and no matter how often I hear it, applied to one or another magnificent species in their various corners of the world, each time I find it tedious afresh. But, beyond quibbling over details of linkage and enforcement, I can't rationally disagree." SA

Steve Mirsky is an editor at Scientific American *and writes the monthly Anti Gravity column.*

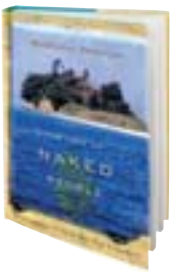
REVIEWS

THE EDITORS **RECOMMEND**

THE LAND OF NAKED PEOPLE: ENCOUNTERS WITH STONE AGE ISLANDERS

by Madhusree Mukerjee. Houghton Mifflin, New York, 2003 ($24)

Imagine a place where the inhabitants use only Stone Age tools, do not know how to spark a fire and fiercely defend their territory against outsiders, using bows and arrows to kill or injure anyone who dares to intrude. That would be the Andaman Islands, the Land of Naked People, an archipelago off the coast of India where a tribe called the Jarawa has thrived for millennia, all but untouched by the influence of other cultures. Mukerjee, a former *Scientific American* editor, worked for years to gain access to the Jarawa and other, less hostile, tribes on the Andamans. Using her Indian family connections and dogged determination to cut through the red tape designed to shield the often corrupt Indian officials who manage the Andamans, Mukerjee visited one of the last aboriginal peoples. She weaves her contemporary observations of the various Andaman tribes together with historical accounts of their contacts with outsiders, yielding a fabric rich with meaning about what vastly different peoples can learn from one another.



A CITIZEN'S GUIDE TO ECOLOGY

by Lawrence B. Slobodkin. Oxford University Press, New York, 2003 ($14.95)

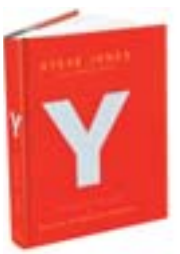
Slobodkin, professor emeritus of ecology and evolution at the State University of New York at Stony Brook, provides a calm voice amid the rancor often arising in discussions of ecology. "I have two goals," he writes. "One is to enhance appreciation of the pleasure and beauty to be found in nature. Another goal is to help individual citizens understand the real and unreal assertions about existing problems and impending disasters in nature." Dismissing ecological fanatics and faddists, he focuses on "real ecological problems that require solutions," in particular, global warming and endangered species. "If ecologists are very successful," he says, "they will help maintain the pleasant and livable properties of the world. If not, the world will change in unpleasant ways."

Y: THE DESCENT OF MAN

by Steve Jones. Houghton Mifflin Company, New York, 2003 ($25)

THE X IN SEX: HOW THE X CHROMOSOME CONTROLS OUR LIVES

by David Bainbridge. Harvard University Press, Cambridge, Mass., 2003 ($22.95)



Jones and Bainbridge arrive in different ways at the same conclusion: women are the more resilient sex. Jones, professor of genetics at University College London, puts it bluntly: "[M]ales are wilting away.... From sperm count to social status, and from fertilization to death, as civilization advances those who bear Y chromosomes are in relative decline." Bainbridge, lecturer in comparative anatomy and physiology at the Royal Veterinary College in London, focuses more on the biology of sex differences. "Almost every woman is, inside and out, a patchwork of two different cells—some using one X chromosome, and some the other.... What more all-encompassing way could one want for women to be more complex than men?" Consequently, they are less vulnerable to such sex-linked diseases as hemophilia, muscular dystrophy and color blindness.

All the books reviewed are available for purchase through www.sciam.com

Missing Hiker

BY DENNIS E. SHASHA

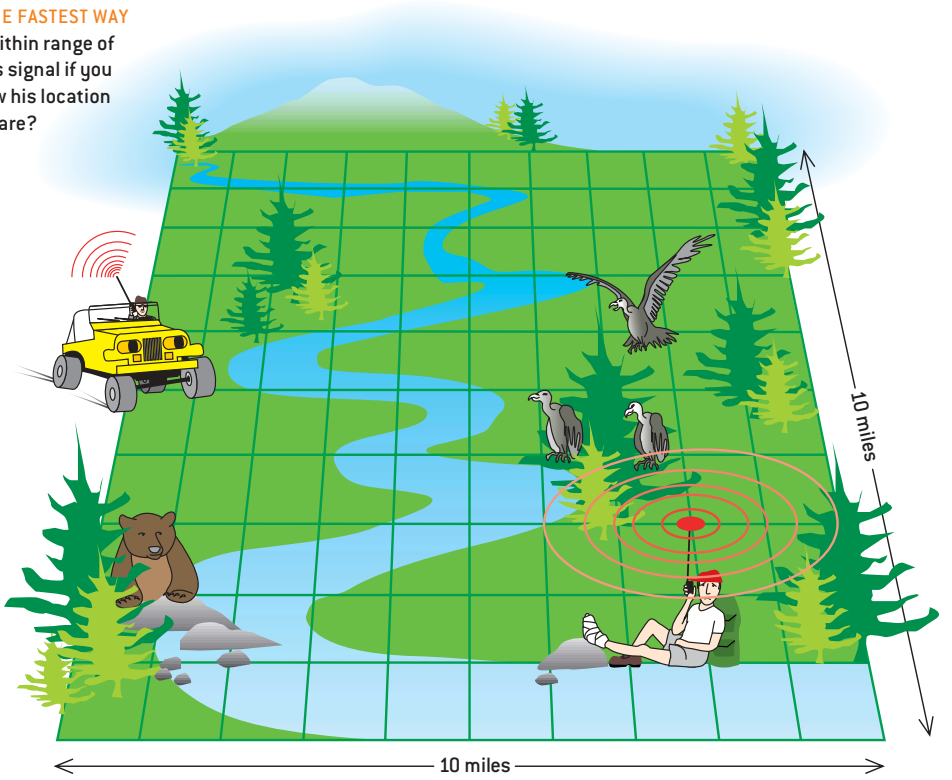
A hiker has been seriously hurt somewhere in a 10-mile-by-10-mile-square area. Unable to move, he sends a distress signal with a range of two miles. When your search party is within range of his signal, your directional finder will lead you right to him. Your task is to guarantee coming within range of the hiker's signal as quickly as possible. Assume you can start from any point on the perimeter of the square and travel continuously. Your Jeep allows you to go a mile every 10 minutes.

As a warm-up problem, consider a rectangle instead of a square. Assume that the rectangle has an area of 100 square miles. To ensure finding the hiker's signal as quickly as possible, what would the dimensions of the rectangle need to be?

For the 10-mile-by-10-mile square, can you find a solution that guarantees detecting the hiker in less than 300 minutes? Many other variants of this puzzle are possible. There may be more than one search party, for example, or travel may be easier along certain paths. The variants that interest me most, however, involve changing the distress signal. For instance, what if the signal is on for a minute and then off for a minute? Is any solution below 350 minutes possible then? SA

Dennis E. Shasha's latest puzzle book is Dr. Ecco's Cyberpuzzles *(W. W. Norton, 2002).*

WHAT'S THE FASTEST WAY to come within range of the hiker's signal if you don't know his location in the square?



CORNELIA BLIK

ANSWER TO WARM-UP PROBLEM: A rectangle 25 miles long and four miles wide would have the fastest detection time. The Jeep starts from the middle of one of the rectangle's short sides and travels in a straight line to the middle of the opposite side. During the 25-mile trek, which takes 250 minutes, the Jeep comes within two miles of every point in the rectangle.

Answer to Last Month's Puzzle

Here is a 14-minute solution for the seven-message case:
Start A, B and F at 0 minutes.
Start G at 3 minutes, D at 6, C at 7 and E at 8.

If we add three more four-minute messages (call them H1, H2 and H3), we can finish in 18 minutes as follows:
Start A, B and H1 at 0 minutes.
Start F at 4 minutes, D at 6, G and H2 at 7, E at 11, and C and H3 at 14.

Web Solution

For a full explanation of last month's puzzle and a peek at the answer to this month's problem, visit www.sciam.com

A Mighty Wind

TALKING ABOUT THE WEATHER, WITH A SLIGHTLY HIGHER AUTHORITY **BY STEVE MIRSKY**

Five years ago I wrote a column saying that televangelist Pat Robertson should concentrate on religion and leave weather forecasting to the professionals. The occasion then was Robertson, speaking for God, warning the city of Orlando to expect hurricanes in retribution for that city's decision to allow a gay celebration. A hurricane in Florida, it seemed to me, could very well be a simple, natural phenomenon. Having made my point, I spent the next half a decade happily deconstructing various other scientific subjects in this space. But a clipping recently landed on my desk that reminded me that vigilance, eternal it would seem, is indeed the price of liberty. It is therefore time, once again, to ask, courteously, of course, that Pat Robertson please stop delving into meteorology.

To be fair, which immediately distinguishes this pasquinade from the literary output of Robertson's Christian Broadcasting Network (CBN), I must divulge that his name doesn't appear on the June 26 Web document "Acts of God: America's Warning Not to Divide Israel." The piece looks a lot like a news story, right up until you read it. And it carries the CBN imprimatur, which makes it Robertson's responsibility, if not his actual, personal production.

The basic thesis of the article is that God is angry with the U.S. for the country's support of the creation of a Palestinian state. We're apparently recklessly fooling with "the covenant God made with the descendants of Abraham," the article states, whereby those descendants get the land that is currently, and eternally it would seem, being contested. And perhaps to teach us a lesson, the article contends, the U.S. got hit with the most awful run of tornadoes on record.

"On April 30, 2003," notes the CBN screed, "America was positioned as the catalyst to jump-start the so-called 'solution' to the Middle East crisis. As U.S.-backed Palestinian Prime Minister Mahmoud Abbas was sworn in, the 'Road Map' peace plan was set in motion. The

very next day began the worst month of tornadoes in American history, more than 500 in a single month." QED, sort of.

Now, I know less about religion than a camel knows about fitting through the eye of a hurricane. And I'm not nearly smart enough to pretend to know how to achieve peace in the Middle East. But I do have questions about CBN's meteorological methodology. The Middle East is a roiling place where most every day sees an outrage. If the tornadoes had struck a week earlier or a month later, no doubt the region or the U.S. response to it would have provided tornado instigation. Still, in keeping with the theory that the tornadoes were caused by some human activity—other than general climate disruption as a result of environmental degradation, of course—I searched for additional possible causes.

On May 1, the day the tornadoes began, the Federal Emergency Management Agency closed the Applicant Assistance Center for September 11 survivors in Lower Manhattan, which could have been deemed wicked. May 1 was also proclaimed by President George W. Bush to be Loyalty Day, which apparently leaves 364 days to be seditious, a bad thing. On April 30, Internet Advertising Report noted that media veteran Martin Yudkovitz left NBC to work for TiVo, which chills my marrow. April 30 likewise marked the end of National Poetry Month, and, as Robert Frost poetically pointed out, "Good fences make good neighbors."

So I would have to reason that any of those events—or much more likely, none of them—could have been responsible for the tornadoes. Indeed, the big problem in this field is figuring out when the weather is a sign of divine intention and when it's just the weather. For example, on August 27, 1998, while my column about Robertson's threats to Orlando was on the newsstands, Hurricane Bonnie smashed into Virginia Beach, Va.—which is home to CBN. Nevertheless, I believe it was just a coincidence. SA

ILLUSTRATION BY MATT COLLINS; PHOTOGRAPH BY FRANK VERONSKY

ASK THE EXPERTS

I was vaccinated against smallpox 40 years ago. Am I still protected?

—M. Herrick, Las Vegas

Gigi Kwik of the Center for Civilian Biodefense Strategies at Johns Hopkins University explains:

Edward Jenner, the English physician who first developed the smallpox vaccine in 1796, believed that vaccination caused a fundamental change in a person's constitution and would lead to lifelong immunity to smallpox. Unfortunately, it is now clear that this immunity wanes over time. A vaccination received 40 years ago most likely does not protect you against smallpox infection today, although it may help prevent a fatal outcome.

It is difficult to determine exactly how long the smallpox vaccine provides defense against the virus. Limited research continues with virus samples at the Centers for Disease Control and Prevention in the U.S. and at a Russian government laboratory in Koltsovo, but smallpox infections no longer occur naturally. Thus, modern scientific techniques cannot be brought fully to bear on this question.

Some researchers believe—but have never proved—that smallpox immunity rests on the presence of neutralizing antibodies in the blood, whose levels decline five to 10 years after an inoculation. With smallpox absent now in the wild, it is not possible to study the relation between antibody levels and susceptibility. Scientists do know, however, that having had a vaccination within five years of exposure offers good protection against smallpox; the effectiveness beyond 10 years is not so clear. Moreover, a 1968 CDC study of smallpox cases "imported" by ailing travelers into countries where the disease was not endemic found that mortality was 52 percent among the unvaccinated residents, 11 percent among those who had been vaccinated more than 20 years earlier and 1.4 percent for those vaccinated within 10 years.

If you think you have been exposed to the virus, you should definitely be revaccinated. Vaccination after exposure to an infected person, even as long as four days later, can prevent the disease. But be aware that the vaccine, which is actually a live virus similar to smallpox, is not as innocuous as a flu shot. Historically, about one in 1,000 smallpox vaccine recipients has experienced severe side effects, including rashes or heart problems, and about one in a million has died from the vaccine. People who are revaccinated are, in general, much less likely to suffer from side effects than those vaccinated for the first time. Risk may be higher for those who have eczema, for pregnant women and for those whose immune systems are impaired.

Why is the South Pole colder than the North Pole?

—E. Jenson, Camarillo, Calif.

Robert Bindschadler, senior fellow and glaciologist at the NASA Goddard Space Flight Center, offers this answer:

The high altitude of the South Pole and the land under it help to make the region the coldest on the planet. The lowest temperature ever recorded there by the permanently manned station was –80.6 degrees Celsius, whereas the most frigid temperature at the North Pole has been measured by satellites to a low of only –48.9 degrees C.

Of course, both polar regions of the earth are cold, primarily because they receive far less solar radiation than the tropics and midlatitudes do. Moreover, most of the sunlight that does shine on the two regions is reflected by the bright white surface.

At the South Pole, the surface of the ice sheet is more than two kilometers above sea level, where the air is much thinner and colder. Antarctica is, on average, by far the highest continent on the earth. In comparison, the North Pole rests in the middle of the Arctic Ocean, where the surface of floating ice rides just a foot or so above the surrounding sea. Unlike the landmass underneath the South Pole, the Arctic Ocean also acts as an effective heat reservoir, warming the cold atmosphere above it in the winter and drawing heat from the atmosphere in the summer. SA

For a complete text of these and other answers from scientists in diverse fields, visit www.sciam.com/askexpert

MATT COLLINS