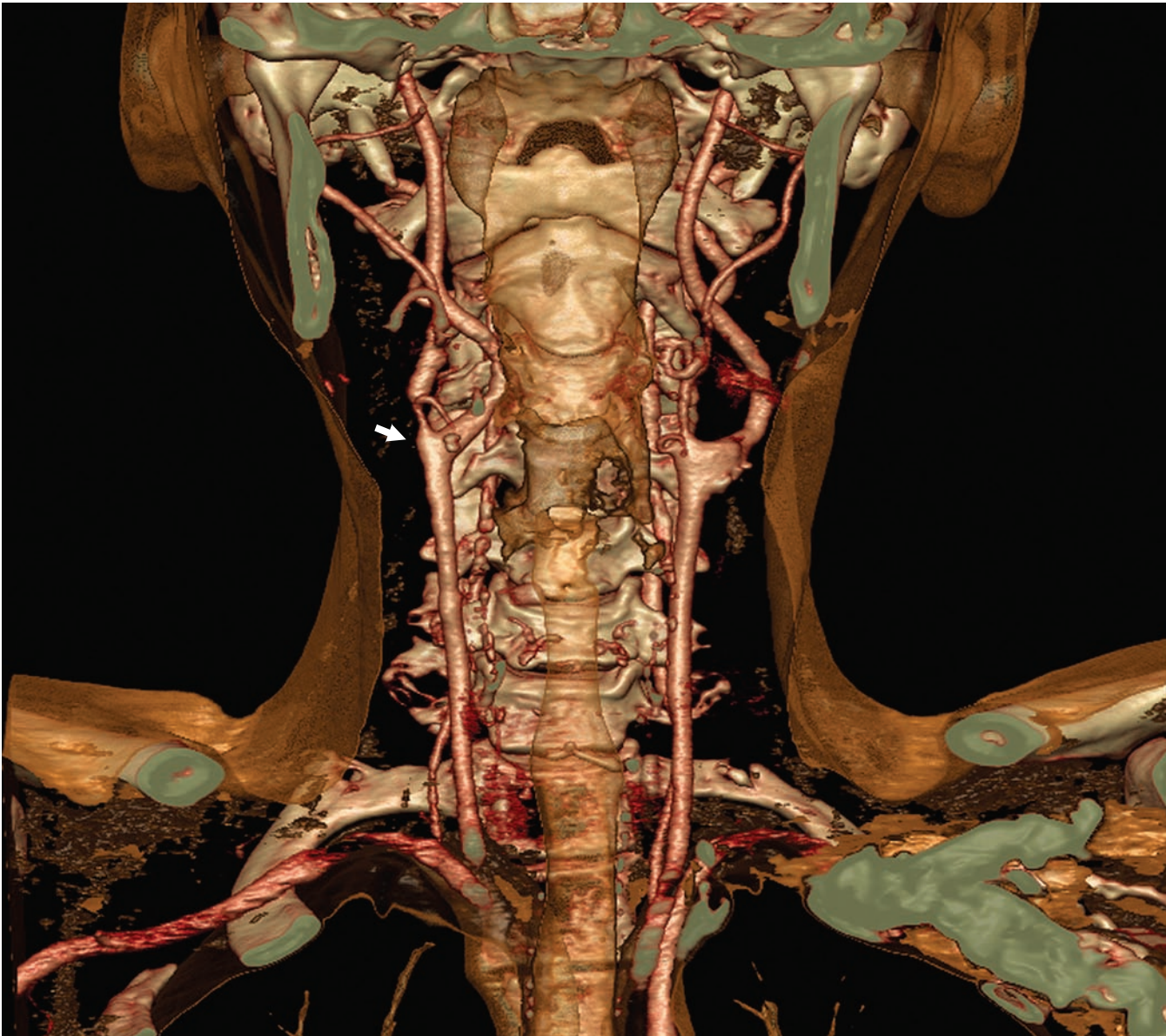
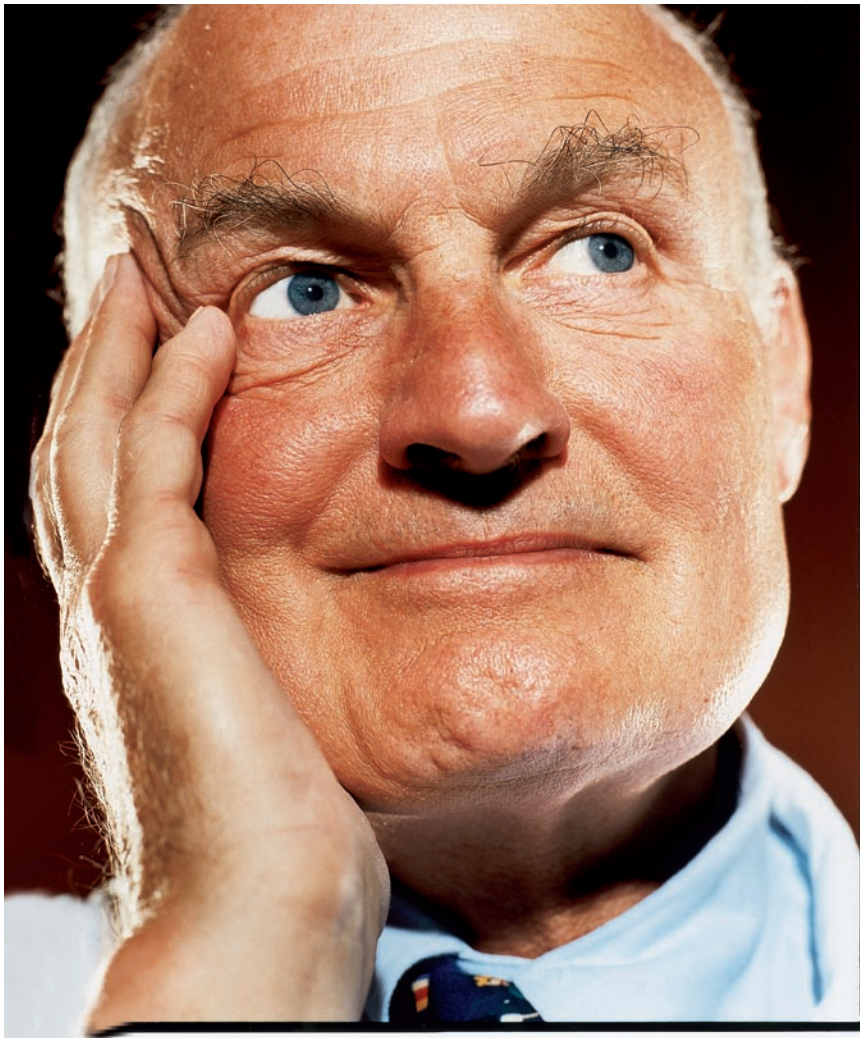


stat

- **OCTOBER 26:** The HapMap—which plots patterns of variation in the human genome, making it easier for scientists to link genes to diseases—will be complete and accessible online at hapmap.org.
- **NOVEMBER 8:** California voters will go to the polls to determine whether to punish pharmaceutical makers for profiteering if they don't discount drugs for uninsured and moderate-income patients.
- **NOVEMBER:** The *Journal of Magnetic Resonance* will feature a superconducting magnet, unveiled in July, that could lead to medical breakthroughs. The 900 MHz, 15-ton magnet will be able to test samples with greater clarity than ever before.



THERE'S SOMETHING VERY WRONG IN THIS PICTURE In the right carotid artery (see arrow above), the narrowed section is severely blocked. The SOMATOM Sensation 64 computed tomography system generates images like these by taking 64 "slices," measuring less than 0.4 mm each, of most human anatomy in less than 10 seconds, allowing physicians an exquisite view. In this case, the image pinpoints the precise area a surgeon may need to repair.



INTERVIEW //

A Beautiful Death

■ INTERVIEW BY RACHEL GOTBAUM

For more than 40 years, ever since serving as an intern at a cardiac care unit in the Bronx, where he was called upon almost daily to counsel the dying, psychiatrist and Jesuit priest Ned Cassem has dealt intimately with death. In 1973 he established the Massachusetts General Hospital's Optimum Care Committee—the first ethics consultation committee in North America.

Q: What's a typical case for your Optimum Care Committee?

A: I'm not sure there is a typical case,

but the common denominator is conflict. Take, for example, an argument with the son from hell. He comes from

■ **“If he doesn't back down, I tell him ‘we don't do this at the MGH.’ My responsibility is always to protect the patient.”**

the opposite coast. He hasn't been part of his mother's life for years.

They've had a horrible relationship. Basically, he hates her. Now he says, “Do everything, doctor. I demand you do everything!” So I tell him, “She weighs under 100 pounds. She has metastatic disease in her ribs and sternum, and it may not be in her best interest to resuscitate her.” Often families don't know that resuscitation may mean crushing the sternum so hard that the ventricle pushes blood out into the aorta. It may mean breaking ribs. That's brutality.

Q: What happens then?

A: I ask the son in my most serious voice, “What do you have against your mother?” That usually gives him pause. But if he doesn't back down, I tell him “we don't do this at the MGH.” My responsibility is always to protect the patient.

Q: Who actually decides what's best for the patient?

A: If the family and the medical team disagree, the Optimum Care Committee meets with the doctors, the people on the floor taking care of the patient and whoever is complaining. It could be the

entire family or just the son and his lawyers. Then we deliberate and make a final decision. We won't transfer the patient to another hospital. The family can go to court if it

wishes, but our obligation is to stand up for the rights of the patient.

Q: Do you sometimes feel like you're playing God?

A: No. I've got the expertise of the whole hospital behind me. I'm just taking the advice of experts—a neurologist or a pulmonologist—and using their judgment to make a logical recommendation. They are a lot more objective than the son from hell.

Q: Are doctors better at handling death and dying now than in the

■ **“A bad death is one in which the dignity and the respect of the patient have not been honored and the patient has been allowed to suffer.”**

past?

A: No. They didn't tell patients they were dying 20 or 30 years ago—and in most cases they're not telling them now. But patients have gotten much more savvy about disease and death. They can read the doctor's gestures and know whether their disease is curable.

Q: You have a rating system for death. What makes a death “beautiful” and what makes it “bad”?

A: It's beautiful when it's meaningful—when the family is there and they all have their hands on the patient. They may light candles; they may hold a vigil. They may have a clergy person preside. It's a type of death in which all present can be proud of their roles when they look back.

A bad death is one in which the dignity and the respect of the patient have not been honored and the patient has been allowed to suffer. To try to keep a dying patient alive puts a burden on that person that is much greater than the benefit of inappropriate treatment.

Q: Another rating system led you to create the Optimum Care Committee.

A: I modeled it on a group that did a simple experiment on rounds every day. The cardiologist would ask the head nurse, the residents and the attending physician: Does this patient

require A, B, C or D? A is the works; anything goes to save him. B is still the works, but we will see how he does today. C means some treatments are outlawed, like CPR or putting the patient on a ventilator. D means stop everything now and let him die a comfortable death.

Q: What have you learned from your decades at the bedside?

A: That death actually has the secret of life in it. If you confront death with somebody you love who is dying, out of that will come learning that transforms your life. It leaves you stronger, braver, calmer.

Q: You don't think death is depressing?

A: I think it's inspiring. It doesn't depress me. It makes me sad, but

THE LIST //

Sting Operations

A run-in with any of the creatures below would typically spell trouble for a human: sweating, dizziness, even death. Yet scientists are finding that the venoms, or zootoxins, of these animals contain compounds that might one day be useful in treating some of our most serious illnesses.



POISON DART FROG

(*Epipedobates tricolor*)

Small doses of this reptile's skin secretions are 200 times more effective at deadening pain than morphine. However, scientists are still working to create a version without the toxic side effects.



CONE SNAIL (*Conus striatus*)

Snail venom contains an extract, ziconotide, that, when injected into the fluid surrounding the spinal cord in the form of the drug Prialt, blocks calcium channels in pain receptors and halts pain messages to the brain.



SEA SQUIRT

(*Ecteinascidia turbinata*)

Ecteinascidin, a man-made drug that replicates the tissue of a sea squirt, halts the growth of tumors of such soft tissue cancers as bone, blood vessel, muscle and breast. In clinical trials, doctors report improvements in patients after injections totaling less than 14 mg.



ISRAELI SCORPION

(*Scorpio maurus*)

The scorpion's venom contains chlorotoxin, a protein that fights brain cancer by selectively attaching to tumor cells with minimal damage to normal ones. In tests, doctors have administered an anti-cancer drug cocktail containing chlorotoxin in the cavity surrounding the tumor.



GILA MONSTER

(*Heloderma suspectum*)

Exenatide, a compound in the reptile's saliva, acts much like human pancreatic hormone, triggering insulin production when blood sugar rises too high. It's being used in the drug Byetta to help improve blood-sugar levels (in conjunction with other drugs) in type 2 diabetes patients.

BY THE NUMBERS // Losing Sleep

76 Percentage of medical residents, in a small 2002 survey, who met the criteria for burnout, including increased callousness toward patients and overall emotional exhaustion

53 Percentage of burned-out residents who admitted providing less than optimal patient care

69 Percentage of residents of one U.S. medical school who, in a 2001 survey, admitted to the possibility of dozing off while filling out charts

82.4 Percentage of U.S. medical school graduates who report having been publicly humiliated at least once during training

23.4 Percentage who say they were required to perform personal services, such as grocery shopping and babysitting, for faculty or hospital staff

100,000 Median debt, in dollars, of graduates of public medical schools

500 Percent increase in that amount over the past 20 years

Street-by-street air-quality warnings could one day be routinely text-messaged to asthma sufferers.



ADVANCES // Air Mail

THE EUROPEAN SPACE AGENCY is text-messaging air-quality warnings to the cell phones of 1,000 asthma sufferers in London. The service, YourAir, predicts the levels of air pollutants—down to individual streets—by analyzing traffic patterns and other sources of pollution. Plans are in the works to include satellite observations to improve the accuracy of the reports.

www.cerc.co.uk/YourAir

THE LENGTH OF GENE SEQUENCES, once dismissed as nonfunctional, may be a key to determining behavioral traits—ranging from who remains a faithful spouse to who is outgoing and who is shy. Scientists at Emory University found that the length of these sequences determined male-female relations as well as parenting performance in a species of voles.

www.sciencemag.org; search for “microsatellite instability”

VIAGRA may benefit children suffering from pulmonary arterial hypertension, a potentially fatal lung disease. A Canadian study followed the progress of patients for a year. After six months on the drug, which increases blood flow by relaxing muscles in blood vessels, children were able to walk farther and breathe easier.

circ.ahajournals.org; search for “childhood pulmonary arterial hypertension”

YOU CAN PICK YOUR FRIENDS, the saying goes, but you can't pick your family. And that could help explain why in one 10-year study, adults 70 and older with a strong group of friends lived longer than those with children and relatives, according to Australian scientists.

jech.bmjournals.com; search for “Australian longitudinal survey”

CHIMPS AND HUMANS share a 99% similarity in their DNA sequences but virtually no recombination hot spots (sites where there are increased DNA exchanges between two parents' chromosomes). Scientists in the U.S., U.K. and Netherlands say that hot spots are evolving faster than the rest of the genome—which may help scientists construct better studies to pinpoint disease-causing genes.

www.sciencemag.org; search for “recombination rates in humans and chimpanzees”

AN INJURED ATHLETE could continue training by watching other athletes, say scientists at UCL (University College London). Once an athlete has learned a skill, their study suggests, parts of the brain can simulate the physical movement while the athlete is simply observing it. This has implications for stroke victims: Watching a motor skill they used to be able to perform could help them relearn it.

cercor.oxfordjournals.org/cgi/content/full/15/8/1243

CONSUMER REPORT //

Push Comes to Shove

■ BY MICHAEL HIRSON

Do advertisements for prescription medications educate consumers—or encourage them to take drugs they don't need? Since 1997, when the Food and Drug Administration relaxed restrictions on direct-to-consumer advertising of prescription medicines, that debate has pitted drugmakers against regulators, consumer groups and many physicians. Now the pharmaceutical industry has made a concession.

In August the Pharmaceutical Research and Manufacturers of America (PhRMA) announced a set of voluntary guiding principles, calling for companies to submit ads to the FDA before they air, to clearly explain risks and benefits, and to spend an “appropriate amount of time” educating physicians prior to advertising new medications. A PhRMA office of accountability will monitor compliance and make reports available to the public.

Each year as many as a third of consumers ask doctors about drugs they've seen advertised, and some 40% of these discussions lead to prescriptions. Pharmaceutical companies cite the benefits of advertising, including studies showing increased awareness of treatments for such conditions as depression. But nearly 80% of doctors believe advertising inclines patients to ask for medications they don't need—requests physicians admit they sometimes oblige.

“Best case, a doctor will explain why an existing drug may be more appropriate,” says Robert Centor, a professor of internal medicine at the University of Alabama. “But physicians sometimes take the path of least resistance and prescribe what the patient wants.” To dis-

courage that, Centor favors counter-detailing, in which managed-care groups respond to drug-company promotions by listing for physicians which drugs have proven safest and most cost effective.

Not likely to be on that list are drugs in a heavily advertised class known as COX-2 inhibitors, including Merck's Vioxx. Responding to studies showing cardiovascular problems associated with such drugs, Senate Majority Leader Bill Frist, a physician, has proposed requiring drug companies to wait two years before advertising newly approved drugs. Bristol Myers-Squibb has already instituted a voluntary 12-month waiting period.

“If you educate physicians about risks and benefits before you advertise to consumers, physicians can have an informed discussion with patients,” says a spokesperson for Bristol Myers-Squibb.

In July the American Medical Association said it would begin studying the effects of drug advertising. But in the meantime, the U.S. remains the only industrialized country (other than New Zealand, and even that nation is on the verge of a ban) that allows direct-to-consumer drug advertising. “We're essentially conducting a vast, uncontrolled experiment on the public,” says Matthew Hollon, an assistant professor of medi-

THEN VS. NOW //

Treating TB



1882



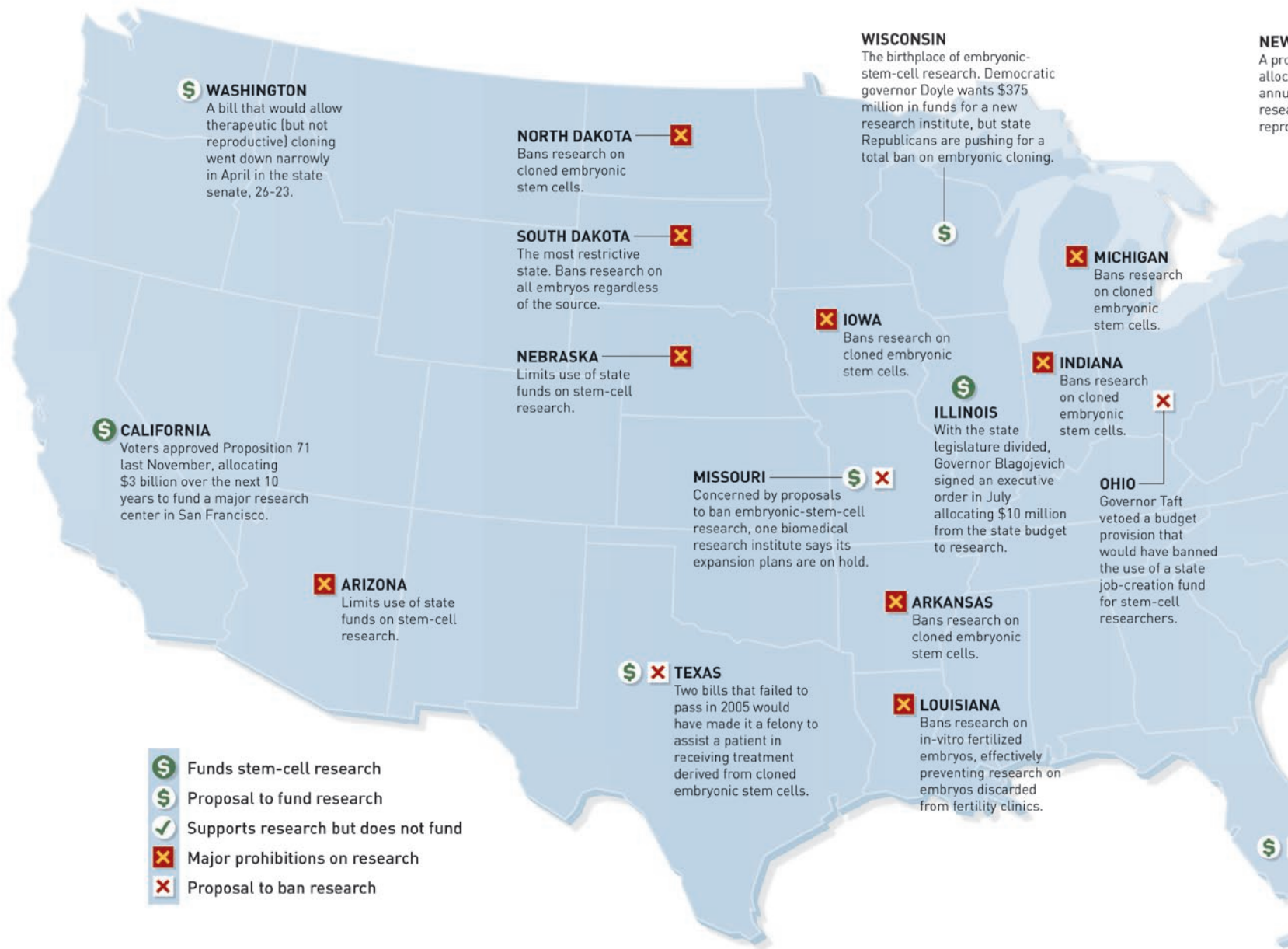
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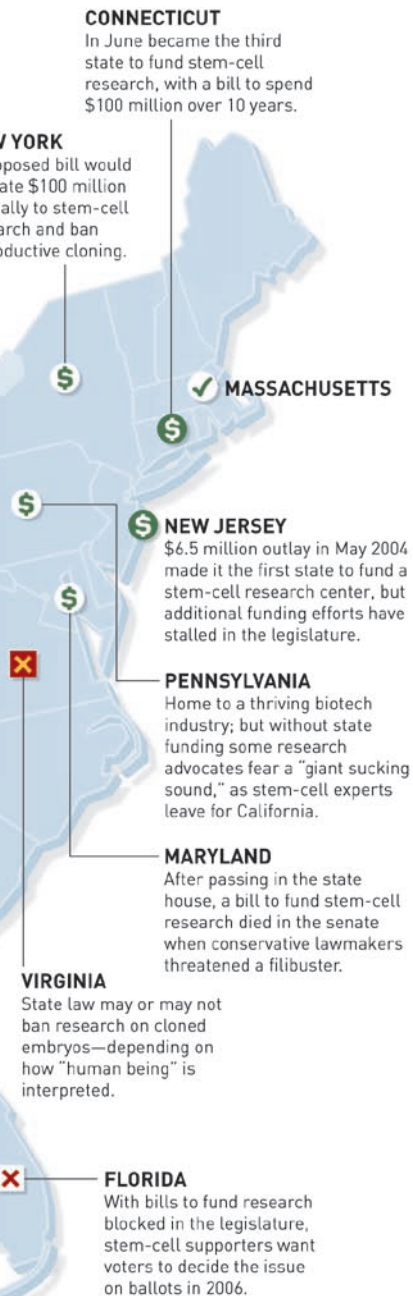
Pneumothorax, one of the oldest known surgeries for lung disease, can be traced to the Hippocratic era. But until the nineteenth century, the treatment meant cutting a hole in the patient's chest and injecting air, often causing infection or even death. Then, in 1882, the Italian physician Carlo Forlanini invented the artificial pneumothorax apparatus. The machine forced air into the chest through a sterilized needle connected to a water manometer, which allowed the physician to accurately measure the pressure and volume of the introduced air and ensure the right amount of lung compression. Patients could visit “pneumo” weekly to have air collapse their diseased lung, pushing together the walls of the tubercular cavities and allowing nature's healing process—fibrous tissue growth—to take place. The method was tenuous, depending largely on each individual's body defense system, and was finally superseded in the mid-twentieth century by antibiotics and chemotherapy.

ROAD MAP //

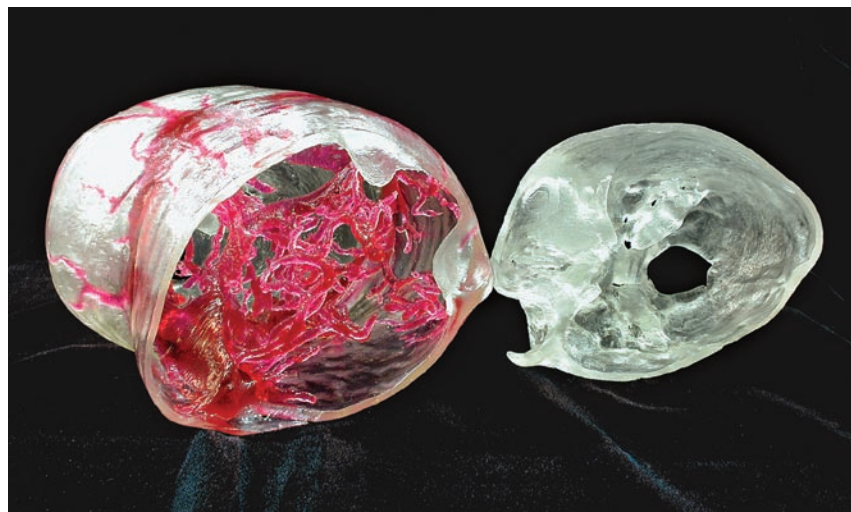
The Great Stem-Cell Divide

While Congress and President George W. Bush debate federal funding policies for embryonic-stem-cell research, equally important—but less noticed—battles are being waged in the states. As this map shows, some states are funding the research (in a bid to become leaders in the new science), others merely allow the work and still others have made it a crime. Meanwhile, legislatures in almost every state continue to consider bills to ban or support the politically sensitive research. INFOGRAPHIC BY JOHN GRIMWADE





COURTESY MEDICAL MODELING LLC



THE CUTTING EDGE //

Made-to-Order Body Parts

A young victim of a bomb blast in Baghdad arrives at a U.S. army hospital requiring facial reconstruction. Surgeons upload data from scans of the boy's skull into a 3-D laser printer, which produces a ceramic bone substitute of his jaw within hours. Known as additive fabrication, or rapid prototyping, the process—in which cross-sections of liquid, powder or sheet materials are fused into objects of ceramic, plastic and metal—is used to create prosthetic devices and models of organs, joints and bones. Recently, surgeons in Dallas used a model (above) of a conjoined skull, replicating bone structure and vasculature, to guide them in separating twins.

POLICY WATCH //

Tracking Adverse Drug Reactions

Last year the pharmaceutical manufacturer Merck withdrew Vioxx after studies showed patients who had used the painkiller for prolonged periods were at increased risk for heart attacks and strokes. That recall reignited criticism of the Food and Drug Administration's system for tracking drug safety. The voluntary system relies largely on physicians and pharmacists to report adverse drug reactions. But drug side effects are notoriously difficult to detect, and studies have shown that fewer than 10% of adverse reactions are ever reported.

In June the Centers for Medicare and Medicaid Services proposed making information from the Medicare prescription drug program available to the FDA. The plan, backed by the FDA and with support in Congress, would expand existing databases to link drug data with

Medicare billing records. With patients' identities protected, researchers could scan the resulting database for worrisome patterns involving particular drugs.

The Medicare program, expected to cover as many as 43 million people in 2006, would give researchers a massive array of data, allowing them to identify side effects that did not occur during clinical trials and to compare the effectiveness of competing drugs—without data from pharmaceutical companies.

"The FDA has only been able to tell us whether a drug is more effective than a placebo, and safe when thousands of people take it," says John Santa of the Center for Evidence-Based Policy at Oregon Health & Sciences University. "We should really ask whether a drug is better than what we already have, and safe when millions take it."

POINT/COUNTERPOINT //

Will Asia overtake the U.S. in biomedical research?

POINT It's true that, two decades ago, American scientists authored a majority of the papers published in physics journals, and today they account for less than a third. But a much more crucial yardstick of the globalization of scientific research—the development of high-risk, high-cost drugs—shows U.S. dominance continuing, and we aren't likely to be challenged anytime soon. Our lead over Europe has increased in recent years, not shrunk, with several major European drug companies relocating at least some of their R&D operations to the U.S. And while China and India are becoming increasingly competitive, it will be a long time before they play a breakthrough role in drug development.

Our edge owes much to infrastructure. Not only do we spend more than any other nation on basic research, but we make it easier to move a good idea from academia to the for-profit sector. By one estimate, more than 1,200 technology companies have been spun off by current and former students and faculty of one West Coast university alone. Then there's quality of life, a perk that helps attract and keep top researchers. While Europe compares favorably in this regard, China and India still have a long way to go. Finally, there's a more entrepreneurial attitude in the U.S., and much more private risk capital. In 2004, U.S. venture capital firms poured \$5.6 billion into almost 600 biotech and medical device companies. That's about five times the amount of venture capital invested that year in all Indian industries.

In five or 10 years, serious drug development may begin in China and particularly in India. But even that will occur mainly around the edges. They'll create variants of old drugs and new delivery systems—turning a four-times-a-day pill into a once a day. That's useful, but nothing like the blockbuster innovations pouring out of U.S. pipelines—for example, the first antiangiogenic cancer drug, Genentech's Avastin. This is a



familiar pattern in technology. Just when it seems the laggards are catching up, a new direction is discovered—usually emerging from basic research—and the countries with the best infrastructure leap ahead once more.

Ultimately, the globalization of biomedical research will be a win-win situation. More research will get done more efficiently, and more drugs will be developed. There may be greater competition for high-tech jobs, but the demand for medical technology is virtually unlimited—the market will expand so much that there will be plenty of room for everybody.

JOHN E. CALFEE is an economist and resident scholar at the American Enterprise Institute in Washington, D.C., where he studies health-care policy and the pharmaceutical industry.

COUNTERPOINT In 2002, U.S. drug companies spent about \$70 million on clinical drug trials in India, where costs are far lower than in the U.S. and where the pool of prospective patients is deeper—much deeper. By 2010 such expenditures could exceed \$1 billion. And the outsourcing of drug trials is just one aspect of an increasingly pronounced trend.

Biomedical research jobs are shifting from the U.S. to other countries, particularly China and India, where highly trained scientists will work for a fraction of the salaries of their American peers. So far this has involved mostly low-end research such as clinical trials and routine chemical analyses, but it will gradually move to the cutting edge, giving talented foreign researchers less incentive to come to

MILESTONES // Morphine at 200

this country to study and work. Actually, it may already have begun: Roche recently opened a research and development center in Shanghai.

Homegrown drug companies in developing countries are also being transformed. India's pharmaceutical industry, which employs 500,000 people, used to churn out knockoffs of Western drugs. But India recently revamped its patent protection laws, forcing domestic firms to invest in developing their own proprietary drugs rather than simply duplicating existing treatments. And McKinsey & Co., the management-consulting firm, projects that the volume of Indian drug exports will quadruple by 2010, to \$6.5 billion. Though not yet centers of innovation, Chinese and Indian firms should be capable of producing blockbuster drugs within 10 to 15 years.

And the U.S.? No other country will challenge us in basic research, such as that funded by the National Institutes of Health, because no one else will spend as much public money as we do. But while some basic research leads to patents (and therefore profits), much is quickly disseminated to the rest of the world through scientific journals—a generous gift from American taxpayers. Eventually the U.S. lead in applied research—the work typically done by drug companies that directly generates profits—will shrink sharply. That means fewer high-paid technology jobs in this country—and fewer talented scientists who will stick around to fill them.

By the middle of the twenty-first century, drug development and production will be a globally dispersed business. Everyone will have the capability to innovate; the question is, who will do it best? To compete, the U.S. will have to find novel ways to capitalize on its lead in basic research. We need the federal government to fund not only biomedical research but also research on how to spur the process of innovation in drug discovery and commercialization.

DAVID BLUMENTHAL is a physician and the director of the Institute for Health Policy at the Massachusetts General Hospital. He is also a professor at Harvard Medical School. ■

Opium had already been killing pain for centuries when a 20-year-old pharmacist's apprentice in Einbeck, Germany, began tinkering with the stuff. Friedrich Wilhelm Adam Sertürner noticed that some batches were more potent than others and took the novel step of trying to isolate the opium poppy's active ingredient. In 1805, after two years of work, Sertürner separated an alkaloid compound he named "morphium," after Morpheus, the Greek god of dreams.

To test his new compound, Sertürner was not averse to inflicting misery. First he tried the compound on neighborhood rats and dogs, finding that it put them to sleep and eventually killed them. That's when he administered a lower oral dose (though still 10 times more potent than dosages prescribed today) to himself and three teenage friends, making them all violently ill. But after further trials revealed that morphium was highly effective in soothing his own toothache, Sertürner published his discovery.

By the 1820s the compound, renamed morphine, was available from many chemical suppliers, helping along the birth of the pharmaceutical industry. But it took the invention of the hypodermic needle in the 1850s (morphine is less potent than other opiates when administered orally) to reveal morphine's full potential for good and ill.

Injected morphine was widely used in the medical tents of the Civil War, resulting

in hundreds of thousands of veterans returning home with the "soldier's disease." In an ironic twist worthy of fiction, the search for a less addictive opiate led in 1874 to the discovery of heroin—named for its heroic ability to fight pain—which was made in mass quantities from 1898 until U.S. production was halted in 1913.

Today morphine and other opiates are still the undisputed kings of painkilling, particularly for the treatment of postoperative, chronic and cancer pain. Jonathan Moss,



professor of anesthesia and critical care at the University of Chicago, says morphine is so effective because it mimics the natural opiates that the body produces, binding to the same receptors. Moss thinks the most promising route for research is not to replace morphine but to eliminate some of its side effects, including nausea and constipation. "We can improve the way it works, but it has been very difficult to make anything better than a drug developed 200 years ago." ■

Finding new therapies in old bottles, pharmacologists are incorporating morphine's matchless pain relief into remedies that are easier to take.