



Family feud. DNA confirms that Neandertals split from modern humans 450,000 years ago.

2 DIGGING OUT FOSSIL DNA. This year, on the 150th anniversary of the discovery of the Neanderthal type specimen, researchers in Europe and the United States transformed the study of this ancient human by sequencing more than 1 million bases of Neanderthal DNA. In November, two groups, one decoding 65,000 Neanderthal bases and the other a million bases, showed that researchers can now find sequence changes between modern and ancient humans, differences that may reveal key steps in our evolution. The studies concluded that Neandertals diverged from our own ancestors at least 450,000 years ago—approximately the time suggested by fossil and mitochondrial DNA studies. One group’s data also suggest that Neandertals and modern humans may have interbred. In the works are a very rough draft of the complete

<< The Runners-Up

Neanderthal genome sequence and, as more fossils become available to sequencers, the development of bacterial libraries containing DNA from several Neandertals.

This breakthrough owes a large debt to earlier sequencing feats that demonstrated the potential of a new approach called metagenomics for deciphering ancient DNA, both human and nonhuman, and of faster sequencing technologies. For metagenomics, a technique developed for assessing microbial diversity, all the DNA in a sample is sequenced, and then sophisticated computer programs pull out only the target DNA based on its similarity to the sequence of a closely related extant organism.

In January 2006, researchers combined metagenomics with a new rapid sequencing technique called pyrosequencing, which uses pulses of light to read the sequence of thousands of bases at once, to get a whopping 13 million bases from a 27,000-year-old mammoth. The same sample also yielded another 15 million bases from bacteria, fungi, viruses, soil microbes, and plants—DNA that will provide clues about this giant mammal’s environment. With those two advances, ancient DNA sequencing is off and running.

3 SHRINKING ICE. Glaciologists nailed down an unsettling observation this year: The world’s two great ice sheets—covering Greenland

and Antarctica—are indeed losing ice to the oceans, and losing it at an accelerating pace. Researchers don’t understand why the massive ice sheets are proving so sensitive to an as-yet-modest warming of air and ocean water. The future of the ice sheets is still rife with uncertainty, but if the unexpectedly rapid shrinkage continues, low-lying coasts around the world—including New Orleans, South Florida, and much of Bangladesh—could face inundation within a couple of centuries rather than millennia.

This disturbing breakthrough rests on decades of measurements by airborne laser altimeters and orbiting radars, and, more recently, by a pair of satellites that measure ice mass directly by its gravitational pull. Different techniques and even different analyses of the same data disagree about just how much ice volume is changing. All of them, however,



Bye-bye. The great ice sheets are losing ice to melting and icebergs faster than it forms.

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Scorecard 2006

How well did the editors forecast the year’s Areas to Watch? The record shows that some of their crystal balls were clouded by wishful thinking.

Avian influenza. Research on flu drugs, vaccines, and epidemiology flourished in 2006, as did studies of the genetic changes that might turn avian influenza into a pandemic. But tracking the worldwide H5N1 outbreak is still difficult because researchers and countries hoard field samples and viral sequences.



Gravity rules. Gravitational-wave fans will have to wait. The Laser Interferometer Gravitational-Wave Observatory in the United States and the smaller GEO-600 facility in Germany won’t publish results until early 2007. Not bad news—just no news.



RNAi-based treatments. The gene-silencing technology boasted promising clinical-trial results in macular degeneration and respiratory syncytial virus, won a Nobel Prize, and enticed drug giant Merck to pay \$1.1 billion for a small biotech company focused on RNAi treatments. But safety worries still loom: A hepatitis B study of RNAi in mice reported that dozens of animals died from treatment.



Catching rays. The massive Pierre Auger Observatory in Argentina seems sure to answer fundamental questions about the highest-energy cosmic rays, such as whether their interactions with the afterglow of the big bang limit their energy and whether they originate from point sources in the sky. But not in 2006, as we predicted. Some answers will likely come at a major conference in Merida, Mexico, in July.



4 NEITHER FISH NOR FOWL.

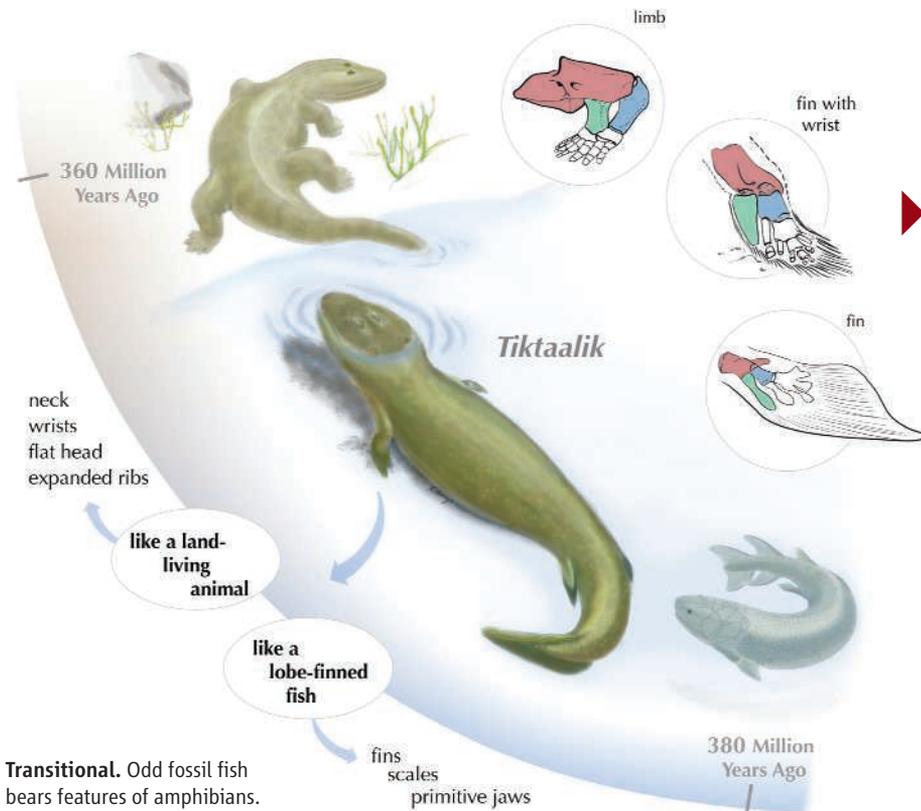
Paleontologists made a major splash this year with the debut of a fossil fish that long ago took a deep breath and made some tentative but ultimately far-reaching steps onto land. With its sturdy, jointed fins, the 375-million-year-old specimen fills an evolutionary gap and provides a glimpse of the features that helped later creatures conquer the continents.

All limbed vertebrates, known as tetrapods, evolved from lobe-finned fishes some 370 million to 360 million years ago. Many of these sophisticated fishes had skeletons with modifications, such as enlarged bones in their fins, that would ultimately prove useful for weight-bearing limbs. The new species is the most tetrapodlike fish yet discovered.

Three specimens were found during a 2004 field expedition to Ellesmere Island in the far north of Nunavut, Canada. They were named *Tiktaalik roseae* for “large freshwater fish” in the Inuktitut language and a donor who helped fund the expedition, respectively. With fins and scales, the 3-meter-long *Tiktaalik* is clearly a fish. It had a flat head with eyes on top and lived in shallow streams.

What makes *Tiktaalik* unique among fish is that each of the front fins has a wrist and elbow, providing flexible motion. Also unlike other fish, *Tiktaalik* sported a neck—the oldest one known in the fossil record—and could move its head. Achieving that flexibility required losing a bone called the operculum, which modern fish use to pump water over their gills. *Tiktaalik* still had well-developed gills, and it probably used its neck and stout limbs to push its head above water to inhale.

Another feature that makes *Tiktaalik* close kin to tetrapods is its robust, overlapping ribs.



Transitional. Odd fossil fish bears features of amphibians.

now show that both Greenland and Antarctica have been losing ice over the past 5 to 10 years. In the north, Greenland is shedding at least 100 gigatons each year. In the south, the figure is less certain but lies in the range of tens of gigatons per year or more.

Current ice sheet losses aren't raising sea level faster than 0.1 meter per century, but researchers fear that the rate could rise to a meter per century or more in the near future. As recently as 5 years ago, they assumed that global warming would simply melt more and more ice from the ice sheets, as it is melting mountain glaciers. But it turns out the ice isn't just melting faster, it is moving faster. Radar mapping shows that in recent years, glaciers carrying ice away from the sheets have

sped up by as much as 100%. In West Antarctica, warming ocean waters seem to have attacked the floating tongues of ice that hold back the ice sheet's outlet glaciers. Around southern Greenland, something else seems to be quickening the pace of outlet glaciers, perhaps lubrication by increasing amounts of surface meltwater seeping to a glacier's base.

Now glaciologists are wondering how the next chapter will play out. Will the relatively strong warming around the ice continue, or will it be weakened by natural variations of climate? Will the ice sheets adjust to the new warmth by eventually slowing their ice loss? And will more glaciers succumb to the spreading warmth? A few more breakthroughs are definitely in order.

Small worlds. As predicted, microbial evolution and ecology emerged among the most exciting areas of biology.

Researchers got a better grasp of what a prokaryote species might be, despite promiscuous lateral gene transfer. And it became clear that symbioses involving microbes (bacteria in the human gut, for example) are pervasive and sometimes extreme.



Seconding supersolidity.

Two groups reproduced the subtle signal that could be evidence that crystalline helium flows—as predicted. But one group reported that the effect disappeared if the frigid crystal was gently heated and cooled to remove imperfections. That suggests that the crystal itself doesn't budge, but thin layers of liquid flow between crystalline grains. The upshot: *Something* is happening, but what?

Homing in on high T_c . We can dream, can't we? The 20th anniversary of high-temperature superconductivity passed without any consensus being reached on how the materials carry electricity without resistance at temperatures as high as 138 kelvin. Experimenters are producing exquisitely precise data, but it seems that every theoretical concept has data pointing in its direction.



Bird to watch for. We hoped new sightings would prove that the ivory-billed woodpecker is alive and pecking. But indirect evidence from trees in Florida failed to sway the skeptics, and the original Arkansas sightings of the bird are looking increasingly shaky. Maybe it drowned in a rogue gravitational wave.



Breakthrough of the Year



Although their function isn't completely clear, researchers think they could have helped support its body out of water and aided in breathing. Forays onto land would have offered an escape from sharks and other predators, as well as insects to eat. *Tiktaalik* isn't a perfect tetrapod, of course—among other traits, it lacks fingers and toes—but it was certainly a big step in the right direction.

5 THE ULTIMATE CAMOUFLAGE. Science veered toward science fiction this year as physicists cobbled together the first rudimentary invisibility cloak. Although far from perfect—the ring-shaped cloak is invisible only when viewed in microwaves of a certain wavelength traveling parallel to the plane of the ring—the device could usher in a potentially revolutionary approach to manipulating electromagnetic waves.

The disappearing act began in May, when two independent analyses predicted that it should be possible to ferry electromagnetic waves around an object to hide it. All that was needed was a properly designed shell of “metamaterial,” an assemblage of tiny metallic rods and c-shaped rings. The waves churn the electrons in the rods and rings, and the sloshing affects the propagation of the waves. Both analyses specified how to sculpt the properties of the metamaterial and left it to experimenters to design the materials to meet those specs.

In October, the team that made one of the predictions did just that—almost. Physicists at Duke University built a ring instead of an all-concealing sphere. They made some approximations that rendered the cloak slightly reflective. Still, the thing whisked

Outta sight. Although not as fashionable as this electronic garment, a cloak unveiled this year is a step toward true invisibility.

microwaves around a plug of copper, proving that the method works. Cloaks for visible light are likely years off, as researchers must figure out how to make metamaterials that work at such short wave-

lengths. Even then, the cloak would be a bust for spying because it would be impossible to see out of it.

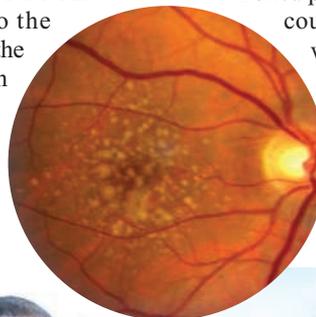
The real breakthrough may lie in the theoretical tools used to make the cloak. In such “transformation optics,” researchers imagine—à la Einstein—warping empty space to bend the path of electromagnetic waves. A mathematical transformation then tells them how to mimic the bending by filling unwarped space with a material whose optical properties vary from point to point. The technique could be used to design antennas, shields, and myriad other devices. Any way you look at it, the ideas behind invisibility are likely to cast a long shadow.

6 A RAY OF HOPE FOR MACULAR DEGENERATION PATIENTS. The year brought good news to the many people suffering from the vision-robbing disease known as age-related macular degeneration (AMD). In October, *The New England Journal of Medicine* published the

results of two clinical trials showing that treatment with the drug ranibizumab improves the vision of roughly one-third of patients with the more serious wet form of AMD and stabilizes the condition of most of the others. Other approved treatments can only slow the progression of AMD.

Vision loss in the wet form of AMD is caused by the growth and leakage of abnormal blood vessels in the macula, the central region of the retina. Ranibizumab, a monoclonal antibody fragment produced by Genentech Inc. does better than other treatments because it specifically targets a protein called VEGF that stimulates that vessel growth. The U.S. Food and Drug Administration approved ranibizumab for AMD treatment this year, but researchers are also looking at a related antibody made by Genentech. That drug, known as bevacizumab, is approved for treating certain cancers but so far not for use in AMD. If it works, however, it could be a cheaper alternative to ranibizumab, which costs \$1950 per monthly dose.

AMD researchers are making progress on another front as well. Over the past year and a half, they have uncovered several genes that influence an individual's susceptibility to the eye disease. One of them is the gene for VEGF itself, and another makes a protein that might also help regulate blood vessel growth. In addition, several groups have zeroed in on genes encoding proteins involved in inflammation, which can damage tissues if not controlled properly. Identifying those genes could help physicians determine whether a person is at high risk for AMD and thus should take preventive steps such as consuming more antioxidants and not smoking. And by shedding light on the causes



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of AMD, genetic studies should also provide targets for devising even better therapies.

7 DOWN THE BIODIVERSITY ROAD.

It doesn't take much to send an organism down speciation's path. Several studies these past 12 months have uncovered genetic changes that nudge a group of individuals toward becoming a separate species by giving them an edge in a new environment. The year's results speak to the power of genomics in helping evolutionary biologists understand one of biology's most fundamental questions: how biodiversity comes about.

For Florida beach mice, a single base difference in the melanocortin-1 receptor gene accounts for up to 36% of the lighter coat color that distinguishes the beach mice, evolutionary biologists reported in July. For cactus finches, the activity of the calmodulin gene is upregulated, causing their relatively long beaks, researchers reported in August.

Genes help drive speciation in other ways as well. Since the late 1930s, researchers have realized that as two incipient species diverge, the sequences of two or more interacting genes can evolve along different paths until the proteins they encode no longer work together in any crossbred offspring. Working with *Drosophila melanogaster* and a sister species, *D. simulans*, evolutionary geneticists have pinpointed the first such pair of incompatible genes, demonstrating in transgenic flies the genes' killing effects in hybrids of the two species. In October, a separate team found another fast-evolving gene and is homing in on its partner. They both seem to be nuclear pore proteins that are no longer compatible in fruit-fly hybrids. In September, fruit-fly researchers found that hybrids had problems because a particular gene was in a different place in the two species, likely because of duplication and loss of the original copy in one of them.

But in at least one case, hybrids do just fine. In June, evolutionary biologists detailed the most convincing case yet of a species that arose through hybridization. They bred two species of passion vine butterflies and got the red and yellow stripe pattern of a third species (image above). The pattern proved unattractive to the parent species, helping to reproductively isolate the hybrid.

Breakdown of the Year: Scientific Fraud

One year ago, as *Science* was assembling its 2005 Breakthrough of the Year issue, the need for a last-minute change became uncomfortably clear. A shadow was creeping across one of this journal's landmark papers, in which a team of South Korean and American researchers, led by Woo Suk Hwang at Seoul National University, claimed to have created the first-ever human embryonic stem cell lines that matched the DNA of patients. After anonymous allegations of irregularities in that paper appeared on a Korean Web site, South Korean authorities launched an investigation. As the story unfolded, *Science's* news editors hastily pulled an item about the Hwang achievements from the issue's roster of runners-up.

Today, the fallout from the Hwang case is plain. Multiple inquiries discredited two papers Hwang published in *Science* in 2004 and 2005, which claimed some of the greatest accomplishments to date with human embryonic stem cells. The papers were retracted. But the scientific fraud, one of the most audacious ever committed, shattered the trust of many researchers and members of the public in scientific journals' ability to catch instances of deliberate deception.

As it turned out, the Hwang debacle marked the beginning of a bad year for honest science. Incidents of publication fraud, if not

on the rise, are garnering more attention, and the review process is under scrutiny. In June, European investigators reported that the bulk of papers by Jon Sudbø, formerly a cancer researcher at the Norwegian Radium Hospital in Oslo, contained bogus data. Those included two articles in *The New England Journal of Medicine* that described a new way of identifying people at high risk of oral cancer, a strategy that many clinicians were keen to apply to patients.

Eric Poehlman, formerly a menopause and obesity researcher at the University of Vermont in Burlington, garnered perhaps the most dubious distinction of all: He became the first researcher in the United States to go to jail for scientific misconduct unrelated to patient deaths.

The Hwang case, however, was unique for its combustible mix of startling achievements in a high-profile field and publication in a high-visibility journal. Manipulated images, purportedly of distinct stem cells matched to patients but in fact showing cells drawn from fertilized embryos, handily fooled outside reviewers and *Science's* own editors. "The reporting of scientific results is based on trust," wrote Editor-in-Chief Donald Kennedy in a January 2006 editorial explaining why journals are not designed to catch fraud. It's a comment echoed often by journal editors facing the nightmare of faked data in their own pages.

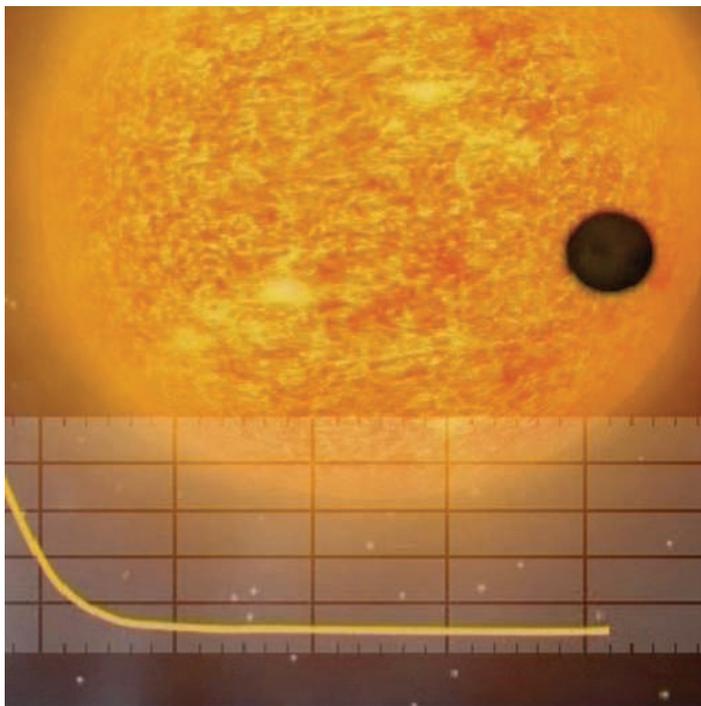
But the shock of the Hwang deception, along with other recent fraud cases, is jolting journals into a new reality. Five scientists and a top editor of *Nature* examined *Science's* handling of the Hwang papers, at the journal's request. Their report, published on *Science's* Web site earlier this month (www.sciencemag.org/sciext/hwang2005), concluded that operating in an atmosphere of trust is no longer sufficient. "*Science* must institutionalize a healthy level of concern in dealing with papers," the group wrote. It recommended "substantially stricter" requirements for reporting primary data and a risk assessment for accepted papers. *Science* and some other journals are also beginning to scrutinize images in certain papers, in an effort to catch any that have been manipulated.

Stem cell researchers, meanwhile, endured deep disappointment as a remarkable scientific advance evaporated before their eyes. Cloning early-stage human embryos, and crafting customized stem cell lines, is not the cakewalk some scientists hoped Hwang's papers had shown it to be. Stem cell researchers are backpedaling to more modest goals, just as *Science* and other journals consider how to prevent a breakdown of this magnitude from striking again.

—JENNIFER COUZIN



Busted. The unraveling of Hwang's stem-cell papers was the first and worst of the year's research scandals.



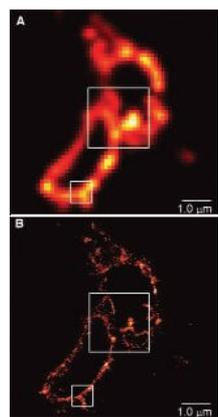
Areas to Watch in 2007

World-weary? Hardly. Four fledgling spacecraft will give planetary scientists plenty to ponder in 2007. Europe's COROT orbiting exoplanet hunter, scheduled for launch 27 December, should detect dozens of new "hot Jupiters" around other stars and may even bag its big quarry: signs of rocky planets just a few times the size of Earth. Closer to home, the Mars Reconnaissance Orbiter will take the sharpest-ever pictures of the martian surface and will use radar to look for rock layers—and ice—as much as 1 kilometer deep. The Venus Express orbiter will be going full tilt, and in February, New Horizons will send back snapshots of Jupiter en route to its 2015 rendezvous with Pluto.

Skulls and bones. In recent years, paleoanthropologists have uncovered new skulls, teeth, and lower limbs of the earliest members of our genus *Homo* at sites in the Republic of Georgia, China, and Kenya. In 2007, the first descriptions of these fossils should give clues to the identity of the first human ancestors to leave Africa about 1.8 million years ago—such as whether the bones all belong to one species (*Homo erectus*) or to two or more. Meanwhile, the long-awaited partial skeleton of *Ardipithecus ramidus*, an early human ancestor that lived in Ethiopia 4.4 million years ago, promises to shed light on how upright walking evolved in early hominids.

8 PEERING BEYOND THE LIGHT BARRIER.

Biologists got a clearer view of the fine structure of cells and proteins this year, as microscopy techniques that sidestep a fundamental limit of optics moved beyond



Clearly. New microscopy techniques resolve nanometer-sized features of proteins.

and this year, researchers used those techniques to do some real biology.

In April, researchers in Germany used a technique known as stimulated emission depletion (STED) to study the tiny capsules in nerve cells called synaptic vesicles. Each vesicle releases its load of neurotransmitter when it merges into the cell membrane. The

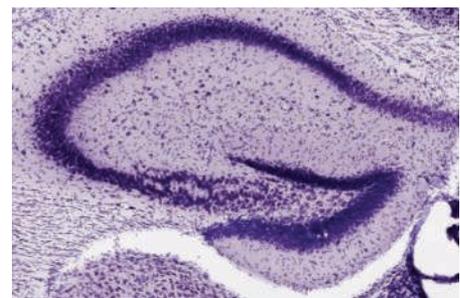
team showed that a protein in the vesicle remains clumped after the merger, suggesting that the clumps do not form from scratch when the process reverses to form new vesicles. The researchers tagged the proteins with a fluorescent dye and zapped the specimen with laser light to excite a spot as small as the diffraction limit allows. Then, by applying a pulse from a second beam with a dark "hole" in the middle, they squeezed the fluorescent spot down to a much smaller pinpoint of light. By scanning the beams across the sample and recording the level of fluorescence, the researchers assembled an image with a resolution of tens of nanometers. The team followed up with two other biological studies.

In August, another team imaged proteins within cells using a simpler technique known as photoactivated localization microscopy (PALM). The researchers used a fluorescent tag that had to be turned on with a pulse of light of one wavelength before it could be excited to fluoresce by light of another wavelength. By applying the first laser at a very low level, the researchers could turn on one tag molecule at a time. The molecule still produced a blurry spot when viewed through the microscope, but the researchers could nail down its position very precisely by finding the center of the blob. Repeating the process over and over, the team mapped proteins in cells with nanometer resolution. Two other groups introduced similar techniques this year.

Just how widely the techniques will be used remains to be seen. PALM is too slow to track dynamic processes, and STED requires fluorescent tags that can withstand intense excitation. Still, researchers are optimistic that more applications will follow, now that the diffraction limit is no longer a limit.

9 THE PERSISTENCE OF MEMORY.

How the brain records new memories is a central question in neuroscience. One attractive possibility involves a process called long-term potentiation (LTP) that strengthens connections between neurons. Many neuroscientists suspect that LTP is a memory mechanism, but proving it hasn't been easy. Several findings reported this year strongly bolstered the case.



Record keeper. Learning and LTP go hand in hand in the rodent hippocampus.

CREDITS (TOP TO BOTTOM): CNES; E. BETZIG ET AL./SCIENCE (2006); BRAINMAPS.ORG

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Loads of new primate genes.

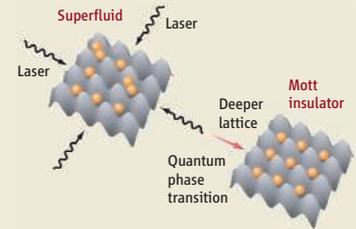
With the human and chimpanzee genomes sequenced, genetic research into our evolutionary past is scrambling up other branches of the primate family tree. Low-resolution maps of gorilla, rhesus macaque, orangutan, marmoset, and gibbon genomes are already available, and refined, error-free versions should be ready in 2007. In addition, look forward to rough drafts of the genomes of the galago, tree shrew, and mouse lemur. If things go as planned, a comparative analysis of all these genomes might finally begin to explain what sets humans apart.



A climate of change? The case for human-induced warming will grow even more ironclad as the Intergovernmental Panel on Climate Change releases its report in February. Meanwhile, the International Polar Year, opening in March, will feature climate research on Earth's coldest climes. And the world is watching the U.S. Congress, which, under Democratic control, is expected to pass some sort of mandatory emission regime, and President George W. Bush, whose response will be sure to shape the debate.

Whole-genome association studies. The trickle of studies comparing the genomes of healthy people to those of the sick is fast becoming a flood. Already, scientists have applied this strategy to macular degeneration, memory, and inflammatory bowel disease, and new projects on schizophrenia, psoriasis, diabetes, and more are heating up. But will the wave of data and new gene possibilities offer real insight into how diseases germinate? And will the genetic associations hold up better than those found the old-fashioned way?

Light crystals. Ultracold atoms continue to be one of the hottest areas in physics. Now researchers are loading the atoms into corrugated patterns of laser light known as optical lattices. The lattices work like artificial crystals, with the spots of light serving as the ions in the crystal lattice and the atoms playing the role of electrons moving through it. Optical lattices could help crack problems such as high-temperature superconductivity and seem sure to produce interesting new physics. Look for rapid progress in this burgeoning effort.



Scientists discovered LTP in the early 1970s, when experiments with rabbits showed that a brief barrage of electrical zaps could bolster synaptic connections between neurons in the hippocampus, a brain region tied to memory. Later studies revealed that drugs that block LTP, when given to an animal before it learns a new task, prevent new memories from being formed.

But some predictions of the LTP-memory hypothesis have been harder to test. One is that it should be possible to observe LTP in the hippocampus when an animal learns something. In January, Spanish scientists reported just such an observation in mice conditioned to blink upon hearing a tone. In August, another research team described LTP in the hippocampus of rats that had learned to avoid an area where they'd previously received a shock.

A study published in August addressed another prediction: that abolishing LTP after learning should erase what was learned. Researchers injected a compound that blocks an enzyme needed to sustain LTP into the hippocampus of rats after they'd been trained to avoid a "shock zone" in their enclosure. The treatment eradicated both LTP and the memory of the shock zone's location.

Although the new results add to evidence that LTP is a molecular mechanism of memory, much work remains. For example, researchers still haven't figured out how the

many forms of LTP identified in brain tissue relate to different kinds of memory. And they may have a while to wait for the ultimate test, which some call the "Marilyn Monroe criterion": inducing LTP at select synapses to create the vivid memory of an event, such as an evening with the voluptuous movie star, that never happened.

10 MINUTE MANIPULATIONS. Small RNA molecules that shut down gene expression have been hot, hot, hot in recent years, and 2006 was no exception. Researchers reported the discovery of what appears to be a new and still-mysterious addition to this exclusive club: *Piwi*-interacting RNAs (piRNAs). Abundant in the testes of several animals, including humans, piRNAs are distinctly different from their small RNA cousins, and scientists are racing to learn more about them and see where else in the body they might congregate.

PiRNAs made their grand entrance last summer, when four independent groups released a burst of papers describing them. In a sense, their sudden prominence is not surprising. The *Piwi* genes to which piRNAs bind belong to a gene family called Argonaute, other members of which

help control small RNAs known as microRNAs (miRNAs) and small interfering RNAs (siRNAs). Scientists already believed that the *Piwi* genes regulate the development and maintenance of sperm cells in many species. With the discovery of piRNAs, they may be close to figuring out how that happens.

Particularly intriguing to biologists is the appearance of piRNAs: Many measure about 30 RNA bases in length, compared with about 22 nucleotides for miRNAs and siRNAs. Although that may not sound like much of a difference, it has gripped biologists and convinced them that piRNAs are another class of small RNAs altogether. Also striking is the molecules' abundance and variety. One group of scientists found nearly 62,000 piRNAs in rat testes; nearly 50,000 of those appeared just once.

But beyond characterizing what piRNAs look like and finding hints that they can silence genes, scientists are mostly in the dark. Still to be determined: where they come from, which enzymes are key to their birth, and perhaps most important, what they do to an organism's genome. Stay tuned.

—THE NEWS STAFF

