of the Year

ing the distribution of those galaxies, the way they clump and spread out, scientists can figure out the forces that cause that clumping and spreading—be they the gravitational attraction of dark matter or the antigravity push of dark energy. In October, the SDSS team revealed its analysis of the first quarter-million galaxies it had collected. It came to the same conclusion that the WMAP researchers had reached: The universe is dominated by dark energy.

This year scientists got their most direct view of dark energy in action. In July, physicists superimposed the galaxy-clustering data of SDSS on the microwave data of WMAP and proved—beyond a reasonable doubt—that dark energy must exist. The proof relies on a phenomenon known as the integrated Sachs-Wolfe effect. The remnant microwave radiation acted as a backlight, shining through the gravitational dimples caused by the galaxy clusters that the SDSS spotted. Scientists saw a gentle crushing—apparent as a slight shift toward shorter wavelengths—of the microwaves shining near those gravitational pits. In an uncurved universe such as our own, this can happen only if there is some antigravitational force—a dark energy—stretching out the fabric of spacetime and flattening the dimples that galaxy clusters sit in.

Some of the work of cosmology can now turn to understanding the forces that shaped the universe when it was a fraction of a millisecond old. After the universe burst forth from a cosmic singularity, the fabric of the newborn universe expanded faster than the speed of light. This was the era of inflation, and that burst of growth—and its abrupt end after less than 10^{-30} seconds—shaped our present-day universe.

For decades, inflation provided few testable hypotheses. Now the exquisite precision of the WMAP data is finally allowing scientists to test inflation directly. Each current version of inflation proposes a slightly different scenario about the precise nature of the inflating force, and each makes a concrete prediction about the CMB, the distribution of galaxies, and even the clustering of gas clouds in the later universe. Scientists are just beginning to winnow out a handful of theories and test some make-or-break hypotheses. And as the SDSS data set grows—yielding information on distant quasars and gas clouds as well as the distribution of galaxies—scientists will challenge inflation theories with more boldness.

The properties of dark energy are also now coming under scrutiny. WMAP, SDSS, and a new set of supernova observations released this year are beginning to give scientists a handle on the way dark energy reacts to being stretched or squished. Physicists have already had to discard some of their assumptions about dark energy. Now they have to consider a form of dark energy that might cause all the matter in the universe to die a violent and sudden death. If the dark energy is stronger than a critical value, then it will eventually tear apart galaxies, solar systems, planets, and even atoms themselves in a "big rip." (Not to worry; cosmologists aren't losing sleep about the prospect.)

For the past 5 years, cosmologists have tested whether the baffling, counterintuitive model of a universe made of dark matter and blown apart by dark energy could be correct. This year, thanks to WMAP, the SDSS data, and new supernova observations, they know the answer is yes—and they're starting to ask new questions. It is, perhaps, a sign that scientists will finally begin to understand the beginning.

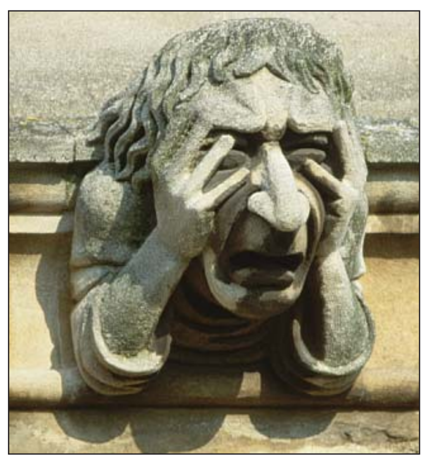
–CHARLES SEIFE

THE RUNNERS–UP

This year's discoveries illuminated realms as small as a single molecule and as large as a gamma ray burst.

#2 **Decoding mental illness.** Schizophrenia, depression, and bipolar disorder often run in families, but only recently have researchers identified particular genes that reliably increase one's risk of disease. Now they're unraveling how these genes can distort the brain's information processing and nudge someone into mental illness.

The chemical messenger serotonin relays its signal through a receptor that's a target of antidepressant drugs. The gene for this receptor comes in two common flavors, or alleles, one of which had been tenuously linked to an increased risk of depression. This year, researchers revealed why the link had been so elusive: The allele increases the risk of depression only when combined with stress. Among people who had suffered bereavement, romantic rejection, or job loss in their early 20s, those who carried the vulnerability gene were more likely to be depressed than those with the other gene variant.



Agony antecedents. New work links genes, brain activity biases, and mental illness.

CREDIT: C. ANDERSON/CHRIS ANDERSON PUBLICATIONS/CORBIS

People with the high-risk allele have unusually heightened activity in a fear-focused brain region called the amygdala when viewing scary pictures. Together, these studies suggest that the gene variant biases people to perceive the world as highly menacing, which amplifies life stresses to the point of inducing depression.

A different brain area, the prefrontal cortex, is regulated in part by a gene called *COMT*, one of the handful associated with risk of schizophrenia. It encodes an enzyme that breaks down neurotransmitters such as dopamine. Two years ago, one version of this gene was shown to muddle the prefrontal cortex, which is necessary for planning and problem-solving skills that are impaired by schizophrenia. Even healthy people who carry the schizophrenia risk allele have extra activity in the prefrontal cortex even when doing relatively simple tasks. The nonschizophrenia allele, which allows more efficient activity in the prefrontal cortex, appears to increase the risk of anxiety, suggesting that the two diseases lie at opposite ends of a spectrum.

Late in 2002, an allele of a gene for brain-derived neurotrophic factor (BDNF) was implicated in bipolar disorder, once known as manic depression. This year the allele was found to curb activity in the hippocampus, a structure necessary for memory that is shrunken in people with mood disorders. BDNF encourages the birth of new neurons in the hippocampus; other work this year showed that antidepressants require this neurogenesis to be effective. Through these and similar insights, researchers hope to understand brain biases underlying mental illnesses well enough to correct them.

Areas to Watch in 2004

Science's editors prognosticate about which research and policy areas are in for big changes next year.

Three on Mars. With luck, planetary scientists will have the equivalent of a martian traffic jam to deal with in early 2004. Three craft are expected to touch down around the turn of the year: The European Space Agency's lander Beagle 2 on Isidis Planitia and NASA's rovers Spirit in Gusev crater and Opportunity on Meridiani Planum. The oohs and ahs will come shortly after touchdown with panoramic views of new martian landscapes, but the science will dribble out during the 90-day missions and long after. Opportunity will likely find minerals that point to hot water within early Mars, but Spirit could have a tougher time figuring out how water shaped an ancient crater lake floor. The low-budget Beagle 2 is taking the big gamble, looking for signs of life, past and even present.

Microbe militia. Biodefense research exploded in 2003, and the boom will continue in 2004. Expect advances in the basic biology of a range of little-studied pathogens that cause diseases including plague, anthrax, tularemia, botulism, and hemorrhagic fevers, as well as a torrent of newly sequenced genomes, often including multiple strains of the same bug. At the same time, look for major steps in the development of new or improved vaccines for smallpox, anthrax, and Ebola, as well as several antiviral drugs and an antidote to botulinum toxin. Meanwhile, measures to keep a lid on data that could help aspiring bioterrorists will continue to provoke debate.

Genome data deluge. With the sequence of the human genome in hand, biologists are finding that they need much more data to make sense of it. Toward that end, several more large-scale, data-intensive projects are in the works. The SNP Consortium and Haplotype Map Project are seeking patterns in human genetic variations; microarrays are generating information on gene expression; proteomics projects are detailing the functions and interactions of proteins; and new pilot programs are working to streamline the identification of gene function. Expect a flood of information in 2004 and a plethora of new databases, software, and standards for how these data are collected and presented—but continued debate about how to use and coordinate it all. New gene discoveries and insights into how organisms are related, particularly what makes humans different from chimps, should make for an interesting year.

Open sesame. Will 2004 be the year scientists open their hearts—and their wallets—to open-access scientific journals? A slew of publishers will launch experiments in which authors will pay publication charges and journals will make their papers freely accessible over the Internet. Advocates say that the author-pays approach will speed the flow of scientific information, but critics predict that the business model will be a flop, particularly outside the relatively flush biomedical sciences.

Bottoms up. Recently, two "B factories" that produce particles containing the heavy "bottom" quark have been hinting at physics beyond the Standard Model. Next year may well set the physics community abuzz as the factories, one in California and the other in Tsukuba, Japan, create another swarm of B's. Unexpectedly, the decay of bottom-quark–containing particles doesn't quite match what the Standard Model predicts. This might be a sign of supersymmetry or other exotic physics. The issue probably won't be fully resolved by year's end, but new data should make the anomaly either stand in stark relief or largely disappear.

Digging deeper. After decades of toiling to identify fungi, nematodes, and innumerable other organisms that live belowground, soil scientists have started to ask—and answer—ecological questions. Look for more studies of how microbes contribute to greenhouse gases and some plants become invasive by escaping soil pathogens. The ultimate pay dirt may be more accurate knowledge of soils' impact on climate change and better strategies for sustainable agriculture.

Science and security. Increasingly tough antiterror measures may not be good for U.S. science. Foreign scientists continue to have trouble entering the country due to tougher visa reviews, and research leaders worry that a host of other rules—from polygraph tests for some Department of Energy scientists, to export regulations—have made science an increasingly unattractive career. Other nations are considering adopting similar rules, which may further complicate the global sharing of ideas. Look for continuing friction over the costs and benefits of tighter security—and government moves to roll back a few rules that may have gone too far.

#3

Is it warm in here? Climate researchers have a century's worth of temperature measurements to show that the globe has been warming. New work shows that the planet has taken notice of the change. The stream of studies suggesting global warming's impact on Earth and its inhabitants surged to a flood in 2003 with reports on melting ice, droughts, decreased plant productivity, and altered plant and animal behavior.

Among the findings this year, climate modelers linked a now fading, years-long, globe-girdling drought to unusually warm waters in the western Pacific and Indian oceans. That warm water looks to be a product of greenhouse gases. In the Arctic, river monitoring showed a 7% increase since 1936 in the flows of the six largest Eurasian rivers that empty into the Arctic Ocean. That fits climate model predictions of increased high-latitude precipitation and follows the observed warming and atmospheric circulation trends. More freshwater flooding into the far North Atlantic could slow the northward flow of heat-laden currents and thus disrupt climate around more populous parts of the North Atlantic region.

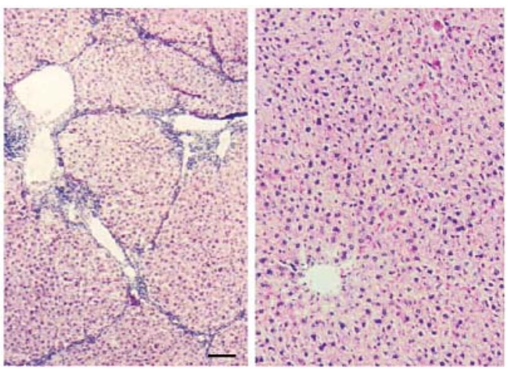
In the biological realm, meta-analyses of studies of plant and animal behaviors strongly suggest that life has taken notice of warming, too. Plants and animals around the globe have shifted their geo-

Paying attention. Plants and animals are responding to global warming.

CREDITS: (TOP TO BOTTOM) ILLUSTRATION BY TERRY SMITH; CAMILLE PARMESAN/UNIVERSITY OF TEXAS, AUSTIN graphic ranges or changed behaviors—such as when they bloom or lay eggs—in ways consistent with reacting to global warming. Climate change also seems to depress both corn and soybean productivity in the U.S. Midwest and plant productivity in Africa's great Lake Tanganyika.

The growing awareness of some of the ways global warming may be altering the planet and its life has accentuated interest in learning how to adapt to these changes. Humans are getting a better idea of some of the adjustments they'll have to make in the coming centuries, such as beefing up irrigation and shifting agricultural regions. Plants and animals have yet to show how adaptable they will be.

#4 **Still hot.** *Science*'s breakthrough of 2002 kept scientists on the edge of their seats in 2003. Having sketched out the role played by miniature RNA molecules in modulating gene expression, this year biologists dove into the details, exploring how small RNAs orchestrate a cell's behavior and how harnessing their power could combat disease.



Interference. Mice injected with siRNAs (*right*) are protected from liver disease (*left*).

CREDITS: (LEFT) E. SONG *ET AL.*, *NATURE MEDICINE*

MicroRNAs, the runts of the RNA litter at about 22 nucleotides in length, were found to guide early development—from shaping plant leaves to mediating cell proliferation in fruit fly embryos. RNA interference (RNAi), which shuts down gene expression, also plays a critical role in development. Mice lacking an RNAi protein called Dicer lost swaths of stem cells and died before birth. Also this year, certain microRNAs in mice were found to help direct stem cells that create the embryo's blood cell system. Humans, meanwhile, are now thought to harbor as many as 255 genes that encode microRNAs—nearly 1% of the genes in the entire genome.

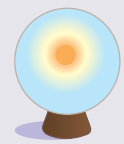
RNAi also proved its worth this year as a tool to screen hundreds or even thousands of genes. RNAi offers a quick and relatively easy way of systematically inhibiting RNA molecules with a complementary sequence, preventing them from synthesizing proteins. By squelching the RNA signal of one gene at a time, researchers are beginning to outline genetic networks that govern everything from a cell's morphology to its signaling systems.

Other RNA enthusiasts are recruiting small interfering RNAs (siRNAs), which are similar in size to their micro counterparts, in the fight against disease. They help power the RNAi machinery and thus are pros at controlling protein production—something that goes awry in many diseases. Researchers showed that siRNAs can ramp down proteins involved in HIV and protect mice from hepatitis by blocking a gene behind liver inflammation. The effort to pit these molecules against disease faces big challenges, however. Among them: getting siRNAs to the right genes and cells and steering them clear of the wrong ones.

#5 **Single molecules groove and glow.** New collaborations between biologists and physicists are detailing the busy lives of single molecules, in real time, as they buzz about their business in the cell. Work this year captured molecular motors in motion; re-

Scorecard 2002

How accurately did our crystal ball predict this year's advances?



Whither the ice? Watching the world's ice paid off in 2003, although it has only heightened concern among glaciologists. Satellite observations provided more evidence that mountain glaciers such as those in Argentinean Patagonia are melting rapidly. Of more concern were signs that climatic warming can get at large ice sheets quickly and easily. The breakup of more of the Larsen Ice Shelf of West Antarctica was followed by surging of the glacial ice streams that feed it, supporting the idea that ice shelves buttress glacial ice against rapid loss to the sea. The Larsen Ice Shelf has thinned so quickly that warming seawater must be the culprit, tying glacial surging to climate warming.

A sun-climate connection. Interest in whether the waxing and waning of the sun affects climate continued to grow in 2003, and researchers came up with more persuasive sun-climate connections. But the quest for an explanatory mechanism barely plodded along. The mechanism du jour—solar-modulated cosmic rays altering cloud cover—does after all involve the most poorly understood part of the climate system, its clouds. A decade rather than a year may provide a fairer assessment.

Budget bust. Asia was the place to be this year for researchers seeking government support. The science budgets of China, Japan, and India all grew at healthy rates. The news from Europe was much bleaker. Cuts were the norm for Italy and France, and German scientists were forced to make do with much smaller increases than promised. The United Kingdom and Canada stood out as exceptions, with scientists enjoying significant increases. In the United States, a still-pending federal budget contains little New Year's cheer, although spending to combat bioterrorism bolstered some sectors. Science support from state governments suffered badly.

R-evolutionary genomics. Comparative analyses of newly sequenced genomes or partial sequences, including those of the rat, dog, two puffers, a bread mold, and anthrax and a close relative, have stimulated new hypotheses about evolution. But questions about how organisms are related to one another on the tree of life, or even what makes chimps and humans different, remain unanswered.

A different light. All in all, 2003 was a good year for astronomers tuning in to wavelengths outside the optical band. Although the Space Infrared Telescope Facility was delayed several months, the European satellite INTEGRAL is providing images of black holes and other phenomena in the gamma ray region of the spectrum. And the Wilkinson Microwave Anisotropy Probe's picture of the cosmic background radiation was such a smashing success it made *Science*'s 2003 Breakthrough of the Year.

Important matter. In 2002, two rival teams using equipment at CERN near Geneva made cold, slow-moving antihydrogen in bulk. The particles should help physicists figure out the differences between matter and antimatter. But since then, little has happened, and the antiproton decelerator at CERN is scheduled to be shut down in 2005. That means the next step—measuring the light that antihydrogen absorbs and emits—is several years away, at least.

Breakdown of the Year: Space Shuttle Columbia

What was to be a stellar year for NASA—continuing work on the international space station and double launches to Mars—turned into a horrible supernova above Texas. On 1 February, the space shuttle Columbia disintegrated as it returned to Earth from a science mission. The tragedy left seven dead, the shuttle fleet grounded, and NASA's future in question.

Picking up the pieces. Thousands of volunteers helped find debris from Columbia, which investigators used to piece together the cause of the tragedy.

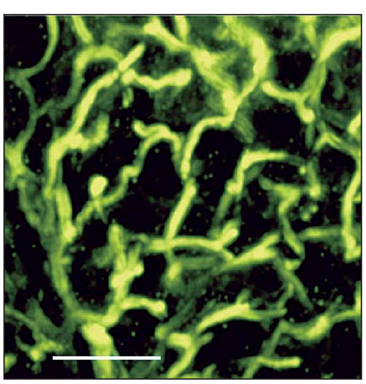
Newly installed NASA Administrator Sean O'Keefe, a former deputy chief of the White House Office of Management and Budget, faced the klieg lights of press conferences and congressional hearings to defend the agency. Meanwhile, a blue-ribbon panel led by retired Admiral Harold Gehman pored over hundreds of thousands of pages of documents and testimony to understand both the technical failure and the management troubles that allowed the failure to occur.

Gehman's panel concluded that a large piece of foam that struck the orbiter's sensitive underside during launch weakened the left wing's protective coating of tiles, allowing hot plasma to pierce the shuttle wing as it reentered Earth's atmosphere. Disturbingly, Gehman's team discovered that mission controllers at Johnson Space Center in Houston failed to heed concerns about the foam strike raised by lower-echelon NASA workers. NASA managers also vetoed a plan for U.S. spy satellites to photograph Columbia's belly in orbit to survey any damage. O'Keefe promised to fix the managerial as well as technical problems—which means the shuttle won't fly again until next fall.

The accident has had ripple effects throughout the space program. Astronomers don't know if and when the Hubble Space Telescope will be serviced again, and international space station research has suffered while the facility has a skeleton crew and no way to launch or return large science payloads. Plans to build a next-generation vehicle to replace the shuttle became mired in a congressional debate about its design, cost, and necessity, and the White House pondered what long-term direction to give the agency in an era of war and recession. What is clear is that the breakdown of 2003 is forcing a painful reexamination of the civil space effort that is sure to take up much of 2004. –ANDREW LAWLER

fined long-lasting, nanoscale, Technicolor markers; and revealed some basic properties of a single enzyme bound to DNA.

So-called optical tweezers exploit a laser light beam to manipulate single particles. This year, biologists remodeled optical tweezers into a minuscule force clamp to measure the stepwise motion of individual kinesin proteins—part of the cell's transportation machinery—as they chug along cellular tracks called microtubules. Kinesins move with a hand-over-hand action, it appears, rather than an inchworm gait as an earlier report suggested. Also this year, a technique exploiting single fluorescent molecules illuminated the hand-over-hand motion of another motor protein called myosin.



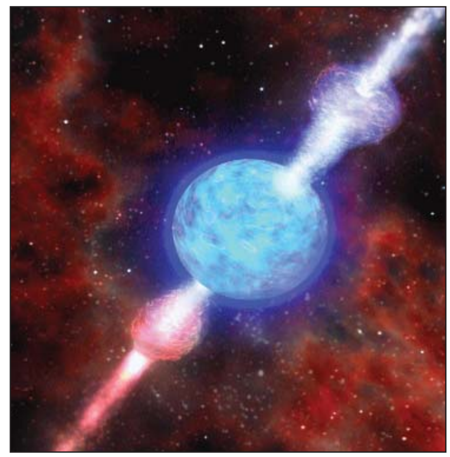
Afterglow. Quantum dots trace capillary networks in a living mouse.

Perhaps the most exciting new technique to emerge from the collaboration of physicists and biologists is the application of quantum dots to imaging. Quantum dots are tiny semiconductor nanocrystals that glow in myriad colors when excited by laser light. This year, researchers tracked the movements of individual glycine receptors within nerve cell membranes using quantum dots attached to antibodies. The glow of quantum dots endures—in this case, for 20 minutes—long after the aura of conventional organic dyes has dimmed. Quantum-dot technology for biological imaging is still in its infancy, but these versatile nanocrystals should answer some tough questions soon.

The physics-biology highway runs in both directions, as physicists are beginning to exploit biological molecules for their own purposes. By stretching a single RNA molecule hundreds of times, researchers last year verified a thermodynamic principle called Jarzynski's equality, which concerns the energy necessary to move a system from one conformation to another. This year, researchers established the kinetics and catalytic rate of a single enzyme as it digests DNA. Expect physicists and biologists to continue bonding over their fascination with single molecules.

#6

Cosmic blasts. Several discoveries this year lifted veils that had shrouded the most energetic explosions in the universe: titanic blasts of energy called gamma ray bursts (GRBs). Most notably, in March, astronomers confirmed the connection between GRBs and supernovas—the death throes of massive stars—when they spotted the unmistakable imprints of a supernova in the glow of a bright GRB.



Jet sets. New black holes may blast narrow jets of gamma rays and fatter sprays seen in x-rays, optical light, and radio waves.

CREDITS: (TOP TO BOTTOM) KENNEDY SPACE CENTER/NASA; DANA BERRY/SKYWORKS DIGITAL; D. LARSON *ET AL.*, *SCIENCE* **300**, 1434 (2003)

Astrophysicists now believe that the burst's jets of energy spewed into space when a star's core imploded, forming a black hole or—in a minority view—a rapidly spinning neutron star with a crushing magnetic field.

Other observations convinced researchers that GRBs confine their fiercest jets into narrow beams, perhaps just 1 to 5 angular degrees across. Only some of these flares happen to point toward Earth, making them far more common in the universe than the number of sightings would suggest. One observation sowed some dissent, however: A claimed detection of a polarized beam from a GRB sparked debate about whether the jets consist almost entirely of highly organized electromagnetic radiation, rather than a blast of particles as theorists have assumed.

More solid were the conclusions by several teams that an enigmatic set of lower-energy bursts, called x-ray flashes, streams from the same kinds of stellar catastrophes that produce GRBs. Theorists think that some x-ray flashes found this year were GRBs seen from the side. Other recent collapsing stars appeared to churn out narrow cones of x-rays and wider sprays of matter that produced optical light and torrents of radio waves, but no gamma rays.

Teamwork was the key to these advances. NASA's High Energy Transient Explorer overcame technical challenges to spot dozens of GRBs and x-ray flashes and beam their locations to astronomers on the ground, where a global network of robotic and traditional telescopes swung into action. This rapid detective work showed that a mysterious class of "dark" GRBs was visible in optical light after all, but only within minutes of the explosion.

The field's frenzy won't subside anytime soon. NASA's Swift satellite, set for launch in mid-2004, should catch GRBs at five times the rate of any previous mission. It will tackle the field's biggest remaining riddle: the origins of GRBs that last mere fractions of a second. Today's model with the most cachet involves the merger of two neutron stars.

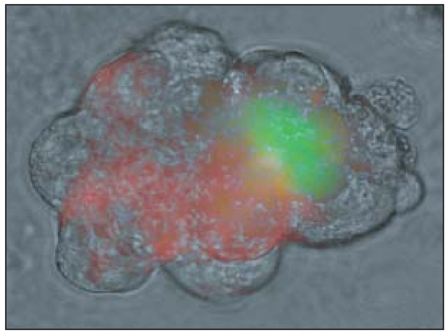
#7

Spontaneous generation. At least one observer called the surprise discovery an "ethical earthquake": Mouse embryonic stem (ES) cells can develop into both sperm and egg cells in culture dishes. The work hatched both scientific and ethical questions. In the short term, the discoveries should help reveal how germ cells develop. If the feat can be reproduced in human cells, it could provide a renewable source of human eggs or sperm for research. But it also opens a Pandora's box of ethical questions: Could a child be born whose genetic parent is a cell line?

In contrast to the complex questions it raised, the discovery itself was deceptively simple. Three separate teams found that germ cells develop spontaneously in dense cultures of ES cells. The trick was identifying them. One group genetically modified ES cells to glow green if they expressed genes characteristic of developing sex cells. Once isolated, the glowing cells seemed to behave like developing oocytes, showing signs of meiosis, the specialized cell division undergone by sperm and eggs but no other cell types.

Perhaps most surprising, after about 40 days in culture, structures that looked like early embryos appeared. The clusters may be parthenotes: embryos that sometimes develop from unfertilized eggs. (Normal mouse oocytes are known to form parthenotes in culture, but despite multiple attempts to implant them in a womb, none has ever survived to birth.) However, attempts to fertilize the lab-grown eggs have so far failed.

Similar techniques showed that ES cells can also give rise to sperm precursors. Preliminary studies this year suggest that these immature sperm, when injected into an egg, can lead to the development of an early embryo. But none has produced a live mouse pup.



Sex cells. Clusters of immature (green) and maturing (red) oocytes form spontaneously in cultures of mouse embryonic stem cells.

Growing sex cells in a dish should provide insights into the molecular processes that control the formation of sperm and eggs and lead to a better understanding of some kinds of infertility. And if human ES cells can serve as a source of human oocytes, they might replace eggs from human donors, which are in short supply, in nuclear transfer experiments that might someday produce patient-specific stem cells for treating disease. Indeed, if artificial egg cells prove to be functional enough for nuclear transfer but not for production of offspring, they might blunt one of the main arguments against therapeutic cloning: that it creates embryos only to destroy them.

#8

About-face. After 2 years of debate, work this year confirmed that certain oddball materials are capable of bending light in the wrong direction. Materials bend light and other types of electromagnetic radiation according to a property known as their index of refraction. The bigger a material's index, the slower light travels through it, and the more light bends. A change in refractive index is why a straw in a glass appears to have a kink where it enters the water. In natural materials, light always bends at a positive angle with respect to the angle at which it entered.

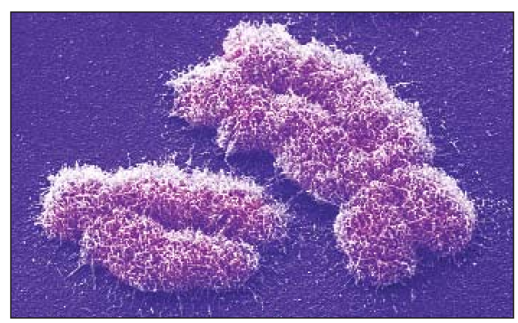
In 1964, a Russian physicist theorized that researchers could tailor materials to reverse the way they manipulate passing electromagnetic radiation. Two years ago, researchers created such "left-handed" materials. They beamed microwaves at a composite of copper rings and wires, which steered microwaves out at a negative instead of a positive angle. Last year other teams challenged those results, but this year definitive proof came from multiple camps.

One group traced the path of microwaves sent through two wedged-shaped samples, one a control made from Teflon, the other an array of rings and wires. The Teflon deflected the microwaves at a positive angle, as expected, whereas the rings and wires sent them out at a negative angle. Another group reported similar results and further showed that they agreed closely with numerical simulations.

Physicists are already finding ways to make use of left-handed materials, which have other properties besides a negative refractive index. Last month, for example, researchers reported that a set of electronic devices wired together to make a left-handed material produced an inverse Doppler effect, the reverse of the effect that causes the whistle of a passing train to drop in pitch. The new find could help researchers make cheap, compact devices useful for nondestructive testing of materials. Another team, meanwhile, snapped the first-ever image with a flat lens made from a left-handed material. Ultimately, such lenses promise to generate far less distortion than standard optics.

#9

The little Y that could. A sequencing tour de force revealed the genetic code of the Y chromosome this year and in the process earned new respectability for the stubby piece of DNA that makes a man a man. Half of the 59 million bases in this chromosome are jumbled, possibly useless, and virtually impossible to decipher. This "junk" suggested that the Y is slowly fading as a chromosome. But the new sequence of the other half of Y's DNA, which contains the genes, shows that it has evolved an unusual, but effective, way to take care of itself.



Man maker. Insights from sequencing the Y chromosome (left) have earned it new respect.

The Y's coding regions had proved difficult to unravel because there are duplicate genes throughout. The sequencers now know that most of these duplicate genes are arranged in eight palindromes, within each of which one set of genes has an identical or nearly identical mirror-image matchup. Palindromes cover up to 3 million bases and include most of the genes related to testis development and function.

The palindromes make up for the fact that Y lacks a partner. All other human chromo-

CREDITS: (TOP TO BOTTOM) K. HÜBNER *ET AL., SCIENCE* **300**, 1251 (2003); ANDREW SYRED/PHOTO RESEARCHERS INC.

SARS: A Pandemic Prevented

In retrospect, it almost seems like a bad dream. When severe acute respiratory syndrome (SARS) roared onto the world scene in March, the fatal, contagious disease seemed unstoppable. Experts warned that it could ignite a pandemic. And then, in early July … gone. The nightmare never became a reality.

The outbreak was a chilling reminder that new infectious diseases are always lurking in the woodwork—and they needn't sicken a lot of people to bring economies to their knees. The episode gave the World Health Organization (WHO) new prominence and showcased public health and science at their best in response to a new challenge—and occasionally at their worst.

In the line of duty. WHO's Carlo Urbani died from SARS after warning the world.

SARS made its debut in November 2002, in the Chinese province of Guangdong, but the Chinese government remained silent about it for months, contributing to its spread. Officials remained in a state of denial even when SARS had started its march across the world from a hotel in Hong Kong. By sticking to a reassuring but false hypothesis—that the disease was caused by more familiar *Chlamydia* bacteria—and discouraging alternative views, the Chinese government prevented its scientists from playing what could have been a pivotal role in the discovery of the new virus.

On the upside, SARS inspired intense collaboration among laboratories worldwide hunting for the real culprit. There was plenty of rivalry and the occasional squabble behind the scenes. But sharing information, specimens, and reagents definitively nailed the agent, a member of the coronavirus family, only 5 weeks after WHO had sounded a global alarm. By that time, the virus's entire genome had already been sequenced.

But in the end it wasn't science that brought SARS under control. Centuries-old measures, such as strict isolation of patients, eventually cornered the virus after more than 8000 reported cases and 774 reported deaths. For doctors and nurses charged with that task, simply going to work took a great deal of courage. Some, including Carlo Urbani, a WHO official in Hanoi who first sounded the alarm, paid with their lives.

Six months later, many questions remain. Perhaps the biggest ones are "Where did SARS come from?" and "Will it come back?" Apart from a Singapore scientist who became infected in the lab in August, no new cases have been reported since July, and most scientists agree that it's unlikely that SARS is going around unnoticed. But the virus's natural reservoir is still unknown, and it's unclear whether its leap to humans was caused by an extremely unlikely event—say, a freak set of mutations—or something that could happen again any day.

Even if SARS does not return, its impact will last. The hunt for the virus set a new standard for the next emergency and helped assert WHO's leadership. The agency is fortifying its Global Outbreak Alert and Response Network—a loose affiliation of labs and institutions that have agreed to respond to emerging threats—and it's pushing hard for the adoption of the Global Health Regulations, a treaty that would oblige member states to act quickly and speak up about dangerous outbreaks within their borders. Meanwhile, the United States and several other countries are taking a critical look at often-antiquated quarantine laws and rethinking the balance between public health and civil liberties.

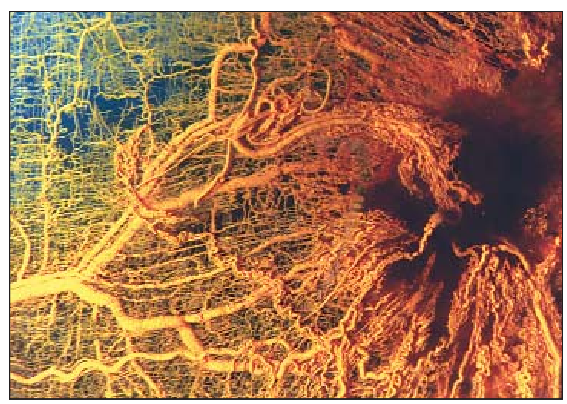
Few doubt that there's more to come. An Institute of Medicine report released in March concluded that with ecological disruption increasing, populations expanding, public health breaking down, and travel and trade booming, the risk of new SARS-like outbreaks, if not of SARS itself, is only increasing. –MARTIN ENSERINK

somes come in pairs. When a gene on one partner goes bad, it can be replaced with a copy of the other partner's good gene. A genomic loner, Y appeared to have no way to prevent mutations from gradually destroying its genes. That's where the palindromes come in: Genes on one end of a palindrome can replace mutated twins on the other end.

By sequencing parts of the Y chromosomes of other primates, researchers now know that at least six of the palindromes predate the evolution of humans and arose more than 5 million years ago. Thus it seems that gene swapping between palindrome arms keeps the Y chromosome's genetic makeup stable.

#10 Starving cancer. It's been a roller-coaster ride for researchers working on anticancer drugs that block development of the blood vessels that feed tumor growth. They've seen their field bounce from obscurity and skepticism to superhype—after a 1998 article in *The New York Times* suggested that antiangiogenesis drugs, as they are called, would cure cancer in 2 years—and then back to skepticism when early clinical trials produced unimpressive results. But this year, they've finally begun to see their efforts pay off.

The drugs' premise is simple. As a cancerous tumor grows, it must chemically induce the growth of new blood vessels to supply it with nutrients. Antiangiogenic agents starve tumors by preventing this blood vessel growth. Numerous agents, both naturally occurring proteins and synthetic drugs, shrink tumors in lab animals, but they had not been able to meet the "gold standard" of clinical cancer trials: extending the lives of patients.



Angiogenesis in action. Blood vessels grow toward a dark sarcoma tumor.

But this June, researchers announced that an antiangiogenesis drug, given with conventional chemotherapy drugs in a large clinical trial, prolonged the lives of patients with advanced colon cancer. The drug had failed a similar test with breast cancer patients, possibly because advanced breast tumors produce more angiogenesis-promoting factors than colon tumors do and are thus harder to control. This suggests that antiangiogenesis therapies will have to be tailored to their targets to be effective.

Researchers have also learned that antiangiogenesis drugs work most effectively in combination, either with each other or with conventional chemotherapeutic drugs or radiation. And clinicians will have plenty of drugs to choose from. Some 60 different antiangiogenesis drugs are currently in clinical trials against a wide variety of cancers, and many more are in preclinical testing.

–THE NEWS AND EDITORIAL STAFFS

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