What Is the Universe Made Of

Every once in a while, cosmologists are dragged, kicking and screaming, into a universe much more unsettling than they had any reason to expect. In the 1500s and 1600s, Copernicus, Kepler, and Newton showed that Earth is just one of many planets orbiting one of many stars, destroying the comfortable Medieval notion of a closed and tiny cosmos. In the 1920s, Edwin Hubble showed that our universe is constantly expanding and evolving, a finding that eventually shattered the idea that the universe is unchanging and eternal. And in the past few decades, cosmologists have discovered that the ordinary matter that makes up stars and galaxies and people is less than 5% of everything there is. Grappling with this new understanding of the cosmos, scientists face one overriding question: What is the universe made of?

In the dark. Dark matter holds galaxies together; supernovae measurements point to a mysterious dark energy.

This question arises from years of progressively stranger observations. In the 1960s, astronomers discovered that galaxies spun around too fast for the collective pull of the stars' gravity to keep them from flying apart. Something unseen appears to be keeping the stars from flinging themselves away from the center: unilluminated matter that exerts extra gravitational force. This is dark matter.

Over the years, scientists have spotted some of this dark matter in space; they have seen ghostly clouds of gas with x-ray telescopes, watched the twinkle of distant stars as invisible clumps of matter pass in front of them, and measured the distortion of space and time caused by invisible mass in galaxies. And thanks to observations of the abundances of elements in primordial gas clouds, physicists have concluded that only 10% of ordinary matter is visible to telescopes.

But even multiplying all the visible "ordinary" matter by 10 doesn't come close to accounting for how the universe is structured. When astronomers look up in the heavens with powerful telescopes, they see a lumpy cosmos. Galaxies don't dot the skies uniformly; they cluster together in thin tendrils and filaments that twine among vast voids. Just as there isn't enough visible matter to keep galaxies spinning at the right speed, there isn't enough ordinary matter to account for this lumpiness. Cosmologists now conclude that the gravitational forces exerted by another form of dark matter, made of an as-yet-undiscovered type of particle, must be sculpting these vast cosmic structures. They estimate that this exotic dark matter makes up about 25% of the stuff in the universe—five times as much as ordinary matter.

But even this mysterious entity pales by comparison to another mystery: dark energy. In the late 1990s, scientists examining distant supernovae discovered that the universe is expanding faster and faster, instead of slowing down as the laws of physics would imply. Is there some sort of antigravity force blowing the universe up?

All signs point to yes. Independent measurements of a variety of phenomena—cosmic background radiation, element abundances, galaxy clustering, gravitational lensing, gas cloud properties—all converge on a consistent, but bizarre, picture of the cosmos. Ordinary matter and exotic, unknown particles together make up only about 30% of the stuff in the universe; the rest is this mysterious antigravity force known as dark energy.

This means that figuring out what the universe is made of will require answers to three increasingly difficult sets of questions. What is ordinary dark matter made of, and where does it reside? Astrophysical observations, such as those that measure the bending of light by massive objects in space, are already yielding the answer. What is exotic dark matter? Scientists have some ideas, and with luck, a dark-matter trap buried deep underground or a high-energy atom smasher will discover a new type of particle within the next decade. And finally, what is dark energy? This question, which wouldn't even have been asked a decade ago, seems to transcend known physics more than any other phenomenon yet observed. Ever-better measurements of supernovae and cosmic background radiation as well as planned observations of gravitational lensing will yield information about dark energy's "equation of state"—essentially a measure of how squishy the substance is. But at the moment, the nature of dark energy is arguably the murkiest question in physics—and the one that, when answered, may shed the most light.

–CHARLES SEIFE

CREDIT: HIGH-Z SUPERNOVA SEARCH TEAM/HST/NASA

So Much More to Know . . . >>

From the nature of the cosmos to the nature of societies, the following 100 questions span the sciences. Some are pieces of questions discussed above; others are big questions in their own right. Some will drive scientific inquiry for the next century; others may soon be answered. Many will undoubtedly spawn new questions.

Is ours the only universe?
A number of quantum theorists and cosmologists are trying to figure out whether our universe is part of a bigger "multiverse." But others suspect that this hard-to-test idea may be a question for philosophers.

What drove cosmic inflation?
In the first moments after the big bang, the universe blew up at an incredible rate. But what did the blowing? Measurements of the cosmic microwave background and other astrophysical observations are narrowing the possibilities.

Published by AAAS

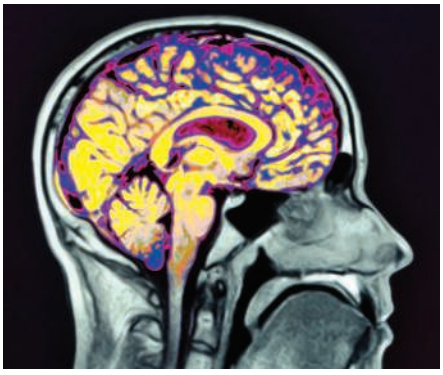
What Is the Biological Basis of Consciousness

For centuries, debating the nature of consciousness was the exclusive purview of philosophers. But if the recent torrent of books on the topic is any indication, a shift has taken place: Scientists are getting into the game.

Has the nature of consciousness finally shifted from a philosophical question to a scientific one that can be solved by doing experiments? The answer, as with any related to this topic, depends on whom you ask. But scientific interest in this slippery, age-old question seems to be gathering momentum. So far, however, although theories abound, hard data are sparse.

The discourse on consciousness has been hugely influenced by René Descartes, the French philosopher who in the mid–17th century declared that body and mind are made of different stuff entirely. It must be so, Descartes concluded, because the body exists in both time and space, whereas the mind has no spatial dimension.

Recent scientifically oriented accounts of consciousness generally reject Descartes's solution; most prefer to treat body and mind as different aspects of the same thing. In this view, consciousness emerges from the properties and organization of neurons in the brain. But how? And how can scientists, with their devotion to objective observation and measurement, gain access to the inherently private and subjective realm of consciousness?



CREDIT: LESTER LEFKOWITZ/CORBIS

Some insights have come from examining neurological patients whose injuries have altered their consciousness. Damage to certain evolutionarily ancient structures in the brainstem robs people of consciousness entirely, leaving them in a coma or a persistent vegetative state. Although these regions may be a master switch for consciousness, they are unlikely to be its sole source. Different aspects of consciousness are probably generated in different brain regions. Damage to visual areas of the cerebral cortex, for example, can produce strange deficits limited to visual awareness. One extensively studied patient, known as D.F., is unable to identify shapes or determine the orientation of a thin slot in a vertical disk. Yet when asked to pick up a card and slide it through the slot, she does so easily. At some level, D.F. must know the orientation of the slot to be able to do this, but she seems not to know she knows.

Cleverly designed experiments can produce similar dissociations of unconscious and conscious knowledge in people without neurological damage. And researchers hope that scanning the brains of subjects engaged in such tasks will reveal clues about the neural activity required for conscious awareness. Work with monkeys also may elucidate some aspects of consciousness, particularly visual awareness. One experimental approach is to present a monkey with an optical illusion that creates a "bistable percept," looking like one thing one moment and another the next. (The orientation-flipping Necker cube is a well-known example.) Monkeys can be trained to indicate which version they perceive. At the same time, researchers hunt for neurons that track the monkey's perception, in hopes that these neurons will lead them to the neural systems involved in conscious visual awareness and ultimately to an explanation of how a particular pattern of photons hitting the retina produces the experience of seeing, say, a rose.

Experiments under way at present generally address only pieces of the consciousness puzzle, and very few directly address the most enigmatic aspect of the conscious human mind: the sense of self. Yet the experimental work has begun, and if the results don't provide a blinding insight into how consciousness arises from tangles of neurons, they should at least refine the next round of questions.

Ultimately, scientists would like to understand not just the biological basis of consciousness but also why it exists. What selection pressure led to its development, and how many of our fellow creatures share it? Some researchers suspect that consciousness is not unique to humans, but of course much depends on how the term is defined. Biological markers for consciousness might help settle the matter and shed light on how consciousness develops early in life. Such markers could also inform medical decisions about loved ones who are in an unresponsive state.

Until fairly recently, tackling the subject of consciousness was a dubious career move for any scientist without tenure (and perhaps a Nobel Prize already in the bag). Fortunately, more young researchers are now joining the fray. The unanswered questions should keep them—and the printing presses—busy for many years to come.

–GREG MILLER

When and how did the first stars and galaxies form?
The broad brush strokes are visible, but the fine details aren't. Data from satellites and ground-based telescopes may soon help pinpoint, among other particulars, when the first generation of stars burned off the hydrogen "fog" that filled the universe.

JPL/NASA

Where do ultra-high-energy cosmic rays come from?
Above a certain energy, cosmic rays don't travel very far before being destroyed. So why are cosmic-ray hunters spotting such rays with no obvious source within our galaxy?

What powers quasars?
The mightiest energy fountains in the universe probably get their power from matter plunging into whirling supermassive black holes. But the details of what drives their jets remain anybody's guess.

E. J. SCHREIER, STSCI/NASA

What is the nature of black holes?
Relativistic mass crammed into a quantum-sized object? It's a recipe for disaster—and scientists are still trying to figure out the ingredients.

continued >>

Published by AAAS

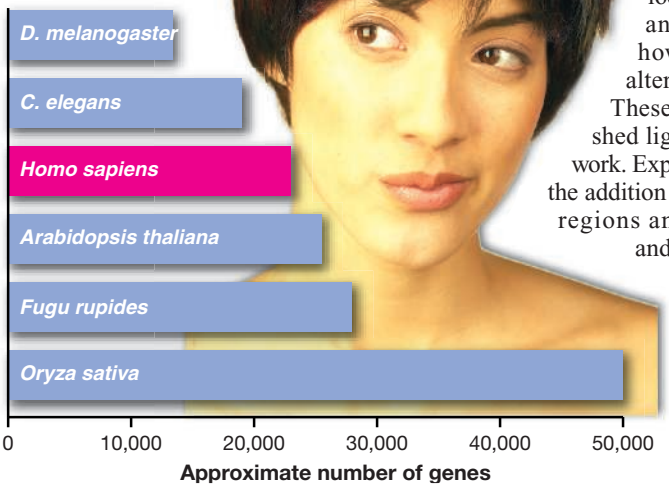
Why Do Humans Have So Few Genes

When leading biologists were unraveling the sequence of the human genome in the late 1990s, they ran a pool on the number of genes contained in the 3 billion base pairs that make up our DNA. Few bets came close. The conventional wisdom a decade or so ago was that we need about 100,000 genes to carry out the myriad cellular processes that keep us functioning. But it turns out that we have only about 25,000 genes—about the same number as a tiny flowering plant called *Arabidopsis* and barely more than the worm *Caenorhabditis elegans*.

That big surprise reinforced a growing realization among geneticists: Our genomes and those of other mammals are far more flexible and complicated than they once seemed. The old notion of one gene/one protein has gone by the board: It is now clear that many genes can make more than one protein. Regulatory proteins, RNA, noncoding bits of DNA, even chemical and structural alterations of the genome itself control how, where, and when genes are expressed. Figuring out how all these elements work together to choreograph gene expression is one of the central challenges facing biologists.

In the past few years, it has become clear that a phenomenon called alternative splicing is one reason human genomes can produce such complexity with so few genes. Human genes contain both coding DNA—exons—and noncoding DNA. In some genes, different combinations of exons can become active at different times, and each combination yields a different protein. Alternative splicing was long considered a rare hiccup during transcription, but researchers have concluded that it may occur in half—some say close to all—of our genes. That finding goes a long way toward explaining how so few genes can produce hundreds of thousands of different proteins. But how the transcription machinery decides which parts of a gene to read at any particular time is still largely a mystery.

The same could be said for the mechanisms that determine which genes or suites of genes are turned on or off at particular times and places. Researchers are discovering that each gene needs a supporting cast of hundreds to get its job done. They include proteins that shut down or activate a gene, for example by adding acetyl or methyl groups to the DNA. Other proteins, called transcription factors, interact with the genes more directly: They bind to landing sites situated near the gene under their control. As with alternative splicing, activation of different combinations of landing sites makes possible exquisite control of gene expression, but researchers have yet to figure out exactly how all these regulatory elements really work or how they fit in with alternative splicing.



In the past decade or so, researchers have also come to appreciate the key roles played by chromatin proteins and RNA in regulating gene expression. Chromatin proteins are essentially the packaging for DNA, holding chromosomes in well-defined spirals. By slightly changing shape, chromatin may expose different genes to the transcription machinery.

Genes also dance to the tune of RNA. Small RNA molecules, many less than 30 bases, now share the limelight with other gene regulators. Many researchers who once focused on messenger RNA and other relatively large RNA molecules have in the past 5 years turned their attention to these smaller cousins, including microRNA and small nuclear RNA. Surprisingly, RNAs in these various guises shut down and otherwise alter gene expression. They also are key to cell differentiation in developing organisms, but the mechanisms are not fully understood.

Researchers have made enormous strides in pinpointing these various mechanisms. By matching up genomes from organisms on different branches on the evolutionary tree, genomicists are locating regulatory regions and gaining insights into how mechanisms such as alternative splicing evolved. These studies, in turn, should shed light on how these regions work. Experiments in mice, such as the addition or deletion of regulatory regions and manipulating RNA, and computer models should also help. But the central question is likely to remain unsolved for a long time: How do all these features meld together to make us whole?

—ELIZABETH PENNISI

CREDIT: JUPITER IMAGES

Why is there more matter than antimatter?
To a particle physicist, matter and antimatter are almost the same. Some subtle difference must explain why matter is common and antimatter rare.

JUPITER IMAGES

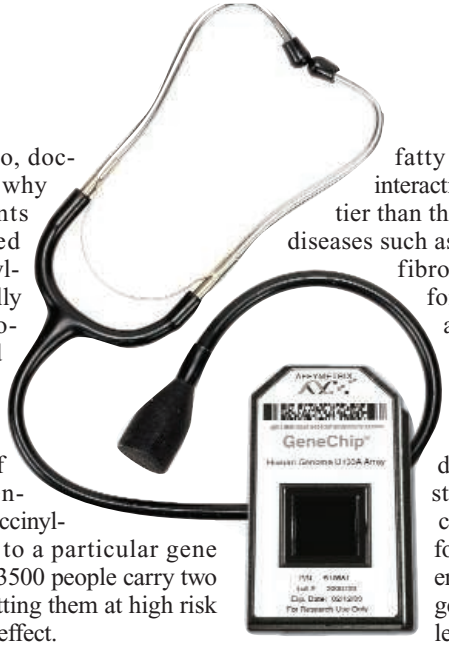
Does the proton decay?
In a theory of everything, quarks (which make up protons) should somehow be convertible to leptons (such as electrons)—so catching a proton decaying into something else might reveal new laws of particle physics.

JUPITER IMAGES

What is the nature of gravity?
It clashes with quantum theory. It doesn't fit in the Standard Model. Nobody has spotted the particle that is responsible for it. Newton's apple contained a whole can of worms.

Why is time different from other dimensions?
It took millennia for scientists to realize that time is a dimension, like the three spatial dimensions, and that time and space are inextricably linked. The equations make sense, but they don't satisfy those who ask why we perceive a "now" or why time seems to flow the way it does.

Published by AAAS



To What Extent Are Genetic Variation and Personal Health Linked

Forty years ago, doctors learned why some patients who received the anesthetic succinylcholine awoke normally but remained temporarily paralyzed and unable to breathe: They shared an inherited quirk that slowed their metabolism of the drug. Later, scientists traced sluggish succinylcholine metabolism to a particular gene variant. Roughly 1 in 3500 people carry two deleterious copies, putting them at high risk of this distressing side effect.

The solution to the succinylcholine mystery was among the first links drawn between genetic variation and an individual's response to drugs. Since then, a small but growing number of differences in drug metabolism have been linked to genetics, helping explain why some patients benefit from a particular drug, some gain nothing, and others suffer toxic side effects.

The same sort of variation, it is now clear, plays a key role in individual risks of coming down with a variety of diseases. Gene variants have been linked to elevated risks for disorders from Alzheimer's disease to breast cancer, and they may help explain why, for example, some smokers develop lung cancer whereas many others don't.

These developments have led to hopes—and some hype—that we are on the verge of an era of personalized medicine, one in which genetic tests will determine disease risks and guide prevention strategies and therapies. But digging up the DNA responsible—if in fact DNA *is* responsible—and converting that knowledge into gene tests that doctors can use remains a formidable challenge.

Many conditions, including various cancers, heart attacks, lupus, and depression, likely arise when a particular mix of genes collides with something in the environment, such as nicotine or a fatty diet. These multigene interactions are subtler and knottier than the single gene drivers of diseases such as hemophilia and cystic fibrosis; spotting them calls for statistical inspiration and rigorous experiments repeated again and again to guard against introducing unproven gene tests into the clinic. And determining treatment strategies will be no less complex: Last summer, for example, a team of scientists linked 124 different genes to resistance to four leukemia drugs.

But identifying gene networks like these is only the beginning. One of the toughest tasks is replicating these studies—an especially difficult proposition in diseases that are not overwhelmingly heritable, such as asthma, or ones that affect fairly small patient cohorts, such as certain childhood cancers. Many clinical trials do not routinely collect DNA from volunteers, making it sometimes difficult for scientists to correlate disease or drug response with genes. Gene microarrays, which measure expression of dozens of genes at once, can be fickle and supply inconsistent results. Gene studies can also be prohibitively costly.

Nonetheless, genetic dissection of some diseases—such as cancer, asthma, and heart disease—is galloping ahead. Progress in other areas, such as psychiatric disorders, is slower. Severely depressed or schizophrenic patients could benefit enormously from tests that reveal which drug and dose will help them the most, but unlike asthma, drug response can be difficult to quantify biologically, making gene-drug relations tougher to pin down.

As DNA sequence becomes more available and technologies improve, the genetic patterns that govern health will likely come into sharper relief. Genetic tools still under construction, such as a haplotype map that will be used to discern genetic variation behind common diseases, could further accelerate the search for disease genes.

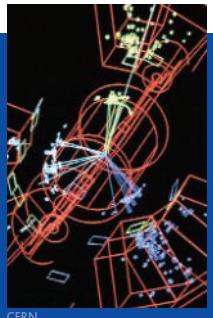
The next step will be designing DNA tests to guide clinical decision-making—and using them. If history is any guide, integrating such tests into standard practice will take time. In emergencies—a heart attack, an acute cancer, or an asthma attack—such tests will be valuable only if they rapidly deliver results.

Ultimately, comprehensive personalized medicine will come only if pharmaceutical companies want it to—and it will take enormous investments in research and development. Many companies worry that testing for genetic differences will narrow their market and squelch their profits.

Still, researchers continue to identify new opportunities. In May, the Icelandic company deCODE Genetics reported that an experimental asthma drug that pharmaceutical giant Bayer had abandoned appeared to decrease the risk of heart attack in more than 170 patients who carried particular gene variants. The drug targets the protein produced by one of those genes. The finding is likely to be just a foretaste of the many surprises in store, as the braids binding DNA, drugs, and disease are slowly unwound.

–JENNIFER COUZIN

CREDITS (TOP TO BOTTOM): JUPITER IMAGES; AFFYMETRIX



CERN

Are there smaller building blocks than quarks?
Atoms were "uncuttable." Then scientists discovered protons, neutrons, and other subatomic particles—which were, in turn, shown to be made up of quarks and gluons. Is there something more fundamental still?

Are neutrinos their own antiparticles?
Nobody knows this basic fact about neutrinos, although a number of underground experiments are under way. Answering this question may be a crucial step to understanding the origin of matter in the universe.

Is there a unified theory explaining all correlated electron systems?
High-temperature superconductors and materials with giant and colossal magnetoresistance are all governed by the collective rather than individual behavior of electrons. There is currently no common framework for understanding them.

continued >>

What is the most powerful laser researchers can build?
Theorists say an intense enough laser field would rip photons into electron-positron pairs, dousing the beam. But no one knows whether it's possible to reach that point.

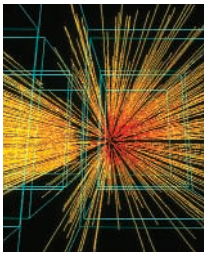
SANDIA NATIONAL LABORATORY

Published by AAAS

Can the Laws of Physics Be Unified

At its best, physics eliminates complexity by revealing underlying simplicity. Maxwell's equations, for example, describe all the confusing and diverse phenomena of classical electricity and magnetism by means of four simple rules. These equations are beautiful; they have an eerie symmetry, mirroring one another in an intricate dance of symbols. The four together feel as elegant, as whole, and as complete to a physicist as a Shakespearean sonnet does to a poet.

The Standard Model of particle physics is an unfinished poem. Most of the pieces are there, and even unfinished, it is arguably the most brilliant opus in the literature of physics. With great precision, it describes all known matter—all the subatomic particles such as quarks and leptons—as well as the forces by which those particles interact with one another. These forces are electromagnetism, which describes how charged objects feel each other's influence: the weak force, which explains how particles can change their identities, and the strong force, which describes how quarks stick together to form protons and other composite particles. But as lovely as the Standard Model's description is, it is in pieces, and some of those pieces—those that describe gravity—are missing. It is a few shards of beauty that hint at something greater, like a few lines of Sappho on a fragment of papyrus.



The beauty of the Standard Model is in its symmetry; mathematicians describe its symmetries with objects known as Lie groups. And a mere glimpse at the Standard Model's Lie group betrays its fragmented nature: $SU(3) \times SU(2) \times U(1)$. Each of those pieces represents one type of symmetry, but the symmetry of the whole is broken. Each of the forces behaves in a slightly different way, so each is described with a slightly different symmetry.

But those differences might be superficial. Electromagnetism and the weak force appear very dissimilar, but in the 1960s physicists showed that at high temperatures, the two forces "unify." It becomes apparent that electromagnetism and the weak force are really the same thing, just as it becomes obvious that ice and liquid water are the same substance if you warm them up together. This connection led physicists to hope that the strong force could also be unified with the other two forces, yielding one large theory described by a single symmetry such as SU(5).

A unified theory should have observable consequences. For example, if the strong force truly is the same as the electroweak force, then protons might not be truly stable; once in a long while, they should decay spontaneously. Despite many searches, nobody has spotted a proton decay, nor has anyone sighted any particles predicted by some symmetry-enhancing modifications to the Standard Model, such as supersymmetry. Worse yet, even such a unified theory can't be complete—as long as it ignores gravity.

Fundamental forces. A theory that ties all four forces together is still lacking.

Gravity is a troublesome force. The theory that describes it, general relativity, assumes that space and time are smooth and continuous, whereas the underlying quantum physics that governs subatomic particles and forces is inherently discontinuous and jumpy. Gravity clashes with quantum theory so badly that nobody has come up with a convincing way to build a single theory that includes all the particles, the strong and electroweak forces, and gravity all in one big bundle. But physicists do have some leads. Perhaps the most promising is superstring theory.

Superstring theory has a large following because it provides a way to unify everything into one large theory with a single symmetry—SO(32) for one branch of superstring theory, for example—but it requires a universe with 10 or 11 dimensions, scads of undetected particles, and a lot of intellectual baggage that might never be verifiable. It may be that there are dozens of unified theories, only one of which is correct, but scientists may never have the means to determine which. Or it may be that the struggle to unify all the forces and particles is a fool's quest.

In the meantime, physicists will continue to look for proton decays, as well as search for supersymmetric particles in underground traps and in the Large Hadron Collider (LHC) in Geneva, Switzerland, when it comes online in 2007. Scientists believe that LHC will also reveal the existence of the Higgs boson, a particle intimately related to fundamental symmetries in the model of particle physics. And physicists hope that one day, they will be able to finish the unfinished poem and frame its fearful symmetry.

—CHARLES SEIFE

CREDITS (TOP TO BOTTOM): JUPITER IMAGES; JUPITER IMAGES; MEHAU KULYK/PHOTO RESEARCHERS INC.; CERN/PHOTO RESEARCHERS INC.

Can researchers make a perfect optical lens?
They've done it with microwaves but never with visible light.

JUPITER IMAGES

Is it possible to create magnetic semiconductors that work at room temperature?
Such devices have been demonstrated at low temperatures but not yet in a range warm enough for spintronics applications.

What is the pairing mechanism behind high-temperature superconductivity?
Electrons in superconductors surf together in pairs. After 2 decades of intense study, no one knows what holds them together in the complex, high-temperature materials.

Can we develop a general theory of the dynamics of turbulent flows and the motion of granular materials?
So far, such "nonequilibrium systems" defy the tool kit of statistical mechanics, and the failure leaves a gaping hole in physics.

JUPITER IMAGES

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How Much Can Human Life Span Be Extended

When Jeanne Calment died in a nursing home in southern France in 1997, she was 122 years old, the longest-living human ever documented. But Calment's uncommon status will fade in subsequent decades if the predictions of some biologists and demographers come true. Life-span extension in species from yeast to mice and extrapolation from life expectancy trends in humans have convinced a swath of scientists that humans will routinely coast beyond 100 or 110 years of age. (Today, 1 in 10,000 people in industrialized countries hold centenarian status.) Others say human life span may be far more limited. The elasticity found in other species might not apply to us. Furthermore, testing life-extension treatments in humans may be nearly impossible for practical and ethical reasons.

Just 2 or 3 decades ago, research on aging was a backwater. But when molecular biologists began hunting for ways to prolong life, they found that life span was remarkably pliable. Reducing the activity of an insulinlike receptor more than doubles the life span of worms to a startling—for them—6 weeks. Put certain strains of mice on near-starvation but nutrient-rich diets, and they live 50% longer than normal.

Some of these effects may not occur in other species. A worm's ability to enter a "dauer" state, which resembles hibernation, may be critical, for example. And shorter-lived species such as worms and fruit flies, whose aging has been delayed the most, may be more susceptible to life-span manipulation. But successful approaches are converging on a few key areas: calorie restriction; reducing levels of insulinlike growth factor 1 (IGF-1), a protein; and preventing oxidative damage to the body's tissues. All three might be interconnected, but so far that hasn't been confirmed (although calorie-restricted animals have low levels of IGF-1).

Can these strategies help humans live longer? And how do we determine whether they will? Unlike drugs for cancer or heart disease, the benefits of antiaging treatments are fuzzier, making studies difficult to set up and to interpret. Safety is uncertain; calorie restriction reduces fertility in animals, and lab flies bred to live long can't compete with their wild counterparts. Furthermore, garnering results—particularly from younger volunteers, who may be likeliest to benefit because they've aged the least—will take so long that by the time results are in, those who began the study will be dead.

That hasn't stopped scientists, some of whom have founded companies, from searching for treatments to slow aging. One intriguing question is whether calorie restriction works in humans. It's being tested in primates, and the National Institute on Aging in Bethesda, Maryland, is funding short-term studies in people. Volunteers in those trials have been on a stringent diet for up to 1 year while researchers monitor their metabolism and other factors that could hint at how they're aging.

Insights could also come from genetic studies of centenarians, who may have inherited long life from their parents. Many scientists believe that average human life span has an inherent upper limit, although they don't agree on whether it's 85 or 100 or 150.

One abiding question in the antiaging world is what the goal of all this work ought to be. Overwhelmingly, scientists favor treatments that will slow aging and stave off age-related diseases rather than simply extending life at its most decrepit. But even so, slowing aging could have profound social effects, upsetting actuarial tables and retirement plans.

Then there's the issue of fairness: If antiaging therapies become available, who will receive them? How much will they cost? Individuals may find they can stretch their life spans. But that may be tougher to achieve for whole populations, although many demographers believe that the average life span will continue to climb as it has consistently for decades. If that happens, much of the increase may come from less dramatic strategies, such as heart disease and cancer prevention, that could also make the end of a long life more bearable. —JENNIFER COUZIN

Are there stable high-atomic-number elements?
A superheavy element with 184 neutrons and 114 protons should be relatively stable, if physicists can create it.

Is superfluidity possible in a solid? If so, how?
Despite hints in solid helium, nobody is sure whether a crystalline material can flow without resistance. If new types of experiments show that such outlandish behavior is possible, theorists would have to explain how.

What is the structure of water?
Researchers continue to tussle over how many bonds each H_2O molecule makes with its nearest neighbors.

JUPITER IMAGES

What is the nature of the glassy state?
Molecules in a glass are arranged much like those in liquids but are more tightly packed. Where and why does liquid end and glass begin?

continued >>

Are there limits to rational chemical synthesis?
The larger synthetic molecules get, the harder it is to control their shapes and make enough copies of them to be useful. Chemists will need new tools to keep their creations growing.

Published by AAAS

What Controls Organ Regeneration

Unlike automobiles, humans get along pretty well for most of their lives with their original parts. But organs do sometimes fail, and we can't go to the mechanic for an engine rebuild or a new water pump—at least not yet. Medicine has battled back many of the acute threats, such as infection, that curtailed human life in past centuries. Now, chronic illnesses and deteriorating organs pose the biggest drain on human health in industrialized nations, and they will only increase in importance as the population ages. Regenerative medicine—rebuilding organs and tissues—could conceivably be the 21st century equivalent of antibiotics in the 20th. Before that can happen, researchers must understand the signals that control regeneration.

Researchers have puzzled for centuries over how body parts replenish themselves. In the mid-1700s, for instance, Swiss researcher Abraham Trembley noted that when chopped into pieces, hydra—tubelike creatures with tentacles that live in fresh water—could grow back into complete, new organisms. Other scientists of the era examined the salamander's ability to replace a severed tail. And a century later, Thomas Hunt Morgan scrutinized planaria, flatworms that can regenerate even when whittled into 279 bits. But he decided that regeneration was an intractable problem and forsook planaria in favor of fruit flies.

Mainstream biology has followed in Morgan's wake, focusing on animals suitable for studying genetic and embryonic development. But some researchers have pressed on with studies of regeneration superstars, and they've devised innovative strategies to tackle the genetics of these organisms. These efforts and investigations of new regeneration models—such as zebrafish and special mouse lines—are beginning to reveal the forces that guide regeneration and those that prevent it.

Animals exploit three principal strategies to regenerate organs. First, working organ cells that normally don't divide can multiply and grow to replenish lost tissue, as occurs in injured salamander hearts. Second, specialized cells can undo their training—a process known as dedifferentiation—and assume a more pliable form that can replicate and later respecialize to reconstruct a missing part. Salamanders and newts take this approach to heal and rebuild a severed limb, as do zebrafish to mend clipped fins. Finally, pools of stem cells can step in to perform required renovations. Planaria tap into this resource when reconstructing themselves.

Self-repair. Newts reprogram their cells to reconstruct a severed limb.

Humans already plug into these mechanisms to some degree. For instance, after surgical removal of part of a liver, healing signals tell remaining liver cells to resume growth and division to expand the organ back to its original size. Researchers have found that when properly enticed, some types of specialized human cells can revert to a more nascent state (see p. 85). And stem cells help replenish our blood, skin, and bones. So why do our hearts fill with scar tissue, our lenses cloud, and our brain cells perish?

Animals such as salamanders and planaria regenerate tissues by rekindling genetic mechanisms that guide the patterning of body structures during embryonic development. We employ similar pathways to shape our parts as embryos, but over the course of evolution, humans may have lost the ability to tap into it as adults, perhaps because the cell division required for regeneration elevated the likelihood of cancer. And we may have evolved the capacity to heal wounds rapidly to repel infection, even though speeding the pace means more scarring. Regeneration pros such as salamanders heal wounds methodically and produce pristine tissue. Avoiding fibrotic tissue could mean the difference between regenerating and not: Mouse nerves grow vigorously if experimentally severed in a way that prevents scarring, but if a scar forms, nerves wither.

Unraveling the mysteries of regeneration will depend on understanding what separates our wound-healing process from that of animals that are able to regenerate. The difference might be subtle: Researchers have identified one strain of mice that seals up ear holes in weeks, whereas typical strains never do. A relatively modest number of genetic differences seems to underlie the effect. Perhaps altering a handful of genes would be enough to turn us into superhealers, too. But if scientists succeed in initiating the process in humans, new questions will emerge. What keeps regenerating cells from running amok? And what ensures that regenerated parts are the right size and shape, and in the right place and orientation? If researchers can solve these riddles—and it's a big "if"—people might be able to order up replacement parts for themselves, not just their '67 Mustangs.

–R. JOHN DAVENPORT

R. John Davenport is an editor of *Science*'s SAGE KE.

CREDIT: J. P. BROCKES AND A. KUMAR, *NATURE REVIEWS MOLECULAR CELL BIOLOGY* **3**, 566 (2002)

What is the ultimate efficiency of photovoltaic cells?
Conventional solar cells top out at converting 32% of the energy in sunlight to electricity. Can researchers break through the barrier?

SOLAR ELECTRIC POWER ASSOCIATION

Will fusion always be the energy source of the future?
It's been 35 years away for about 50 years, and unless the international community gets its act together, it'll be 35 years away for many decades to come.

What drives the solar magnetic cycle?
Scientists believe differing rates of rotation from place to place on the sun underlie its 22-year sunspot cycle. They just can't make it work in their simulations. Either a detail is askew, or it's back to the drawing board.

How do planets form?
How bits of dust and ice and gobs of gas came together to form the planets without the sun devouring them all is still unclear. Planetary systems around other stars should provide clues.

JPL/NASA

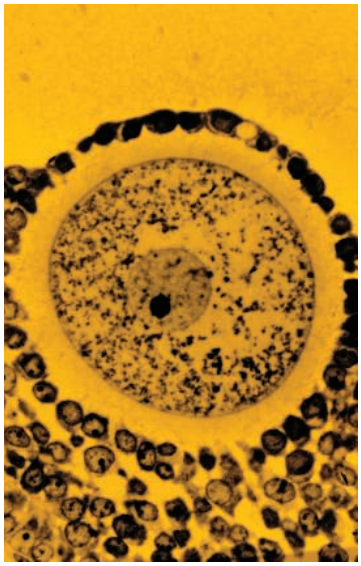
Published by AAAS

How Can a Skin Cell Become a Nerve Cell

Like Medieval alchemists who searched for an elixir that could turn base metals into gold, biology's modern alchemists have learned how to use oocytes to turn normal skin cells into valuable stem cells, and even whole animals. Scientists, with practice, have now been able to make nuclear transfer nearly routine to produce cattle, cats, mice, sheep, goats, pigs, and—as a Korean team announced in May—even human embryonic stem (ES) cells. They hope to go still further and turn the stem cells into treatments for previously untreatable diseases. But like the medieval alchemists, today's cloning and stem cell biologists are working largely with processes they don't fully understand: What actually happens inside the oocyte to reprogram the nucleus is still a mystery, and scientists have a lot to learn before they can direct a cell's differentiation as smoothly as nature's program of development does every time a fertilized egg gives rise to the multiple cell types that make up a live baby.

Scientists have been investigating the reprogramming powers of the oocyte for half a century. In 1957, developmental biologists first discovered that they could insert the nucleus of adult frog cells into frog eggs and create dozens of genetically identical tadpoles. But in 50 years, the oocyte has yet to give up its secrets.

The answers lie deep in cell biology. Somehow, scientists know, the genes that control development—generally turned off in adult cells—get turned back on again by the oocyte, enabling the cell to take on the youthful potential of a newly fertilized egg. Scientists understand relatively little about these on-and-off switches in normal cells, however, let alone the unusual reversal that takes place during nuclear transfer.



CREDIT: DON W. FAWCETT/VISUALS UNLIMITED

Cellular alchemist. A human oocyte.

As cells differentiate, their DNA becomes more tightly packed, and genes that are no longer needed—or those which should not be expressed—are blocked. The DNA wraps tightly around proteins called histones, and genes are then tagged with methyl groups that prevent the proteinmaking machinery in the cell from reaching them. Several studies have shown that enzymes that remove those methyl groups are crucial for nuclear transfer to work. But they are far from the only things that are needed.

If scientists could uncover the oocyte's secrets, it might be possible to replicate its tricks without using oocytes themselves, a resource that is fairly difficult to obtain and the use of which raises numerous ethical questions. If scientists could come up with a cell-free bath that turned the clock back on already-differentiated cells, the implications could be enormous. Labs could rejuvenate cells from patients and perhaps then grow them into new tissue that could repair parts worn out by old age or disease.

But scientists are far from sure if such cell-free alchemy is possible. The egg's very structure, its scaffolding of proteins that guide the chromosomes during cell division, may also play a key role in turning on the necessary genes. If so, developing an elixir of proteins that can turn back a cell's clock may remain elusive.

To really make use of the oocyte's power, scientists still need to learn how to direct the development of the rejuvenated stem cells and guide them into forming specific tissues. Stem cells, especially those from embryos, spontaneously form dozens of cell types, but controlling that development to produce a single type of cell has proved more difficult. Although some teams have managed to produce nearly pure colonies of certain kinds of neural cells from ES cells, no one has managed to concoct a recipe that will direct the cells to become, say, a pure population of dopamine-producing neurons that could replace those missing in Parkinson's disease.

Scientists are just beginning to understand how cues interact to guide a cell toward its final destiny. Decades of work in developmental biology have provided a start: Biologists have used mutant frogs, flies, mice, chicks, and fish to identify some of the main genes that control a developing cell's decision to become a bone cell or a muscle cell. But observing what goes wrong when a gene is missing is easier than learning to orchestrate differentiation in a culture dish. Understanding how the roughly 25,000 human genes work together to form tissues—and tweaking the right ones to guide an immature cell's development—will keep researchers occupied for decades. If they succeed, however, the result will be worth far more than its weight in gold.

–GRETCHEN VOGEL

What causes ice ages?
Something about the way the planet tilts, wobbles, and careens around the sun presumably brings on ice ages every 100,000 years or so, but reams of climate records haven't explained exactly how.

What causes reversals in Earth's magnetic field?
Computer models and laboratory experiments are generating new data on how Earth's magnetic poles might flip-flop. The trick will be matching simulations to enough aspects of the magnetic field beyond the inaccessible core to build a convincing case.

Are there earthquake precursors that can lead to useful predictions?
Prospects for finding signs of an imminent quake have been waning since the 1970s. Understanding faults will progress, but routine prediction would require an as-yet-unimagined breakthrough.

USGS

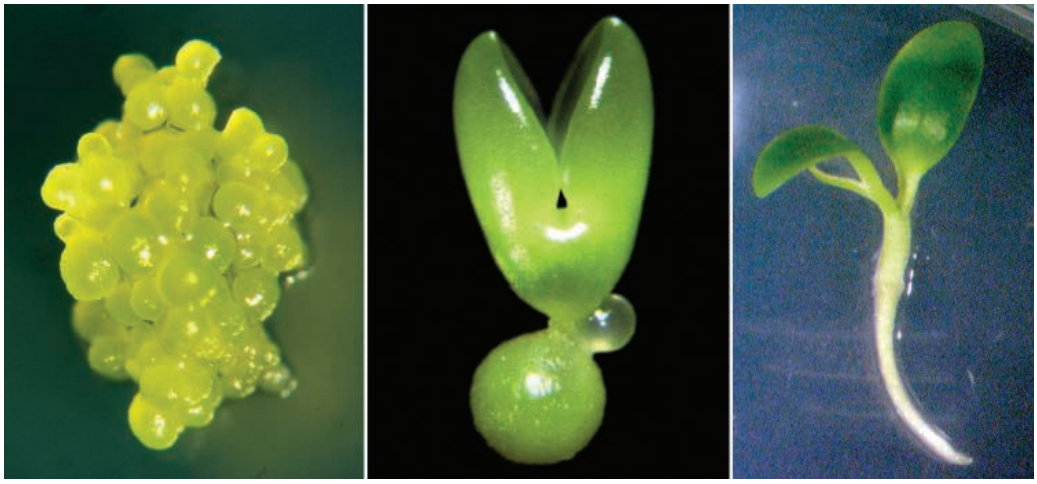
Is there—or was there—life elsewhere in the solar system?
The search for life—past or present—on other planetary bodies now drives NASA's planetary exploration program, which focuses on Mars, where water abounded when life might have first arisen.

continued >>

Published by AAAS

How Does a Single Somatic Cell Become A Whole Plant

It takes a certain amount of flexibility for a plant to survive and reproduce. It can stretch its roots toward water and its leaves toward sunlight, but it has few options for escaping predators or finding mates. To compensate, many plants have evolved repair mechanisms and reproductive strategies that allow them to produce offspring even without the meeting of sperm and egg. Some can reproduce from outgrowths of stems, roots, and bulbs, but others are even more radical, able to create new embryos from single somatic cells. Most citrus trees, for example, can form embryos from the tissues surrounding the unfertilized gametes—a feat no animal can manage. The houseplant *Bryophyllum* can sprout embryos from the edges of its leaves, a bit like Athena springing from Zeus's head.



Power of one. Orange tree embryos can sprout from a single somatic cell.

Nearly 50 years ago, scientists learned that they could coax carrot cells to undergo such embryogenesis in the lab. Since then, people have used so-called somatic embryogenesis to propagate dozens of species, including coffee, magnolias, mangos, and roses. A Canadian company has planted entire forests of fir trees that started life in tissue culture. But like researchers who clone animals (see p. 85), plant scientists understand little about what actually controls the process. The search for answers might shed light on how cells' fates become fixed during development, and how plants manage to retain such flexibility.

Scientists aren't even sure which cells are capable of embryogenesis. Although earlier work assumed that all plant cells were equally labile, recent evidence suggests that only a subset of cells can transform into embryos. But what those cells look like before their transformation is a mystery. Researchers have videotaped cultures in which embryos develop but found no visual pattern that hints at which cells are about to sprout, and staining for certain patterns of gene expression has been inconclusive.

Researchers do have a few clues about the molecules that might be involved. In the lab, the herbicide 2,4-dichlorophenoxyacetic acid (sold as weed killer and called 2,4-D) can prompt cells in culture to elongate, build a new cell wall, and start dividing to form embryos. The herbicide is a synthetic analog of the plant hormones called auxins, which control everything from the plant's response to light and gravity to the ripening of fruit. Auxins might also be important in natural somatic embryogenesis: Embryos that sprout on top of veins near the leaf edge are exposed to relatively high levels of auxins. Recent work has also shown that over- or underexpression of certain genes in *Arabidopsis* plants can prompt embryogenesis in otherwise normal-looking leaf cells.

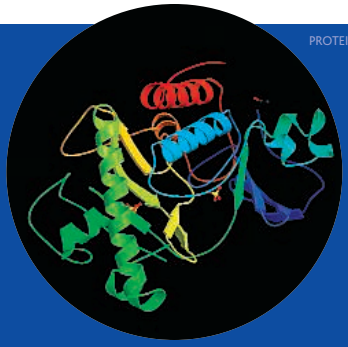
Sorting out sex-free embryogenesis might help scientists understand the cellular switches that plants use to stay flexible while still keeping growth under control. Developmental biologists are keen to learn how those mechanisms compare in plants and animals. Indeed, some of the processes that control somatic embryogenesis may be similar to those that occur during animal cloning or limb regeneration (see p. 84).

On a practical level, scientists would like to be able to use lab-propagation techniques on crop plants such as maize that still require normal pollination. That would speed up both breeding of new varieties and the production of hybrid seedlings—a flexibility that farmers and consumers could both appreciate.

—GRETCHEN VOGEL

CREDITS: USHRL/ARS/USDA

What is the origin of homochirality in nature?
Most biomolecules can be synthesized in mirror-image shapes. Yet in organisms, amino acids are always left-handed, and sugars are always right-handed. The origins of this preference remain a mystery.



PROTEIN DATA BANK

Can we predict how proteins will fold?
Out of a near infinitude of possible ways to fold, a protein picks one in just tens of microseconds. The same task takes 30 years of computer time.

How many proteins are there in humans?
It has been hard enough counting genes. Proteins can be spliced in different ways and decorated with numerous functional groups, all of which makes counting their numbers impossible for now.

How do proteins find their partners?
Protein-protein interactions are at the heart of life. To understand how partners come together in precise orientations in seconds, researchers need to know more about the cell's biochemistry and structural organization.

Published by AAAS

A long way to go. Grasping the workings of plate tectonics will require deeper probing.

CREDIT: ROGER RESSMEYER/CORBIS

How Does Earth's Interior Work

The plate tectonics revolution went only so deep. True, it made wonderful sense of most of the planet's geology. But that's something like understanding the face of Big Ben; there must be a lot more inside to understand about how and why it all works. In the case of Earth, there's another 6300 kilometers of rock and iron beneath the tectonic plates whose churnings constitute the inner workings of a planetary heat engine. Tectonic plates jostling about the surface are like the hands sweeping across the clock face: informative in many ways but largely mute as to what drives them.

Earth scientists inherited a rather simple picture of Earth's interior from their pre–plate tectonics colleagues. Earth was like an onion. Seismic waves passing through the deep Earth suggested that beneath the broken skin of plates lies a 2800-kilometer layer of rocky mantle overlying 3470 kilometers of molten and—at the center—solid iron. The mantle was further subdivided at a depth of 670 kilometers into upper and lower layers, with a hint of a layer a couple of hundred kilometers thick at the bottom of the lower mantle.

In the postrevolution era, the onion model continued to loom large. The dominant picture of Earth's inner workings divided the planet at the 670-kilometer depth, forming with the core a three-layer machine. Above the 670, the mantle churned slowly like a very shallow pot of boiling water, delivering heat and rock at mid-ocean ridges to make new crust and cool the interior and accepting cold sinking slabs of old plate at deep-sea trenches. A plume of hot rock might rise from just above the 670 to form a volcanic hot spot like Hawaii. But no hot rock rose up through the 670 barrier, and no cold rock sank down through it. Alternatively, argued a smaller contingent, the mantle churned from bottom to top like a deep stockpot, with plumes rising all the way from the core-mantle boundary.

Forty years of probing inner Earth with ever more sophisticated seismic imaging has boosted the view of the engine's complexity without much calming the debate about how it works. Imaging now clearly shows that the 670 is no absolute barrier. Slabs penetrate the boundary, although with difficulty. Layered-earth advocates have duly dropped their impenetrable boundary to 1000 kilometers or deeper. Or maybe there's a flexible, semipermeable boundary somewhere that limits mixing to only the most insistent slabs or plumes.

Now seismic imaging is also outlining two great globs of mantle rock standing beneath Africa and the Pacific like pistons. Researchers disagree whether they are hotter than average and rising under their own buoyancy, denser and sinking, or merely passively being carried upward by adjacent currents. Thin lenses of partially melted rock dot the mantle bottom, perhaps marking the bottom of plumes, or perhaps not. Geochemists reading the entrails of elements and isotopes in mantle-derived rocks find signs of five long-lived "reservoirs" that must have resisted mixing in the mantle for billions of years. But they haven't a clue where in the depths of the mantle those reservoirs might be hiding.

How can we disassemble the increasingly complex planetary machine and find what makes it tick? With more of the same, plus a large dose of patience. After all, plate tectonics was more than a half-century in the making, and those revolutionaries had to look little deeper than the sea floor.

Seismic imaging will continue to improve as better seismometers are spread more evenly about the globe. Seismic data are already distinguishing between temperature and compositional effects, painting an even more complex picture of mantle structure. Mineral physicists working in the lab will tease out more properties of rock under deep mantle conditions to inform interpretation of the seismic data, although still handicapped by the uncertain details of mantle composition. And modelers will more faithfully simulate the whole machine, drawing on seismics, mineral physics, and subtle geophysical observations such as gravity variations. Another 40 years should do it.

–RICHARD A. KERR

How many forms of cell death are there?
In the 1970s, apoptosis was finally recognized as distinct from necrosis. Some biologists now argue that the cell death story is even more complicated. Identifying new ways cells die could lead to better treatments for cancer and degenerative diseases.

KATHARINE SUTLIFF/*SCIENCE*

What keeps intracellular traffic running smoothly?
Membranes inside cells transport key nutrients around, and through, various cell compartments without sticking to each other or losing their way. Insights into how membranes stay on track could help conquer diseases, such as cystic fibrosis.

What enables cellular components to copy themselves independent of DNA?
Centrosomes, which help pull apart paired chromosomes, and other organelles replicate on their own time, without DNA's guidance. This independence still defies explanation.

C. SLAYDEN/*SCIENCE*

What roles do different forms of RNA play in genome function?
RNA is turning out to play a dizzying assortment of roles, from potentially passing genetic information to offspring to muting gene expression. Scientists are scrambling to decipher this versatile molecule.

continued >>

Published by AAAS

Are We Alone In the Universe

Alone, in all that space? Not likely. Just do the numbers: Several hundred billion stars in our galaxy, hundreds of billions of galaxies in the observable universe, and 150 planets spied already in the immediate neighborhood of the sun. That should make for plenty of warm, scummy little ponds where life could come together to begin billions of years of evolution toward technology-wielding creatures like ourselves. No, the really big question is when, if ever, we'll have the technological wherewithal to reach out and touch such intelligence. With a bit of luck, it could be in the next 25 years.

Workers in the search for extraterrestrial intelligence (SETI) would have needed more than a little luck in the first 45 years of the modern hunt for like-minded colleagues out there. Radio astronomer Frank Drake's landmark Project Ozma was certainly a triumph of hope over daunting odds. In 1960, Drake pointed a 26-meter radio telescope dish in Green Bank, West Virginia, at two stars for a few days each. Given the vacuum-tube technology of the time, he could scan across 0.4 megahertz of the microwave spectrum one channel at a time.

Almost 45 years later, the SETI Institute in Mountain View, California, completed its 10-year-long Project Phoenix. Often using the 350-meter antenna at Arecibo, Puerto Rico, Phoenix researchers searched 710 star systems at 28 million channels simultaneously across an 1800-megahertz range. All in all, the Phoenix search was 100 trillion times more effective than Ozma was.

Besides stunning advances in search power, the first 45 years of modern SETI have also seen a diversification of search strategies. The Search for Extraterrestrial Radio Emissions from Nearby Developed Intelligent Populations (SERENDIP) has scanned billions of radio sources in the Milky Way by piggybacking receivers on antennas in use by observational astronomers, including Arecibo. And other groups are turning modest-sized optical telescopes to searching for nanosecond flashes from alien lasers.

Still, nothing has been heard. But then, Phoenix, for example, scanned just one or two nearby sunlike stars out of each 100 million stars out there. For such sparse sampling to work, advanced, broadcasting civilizations would have to be abundant, or searchers would have to get very lucky.

To find the needle in a galaxy-size haystack, SETI workers are counting on the consistently exponential growth of computing power to continue for another couple of decades. In northern California, the SETI Institute has already begun constructing an array composed of individual 6-meter antennas. Ever-cheaper computer power will eventually tie 350 such antennas into "virtual telescopes," allowing scientists to search many targets at once. If Moore's law—that the cost of computation halves every 18 months—holds for another 15 years or so, SETI workers plan to use this antenna array approach to check out not a few thousand but perhaps a few million or even tens of millions of stars for alien signals. If there were just 10,000 advanced civilizations in the galaxy, they could well strike pay dirt before *Science* turns 150.

The technology may well be available in coming decades, but SETI will also need money. That's no easy task in a field with as high a "giggle factor" as SETI has. The U.S. Congress forced NASA to wash its hands of SETI in 1993 after some congressmen mocked the whole idea of spending federal money to look for "little green men with misshapen heads," as one of them put it. Searching for another tippy-top branch of the evolutionary tree still isn't part of the NASA vision. For more than a decade, private funding alone has driven SETI. But the SETI Institute's planned $35 million array is only a prototype of the Square Kilometer Array that would put those tens of millions of stars within reach of SETI workers. For that, mainstream radio astronomers will have to be onboard—or we'll be feeling alone in the universe a long time indeed.

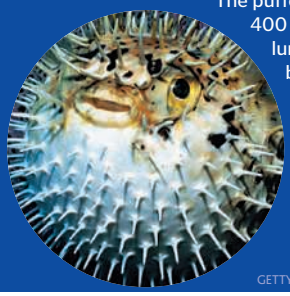
—RICHARD A. KERR

Listening for E.T. The SETI Institute is deploying an array of antennas and tying them into a giant "virtual telescope."

CREDIT: SETI

What role do telomeres and centromeres play in genome function?
These chromosome features will remain mysteries until new technologies can sequence them.

Why are some genomes really big and others quite compact?
The puffer fish genome is 400 million bases; one lungfish's is 133 billion bases long. Repetitive and duplicated DNA don't explain why this and other size differences exist.



GETTY IMAGES

What is all that "junk" doing in our genomes?
DNA between genes is proving important for genome function and the evolution of new species. Comparative sequencing, microarray studies, and lab work are helping genomicists find a multitude of genetic gems amid the junk.

NIST

How much will new technologies lower the cost of sequencing?
New tools and conceptual breakthroughs are driving the cost of DNA sequencing down by orders of magnitude. The reductions are enabling research from personalized medicine to evolutionary biology to thrive.

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How and Where Did Life on Earth Arise

For the past 50 years, scientists have attacked the question of how life began in a pincer movement. Some approach it from the present, moving backward in time from life today to its simpler ancestors. Others march forward from the formation of Earth 4.55 billion years ago, exploring how lifeless chemicals might have become organized into living matter.

Working backward, paleontologists have found fossils of microbes dating back at least 3.4 billion years. Chemical analysis of even older rocks suggests that photosynthetic organisms were already well established on Earth by 3.7 billion years ago. Researchers suspect that the organisms that left these traces shared the same basic traits found in all life today. All free-living organisms encode genetic information in DNA and catalyze chemical reactions using proteins. Because DNA and proteins depend so intimately on each other for their survival, it's hard to imagine one of them having evolved first. But it's just as implausible for them to have emerged simultaneously out of a prebiotic soup.

Experiments now suggest that earlier forms of life could have been based on a third kind of molecule found in today's organisms: RNA. Once considered nothing more than a cellular courier, RNA turns out to be astonishingly versatile, not only encoding genetic information but also acting like a protein. Some RNA molecules switch genes on and off, for example, whereas others bind to proteins and other molecules. Laboratory experiments suggest that RNA could have replicated itself and carried out the other functions required to keep a primitive cell alive.

Only after life passed through this "RNA world," many scientists now agree, did it take on a more familiar cast. Proteins are thousands of times more efficient as a catalyst than RNA is, and so once they emerged they would have been favored by natural selection. Likewise, genetic information can be replicated from DNA with far fewer errors than it can from RNA.

Other scientists have focused their efforts on figuring out how the lifeless chemistry of a prebiotic Earth could have given rise to an RNA world. In 1953, working at the University of Chicago, Stanley Miller and Harold Urey demonstrated that experiments could shed light on this question. They ran an electric current through a mix of ammonia, methane, and other gases believed at the time to have been present on early Earth. They found that they could produce amino acids and other important building blocks of life.

Today, many scientists argue that the early atmosphere was dominated by other gases, such as carbon dioxide. But experiments in recent years have shown that under these conditions, many building blocks of life can be formed. In addition, comets and meteorites may have delivered organic compounds from space.

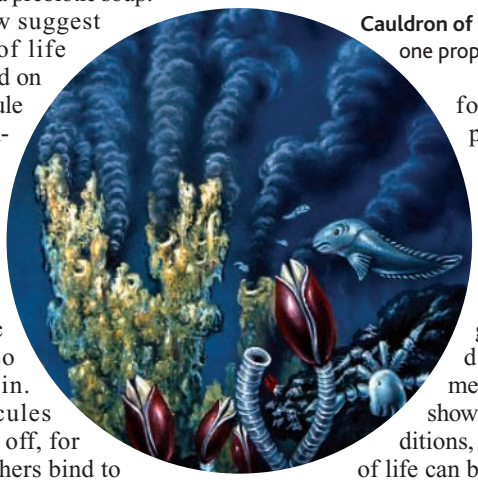
Just where on Earth these building blocks came together as primitive life forms is a subject of debate. Starting in the 1980s, many scientists argued that life got its start in the scalding, mineral-rich waters streaming out of deep-sea hydrothermal vents. Evidence for a hot start included studies on the tree of life, which suggested that the most primitive species of microbes alive today thrive in hot water. But the hot-start hypothesis has cooled off a bit. Recent studies suggest that heat-loving microbes are not living fossils. Instead, they may have descended from less hardy species and evolved new defenses against heat. Some skeptics also wonder how delicate RNA molecules could have survived in boiling water. No single strong hypothesis has taken the hot start's place, however, although suggestions include tidal pools or oceans covered by glaciers.

Research projects now under way may shed more light on how life began. Scientists are running experiments in which RNA-based cells may be able to reproduce and evolve. NASA and the European Space Agency have launched probes that will visit comets, narrowing down the possible ingredients that might have been showered on early Earth.

Most exciting of all is the possibility of finding signs of life on Mars. Recent missions to Mars have provided strong evidence that shallow seas of liquid water once existed on the Red Planet—suggesting that Mars might once have been hospitable to life. Future Mars missions will look for signs of life hiding in underground refuges, or fossils of extinct creatures. If life does turn up, the discovery could mean that life arose independently on both planets—suggesting that it is common in the universe—or that it arose on one planet and spread to the other. Perhaps martian microbes were carried to Earth on a meteorite 4 billion years ago, infecting our sterile planet.

—CARL ZIMMER

Carl Zimmer is the author of *Soul Made Flesh: The Discovery of the Brain—and How it Changed the World*.



CREDIT: DAVID A. HARDY/PHOTO RESEARCHERS INC.

Cauldron of life? Deep-sea vents are one proposed site for life's start.

How do organs and whole organisms know when to stop growing?
A person's right and left legs almost always end up the same length, and the hearts of mice and elephants each fit the proper rib cage. How genes set limits on cell size and number continues to mystify.

JUPITER IMAGES

How can genome changes other than mutations be inherited?
Researchers are finding ever more examples of this process, called epigenetics, but they can't explain what causes and preserves the changes.

How is asymmetry determined in the embryo?
Whirling cilia help an embryo tell its left from its right, but scientists are still looking for the first factors that give a relatively uniform ball of cells a head, tail, front, and back.

CENTER FOR FUNCTIONAL GENOMICS, SUNY AT ALBANY

How do limbs, fins, and faces develop and evolve?
The genes that determine the length of a nose or the breadth of a wing are subject to natural and sexual selection. Understanding how selection works could lead to new ideas about the mechanics of evolution with respect to development.

continued >>

Published by AAAS

Special Section

What Determines Species Diversity

Countless species of plants, animals, and microbes fill every crack and crevice on land and in the sea. They make the world go 'round, converting sunlight to energy that fuels the rest of life, cycling carbon and nitrogen between inorganic and organic forms, and modifying the landscape.

In some places and some groups, hundreds of species exist, whereas in others, very few have evolved; the tropics, for example, are a complex paradise compared to higher latitudes. Biologists are striving to understand why. The interplay between environment and living organisms and between the organisms themselves play key roles in encouraging or discouraging diversity, as do human disturbances, predator-prey relationships, and other food web connections. But exactly how these and other forces work together to shape diversity is largely a mystery.

The challenge is daunting. Baseline data are poor, for example: We don't yet know how many plant and animal species there are on Earth, and researchers can't even begin to predict the numbers and kinds of organisms that make up the microbial world. Researchers probing the evolution of, and limits to, diversity also lack a standardized time scale because evolution takes place over periods lasting from days to millions of years. Moreover, there can be almost as much variation within a species as between two closely related ones. Nor is it clear what genetic changes will result in a new species and what their true influence on speciation is.

Understanding what shapes diversity will require a major interdisciplinary effort, involving paleontological interpretation, field studies, laboratory experimentation, genomic comparisons, and effective statistical analyses. A few exhaustive inventories, such as the United Nations' Millennium Project and an around-the-world assessment of genes from marine microbes, should improve baseline data, but they will barely scratch the surface. Models that predict when one species will split into two will help. And an emerging discipline called evo-devo is probing how genes involved in development contribute to evolution. Together, these efforts will go a long way toward clarifying the history of life.

Paleontologists have already made headway in tracking the expansion and contraction of the ranges of various organisms over the millennia. They are finding that geographic distribution plays a key role in speciation. Future studies should continue to reveal large-scale patterns of distribution and perhaps shed more light on the origins of mass extinctions and the effects of these catastrophes on the evolution of new species.

From field studies of plants and animals, researchers have learned that habitat can influence morphology and behavior—particularly sexual selection—in ways that hasten or slow down speciation. Evolutionary biologists have also discovered that speciation can stall out, for example, as separated populations become reconnected, homogenizing genomes that would otherwise diverge. Molecular forces, such as low mutation rates or meiotic drive—in which certain alleles have an increased likelihood of being passed from one generation to the next—influence the rate of speciation.

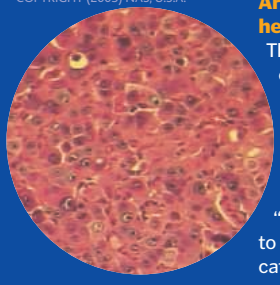
And in some cases, differences in diversity can vary within an ecosystem: Edges of ecosystems sometimes support fewer species than the interior.

Evolutionary biologists are just beginning to sort out how all these factors are intertwined in different ways for different groups of organisms. The task is urgent: Figuring out what shapes diversity could be important for understanding the nature of the wave of extinctions the world is experiencing and for determining strategies to mitigate it.

–ELIZABETH PENNISI

CREDITS (TOP TO BOTTOM): STEPHEN FRINK/CORBIS IMAGES; KEN LUCAS/VISUALS UNLIMITED; HANS PFLETSCHINGER/PETER ARNOLD

What triggers puberty?
Nutrition—including that received in utero—seems to help set this mysterious biological clock, but no one knows exactly what forces childhood to end.



M. CLARKE *ET AL.*, *PNAS* **100** (7), 3983 COPYRIGHT (2003) NAS, U.S.A.

Are stem cells at the heart of all cancers?
The most aggressive cancer cells look a lot like stem cells. If cancers are caused by stem cells gone awry, studies of a cell's "stemness" may lead to tools that could catch tumors sooner and destroy them more effectively.

Is cancer susceptible to immune control?
Although our immune responses can suppress tumor growth, tumor cells can combat those responses with countermeasures. This defense can stymie researchers hoping to develop immune therapies against cancer.

L. HEUSER AND R. ACKLAND/UNIVERSITY OF LOUISVILLE SCHOOL OF MEDICINE

Can cancers be controlled rather than cured?
Drugs that cut off a tumor's fuel supplies—say, by stopping blood-vessel growth—can safely check or even reverse tumor growth. But how long the drugs remain effective is still unknown.

Published by AAAS

What Genetic Changes Made Us Uniquely Human

Every generation of anthropologists sets out to explore what it is that makes us human. Famed paleoanthropologist Louis Leakey thought tools made the man, and so when he uncovered hominid bones near stone tools in Tanzania in the 1960s, he labeled the putative toolmaker *Homo habilis*, the earliest member of the human genus. But then primatologist Jane Goodall demonstrated that chimps also use tools of a sort, and today researchers debate whether *H. habilis* truly belongs in *Homo*. Later studies have honed in on traits such as bipedality, culture, language, humor, and, of course, a big brain as the unique birthright of our species. Yet many of these traits can also be found, at least to some degree, in other creatures: Chimps have rudimentary culture, parrots speak, and some rats seem to giggle when tickled.

What is beyond doubt is that humans, like every other species, have a unique genome shaped by our evolutionary history. Now, for the first time, scientists can address anthropology's fundamental question at a new level: What are the genetic changes that make us human?

With the human genome in hand and primate genome data beginning to pour in, we are entering an era in which it may become possible to pinpoint the genetic changes that help separate us from our closest relatives. A rough draft of the chimp sequence has already been released, and a more detailed version is expected soon. The genome of the macaque is nearly complete, the orangutan is under way, and the marmoset was recently approved. All these will help reveal the ancestral genotype at key places on the primate tree.

The genetic differences revealed between humans and chimps are likely to be profound, despite the oft-repeated statistic that only about 1.2% of our DNA differs from that of chimps. A change in every 100th base could affect thousands of genes, and the percentage difference becomes much larger if you count insertions and deletions. Even if we document all of the perhaps 40 million sequence differences between humans and chimps, what do they mean? Many are probably simply the consequence of 6 million years of genetic drift, with little effect on body or behavior, whereas other small changes—perhaps in regulatory, noncoding sequences—may have dramatic consequences. Half of the differences might define a chimp rather than a human. How can we sort them all out?

One way is to zero in on the genes that have been favored by natural selection in humans. Studies seeking subtle signs of selection in the DNA of humans and other primates have identified dozens of genes, in particular those involved in host-pathogen interactions, reproduction, sensory systems such as olfaction and taste, and more.

But not all of these genes helped set us apart from our ape cousins originally. Our genomes reveal that we have evolved in response to malaria, but malaria defense didn't make us human. So some researchers have started with clinical mutations that impair key traits, then traced the genes' evolution, an approach that has identified a handful of tantalizing genes. For example, *MCPH1* and *ASPM* cause microcephaly when mutated, *FOXP2* causes speech defects, and all three show signs of selection pressure during human, but not chimp, evolution. Thus they may have played roles in the evolution of humans' large brains and speech.

But even with genes like these, it is often difficult to be completely sure of what they do. Knockout experiments, the classic way to reveal function, can't be done in humans and apes for ethical reasons. Much of the work will therefore demand comparative analyses of the genomes and phenotypes of large numbers of humans and apes. Already, some researchers are pushing for a "great ape 'phenome' project" to match the incoming tide of genomic data with more phenotypic information on apes. Other researchers argue that clues to function can best be gleaned by mining natural human variability, matching mutations in living people to subtle differences in biology and behavior. Both strategies face logistical and ethical problems, but some progress seems likely.

A complete understanding of uniquely human traits will, however, include more than DNA. Scientists may eventually circle back to those long-debated traits of sophisticated language, culture, and technology, in which nurture as well as nature plays a leading role. We're in the age of the genome, but we can still recognize that it takes much more than genes to make the human.

–ELIZABETH CULOTTA

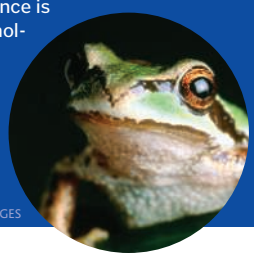
CREDITS (LEFT TO RIGHT): FRITZ POLKING/VISUALS UNLIMITED; TERRY HUSEBYE/GETTY IMAGES

Is inflammation a major factor in all chronic diseases?
It's a driver of arthritis, but cancer and heart disease? More and more, the answer seems to be yes, and the question remains why and how.

ART DAVIS/USDA

How do prion diseases work?
Even if one accepts that prions are just misfolded proteins, many mysteries remain. How can they go from the gut to the brain, and how do they kill cells once there, for example.

How much do vertebrates depend on the innate immune system to fight infection?
This system predates the vertebrate adaptive immune response. Its relative importance is unclear, but immunologists are working to find out.



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Does immunologic memory require chronic exposure to antigens?
Yes, say a few prominent thinkers, but experiments with mice now challenge the theory. Putting the debate to rest would require proving that something is not there, so the question likely will not go away.

Published by AAAS

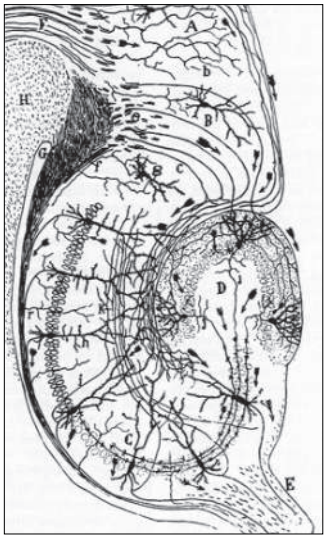
How Are Memories Stored and Retrieved

Packed into the kilogram or so of neural wetware between the ears is everything we know: a compendium of useful and trivial facts about the world, the history of our lives, plus every skill we've ever learned, from riding a bike to persuading a loved one to take out the trash. Memories make each of us unique, and they give continuity to our lives. Understanding how memories are stored in the brain is an essential step toward understanding ourselves.

Neuroscientists have already made great strides, identifying key brain regions and potential molecular mechanisms. Still, many important questions remain unanswered, and a chasm gapes between the molecular and whole-brain research.

The birth of the modern era of memory research is often pegged to the publication, in 1957, of an account of the neurological patient H.M. At age 27, H.M. had large chunks of the temporal lobes of his brain surgically removed in a last-ditch effort to relieve chronic epilepsy. The surgery worked, but it left H.M. unable to remember anything that happened—or anyone he met—after his surgery. The case showed that the medial temporal lobes (MTL), which include the hippocampus, are crucial for making new memories. H.M.'s case also revealed, on closer examination, that memory is not a monolith: Given a tricky mirror drawing task, H.M.'s performance improved steadily over 3 days even though he had no memory of his previous practice. Remembering how is not the same as remembering what, as far as the brain is concerned.

Thanks to experiments on animals and the advent of human brain imaging, scientists now have a working knowledge of the various kinds of memory as well as which parts of the brain are involved in each. But persistent gaps remain. Although the MTL has indeed proved critical for declarative memory—the recollection of facts and events—the region remains something of a black box. How its various components interact during memory encoding and retrieval is unresolved. Moreover, the MTL is not the final repository of declarative memories. Such memories are apparently filed to the cerebral cortex for long-term storage, but how this happens, and how memories are represented in the cortex, remains unclear.



Memorable diagram. Santiago Ramón y Cajal's drawing of the hippocampus. He proposed that memories involve strengthened neural connections.

More than a century ago, the great Spanish neuroanatomist Santiago Ramón y Cajal proposed that making memories must require neurons to strengthen their connections with one another. Dogma at the time held that no new neurons are born in the adult brain, so Ramón y Cajal made the reasonable assumption that the key changes must occur between existing neurons. Until recently, scientists had few clues about how this might happen.

Since the 1970s, however, work on isolated chunks of nervous-system tissue has identified a host of molecular players in memory formation. Many of the same molecules have been implicated in both declarative and nondeclarative memory and in species as varied as sea slugs, fruit flies, and rodents, suggesting that the molecular machinery for memory has been widely conserved. A key insight from this work has been that short-term memory (lasting minutes) involves chemical modifications that strengthen existing connections, called synapses, between neurons, whereas long-term memory (lasting days or weeks) requires protein synthesis and probably the construction of new synapses.

Tying this work to the whole-brain research is a major challenge. A potential bridge is a process called long-term potentiation (LTP), a type of synaptic strengthening that has been scrutinized in slices of rodent hippocampus and is widely considered a likely physiological basis for memory. A conclusive demonstration that LTP really does underlie memory formation in vivo would be a big breakthrough.

Meanwhile, more questions keep popping up. Recent studies have found that patterns of neural activity seen when an animal is learning a new task are replayed later during sleep. Could this play a role in solidifying memories? Other work shows that our memories are not as trustworthy as we generally assume. Why is memory so labile? A hint may come from recent studies that revive the controversial notion that memories are briefly vulnerable to manipulation each time they're recalled. Finally, the no-new-neurons dogma went down in flames in the 1990s, with the demonstration that the hippocampus, of all places, is a virtual neuron nursery throughout life. The extent to which these newborn cells support learning and memory remains to be seen.

—GREG MILLER

Why doesn't a pregnant woman reject her fetus?
Recent evidence suggests that the mother's immune system doesn't "realize" that the fetus is foreign even though it gets half its genes from the father. Yet just as Nobelist Peter Medawar said when he first raised this question in 1952, "the verdict has yet to be returned."

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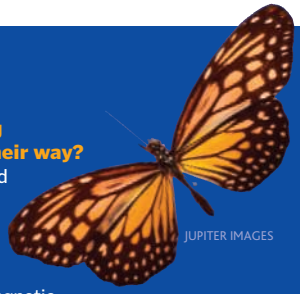
What synchronizes an organism's circadian clocks?
Circadian clock genes have popped up in all types of creatures and in many parts of the body. Now the challenge is figuring out how all the gears fit together and what keeps the clocks set to the same time.

How do migrating organisms find their way?
Birds, butterflies, and whales make annual journeys of thousands of kilometers. They rely on cues such as stars and magnetic fields, but the details remain unclear.



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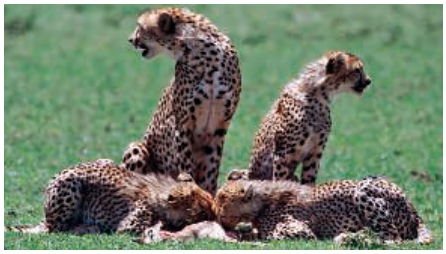
Why do we sleep?
A sound slumber may refresh muscles and organs or keep animals safe from dangers lurking in the dark. But the real secret of sleep probably resides in the brain, which is anything but still while we're snoring away.

Published by AAAS

How Did Cooperative Behavior Evolve

When Charles Darwin was working out his grand theory on the origin of species, he was perplexed by the fact that animals from ants to people form social groups in which most individuals work for the common good. This seemed to run counter to his proposal that individual fitness was key to surviving over the long term.

By the time he wrote *The Descent of Man*, however, he had come up with a few explanations. He suggested that natural selection could encourage altruistic behavior among kin so as to improve the reproductive potential of the "family." He also introduced the idea of reciprocity: that unrelated but familiar individuals would help each other out if both were altruistic. A century of work with dozens of social species has borne out his ideas to some degree, but the details of how and why cooperation evolved remain to be worked out. The answers could help explain human behaviors that seem to make little sense from a strict evolutionary perspective, such as risking one's life to save a drowning stranger.



CREDITS (TOP TO BOTTOM): TOM BRAKEFIELD/CORBIS; M. THOMSEN/CORBIS

Animals help each other out in many ways. In social species from honeybees to naked mole rats, kinship fosters cooperation: Females forgo reproduction and instead help the dominant female with her young. And common agendas help unrelated individuals work together. Male chimpanzees, for example, gang up against predators, protecting each other at a potential cost to themselves.

Generosity is pervasive among humans. Indeed, some anthropologists argue that the evolution of the tendency to trust one's relatives and neighbors helped humans become Earth's dominant vertebrate: The ability to work together provided our early ancestors more food, better protection, and better childcare, which in turn improved reproductive success.

However, the degree of cooperation varies. "Cheaters" can gain a leg up on the rest of humankind, at least in the short term. But cooperation prevails among many species, suggesting that this behavior is a better survival strategy, over the long run, despite all the strife among ethnic, political, religious, even family groups now rampant within our species.

Evolutionary biologists and animal behavior researchers are searching out the genetic basis and molecular drivers of cooperative behaviors, as well as the physiological, environmental, and behavioral impetus for sociality. Neuroscientists studying mammals from voles to hyenas are discovering key correlations between brain chemicals and social strategies.

Others with a more mathematical bent are applying evolutionary game theory, a modeling approach developed for economics, to quantify cooperation and predict behavioral outcomes under different circumstances. Game theory has helped reveal a seemingly innate desire for fairness: Game players will spend time and energy to punish unfair actions, even though there's nothing to be gained by these actions for themselves. Similar studies have shown that even when two people meet just once, they tend to be fair to each other. Those actions are hard to explain, as they don't seem to follow the basic tenet that cooperation is really based on self-interest.

The models developed through these games are still imperfect. They do not adequately consider, for example, the effect of emotions on cooperation. Nonetheless, with game theory's increasing sophistication, researchers hope to gain a clearer sense of the rules that govern complex societies.

Together, these efforts are helping social scientists and others build on Darwin's observations about cooperation. As Darwin predicted, reciprocity is a powerful fitness tactic. But it is not a pervasive one.

Modern researchers have discovered that a good memory is a prerequisite: It seems reciprocity is practiced only by organisms that can keep track of those who are helpful and those who are not. Humans have a great memory for faces and thus can maintain lifelong good—or hard—feelings toward people they don't see for years. Most other species exhibit reciprocity only over very short time scales, if at all.

Limited to his personal observations, Darwin was able to come up with only general rationales for cooperative behavior. Now, with new insights from game theory and other promising experimental approaches, biologists are refining Darwin's ideas and, bit by bit, hope that one day they will understand just what it takes to bring out our cooperative spirit.

—ELIZABETH PENNISI

Why do we dream?
Freud thought dreaming provides an outlet for our unconscious desires. Now, neuroscientists suspect that brain activity during REM sleep—when dreams occur—is crucial for learning. Is the experience of dreaming just a side effect?

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Why are there critical periods for language learning?
Monitoring brain activity in young children—including infants—may shed light on why children pick up languages with ease while adults often struggle to learn train station basics in a foreign tongue.

Do pheromones influence human behavior?
Many animals use airborne chemicals to communicate, particularly when mating. Controversial studies have hinted that humans too use pheromones. Identifying them will be key to assessing their sway on our social lives.

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How do general anesthetics work?
Scientists are chipping away at the drugs' effects on individual neurons, but understanding how they render us unconscious will be a tougher nut to crack.

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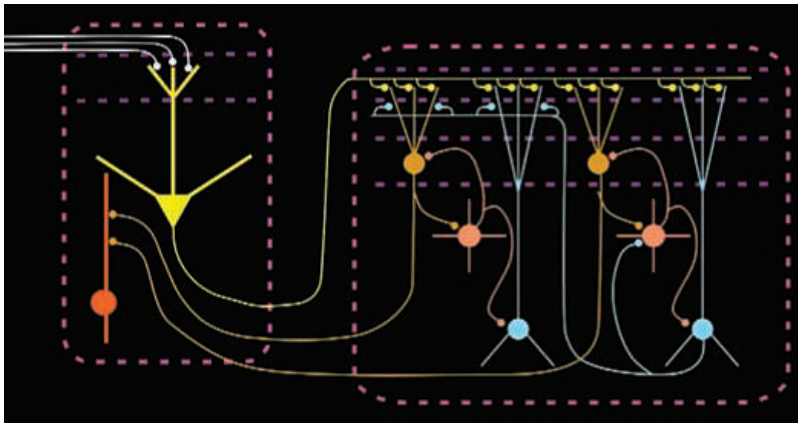
How Will Big Pictures Emerge From a Sea of Biological Data

Biology is rich in descriptive data—and getting richer all the time. Large-scale methods of probing samples, such as DNA sequencing, microarrays, and automated gene-function studies, are filling new databases to the brim. Many subfields from biomechanics to ecology have gone digital, and as a result, observations are more precise and more plentiful. A central question now confronting virtually all fields of biology is whether scientists can deduce from this torrent of molecular data how systems and whole organisms work. All this information needs to be sifted, organized, compiled, and—most importantly—connected in a way that enables researchers to make predictions based on general principles.

Enter systems biology. Loosely defined and still struggling to find its way, this newly emerging approach aims to connect the dots that have emerged from decades of molecular, cellular, organismal, and even environmental observations. Its proponents seek to make biology more quantitative by relying on mathematics, engineering, and computer science to build a more rigid framework for linking disparate findings. They argue that it is the only way the field can move forward. And they suggest that biomedicine, particularly deciphering risk factors for disease, will benefit greatly.



Systems approach. Circuit diagrams help clarify nerve cell functions.

The field got a big boost from the completion of the human genome sequence. The product of a massive, trip-to-the-moon logistical effort, the sequence is now a hard and fast fact. The biochemistry of human inheritance has been defined and measured. And that has inspired researchers to try to make other aspects of life equally knowable.

Molecular geneticists dream of having a similarly comprehensive view of networks that control genes: For example, they would like to identify rules explaining how a single DNA sequence can express different proteins, or varying amounts of protein, in different circumstances (see p. 80). Cell biologists would like to reduce the complex communication patterns traced by molecules that regulate the health of the cell to a set of signaling rules. Developmental biologists would like a comprehensive picture of how the embryo manages to direct a handful of cells into a myriad of specialized functions in bone, blood, and skin tissue. These hard puzzles can only be solved by systems biology, proponents say. The same can be said for neuroscientists trying to work out the emergent properties—higher thought, for example—hidden in complex brain circuits. To understand ecosystem changes, including global warming, ecologists need ways to incorporate physical as well as biological data into their thinking.

Today, systems biologists have only begun to tackle relatively simple networks. They have worked out the metabolic pathway in yeast for breaking down galactose, a carbohydrate. Others have tracked the first few hours of the embryonic development of sea urchins and other organisms with the goal of seeing how various transcription factors alter gene expression over time. Researchers are also developing rudimentary models of signaling networks in cells and simple brain circuits.

Progress is limited by the difficulty of translating biological patterns into computer models. Network computer programs themselves are relatively simple, and the methods of portraying the results in ways that researchers can understand and interpret need improving. New institutions around the world are gathering interdisciplinary teams of biologists, mathematicians, and computer specialists to help promote systems biology approaches. But it is still in its early days.

No one yet knows whether intensive interdisciplinary work and improved computational power will enable researchers to create a comprehensive, highly structured picture of how life works.

—ELIZABETH PENNISI

CREDIT: MICHAEL T. SHIPLEY

What causes schizophrenia?
Researchers are trying to track down genes involved in this disorder. Clues may also come from research on traits schizophrenics share with normal people.

What causes autism?
Many genes probably contribute to this baffling disorder, as well as unknown environmental factors. A biomarker for early diagnosis would help improve existing therapy, but a cure is a distant hope.

To what extent can we stave off Alzheimer's?
A 5- to 10-year delay in this late-onset disease would improve old age for millions. Researchers are determining whether treatments with hormones or antioxidants, or mental and physical exercise, will help.

ROYALTY-FREE/CORBIS

What is the biological basis of addiction?
Addiction involves the disruption of the brain's reward circuitry. But personality traits such as impulsivity and sensation-seeking also play a part in this complex behavior.

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How Far Can We Push Chemical Self-Assembly

Most physical scientists nowadays focus on uncovering nature's mysteries; chemists build things. There is no synthetic astronomy or synthetic physics, at least for now. But chemists thrive on finding creative new ways to assemble molecules. For the last 100 years, they have done that mostly by making and breaking the strong covalent bonds that form when atoms share electrons. Using that trick, they have learned to combine as many as 1000 atoms into essentially any molecular configuration they please.

Impressive as it is, this level of complexity pales in comparison to what nature flaunts all around us. Everything from cells to cedar trees is knit together using a myriad of weaker links between small molecules. These weak interactions, such as hydrogen bonds, van der Waals forces, and π–π interactions, govern the assembly of everything from DNA in its famous double helix to the bonding of H_2O molecules in liquid water. More than just riding herd on molecules, such subtle forces make it possible for structures to assemble themselves into an ever more complex hierarchy. Lipids coalesce to form cell membranes. Cells organize to form tissues. Tissues combine to create organisms. Today, chemists can't approach the complexity of what nature makes look routine. Will they ever learn to make complex structures that self-assemble?

Well, they've made a start. Over the past 3 decades, chemists have made key strides in learning the fundamental rules of noncovalent bonding. Among these rules: *Like prefers like*. We see this in hydrophobic and hydrophilic interactions that propel lipid molecules in water to corral together to form the two-layer membranes that serve as the coatings surrounding cells. They bunch their oily tails together to avoid any interaction with water and leave their more polar head groups facing out into the liquid. Another rule: *Self-assembly is governed by energetically favorable reactions*. Leave the right component molecules alone, and they will assemble themselves into complex ordered structures.

Chemists have learned to take advantage of these and other rules to design self-assembling systems with a modest degree of complexity. Drug-carrying liposomes, made with lipid bilayers resembling those in cells, are used commercially to ferry drugs to cancerous tissues in patients. And self-assembled molecules called rotaxanes, which can act as molecular switches that oscillate back and forth between two stable states, hold promise as switches in future molecular-based computers.

But the need for increased complexity is growing, driven by the miniaturization of computer circuitry and the rise of nanotechnology. As features on computer chips continue to shrink, the cost of manufacturing these ever-smaller components is skyrocketing. Right now, companies make them by whittling materials down to the desired size. At some point, however, it will become cheaper to design and build them chemically from the bottom up.

Self-assembly is also the only practical approach for building a wide variety of nanostructures. Making sure the components assemble themselves correctly, however, is not an easy task. Because the forces at work are so small, self-assembling molecules can get trapped in undesirable conformations, making defects all but impossible to avoid. Any new system that relies on self-assembly must be able either to tolerate those defects or repair them. Again, biology offers an example in DNA. When enzymes copy DNA strands during cell division, they invariably make mistakes—occasionally inserting an A when they should have inserted a T, for example. Some of those mistakes get by, but most are caught by DNA-repair enzymes that scan the newly synthesized strands and correct copying errors.

Strategies like that won't be easy for chemists to emulate. But if they want to make complex, ordered structures from the ground up, they'll have to get used to thinking a bit more like nature.

–ROBERT F. SERVICE

CREDIT: ERIC V. GRAVE/PHOTO RESEARCHERS INC.

Is morality hard-wired into the brain?
That question has long puzzled philosophers; now some neuroscientists think brain imaging will reveal circuits involved in reasoning.

LOUIE PSIHOYOS/CORBIS

What are the limits of learning by machines?
Computers can already beat the world's best chess players, and they have a wealth of information on the Web to draw on. But abstract reasoning is still beyond any machine.

How much of personality is genetic?
Aspects of personality are influenced by genes; environment modifies the genetic effects. The relative contributions remain under debate.

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What is the biological root of sexual orientation?
Much of the "environmental" contribution to homosexuality may occur before birth in the form of prenatal hormones, so answering this question will require more than just the hunt for "gay genes."

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What Are the Limits of Conventional Computing

At first glance, the ultimate limit of computation seems to be an engineering issue. How much energy can you put in a chip without melting it? How fast can you flip a bit in your silicon memory? How big can you make your computer and still fit it in a room? These questions don't seem terribly profound.

In fact, computation is more abstract and fundamental than figuring out the best way to build a computer. This realization came in the mid-1930s, when Princeton mathematicians Alonzo Church and Alan Turing showed—roughly speaking—that any calculation involving bits and bytes can be done on an idealized computer known as a Turing machine. By showing that all classical computers are essentially alike, this discovery enabled scientists and mathematicians to ask fundamental questions about computation without getting bogged down in the minutiae of computer architecture.

For example, theorists can now classify computational problems into broad categories. *P* problems are those, broadly speaking, that can be solved quickly, such as alphabetizing a list of names. *NP* problems are much tougher to solve but relatively easy to check once you've reached an answer. An example is the traveling salesman problem, finding the shortest possible route through a series of locations. All known algorithms for getting an answer take lots of computing power, and even relatively small versions might be out of reach of any classical computer.

Mathematicians have shown that if you could come up with a quick and easy shortcut to solving any one of the hardest type of *NP* problems, you'd be able to crack them all. In effect, the *NP* problems would turn into *P* problems. But it's uncertain whether such a shortcut exists—whether $P = NP$. Scientists think not, but proving this is one of the great unanswered questions in mathematics.

In the 1940s, Bell Labs scientist Claude Shannon showed that bits are not just for computers; they are the fundamental units of describing the information that flows from one object to another. There are physical laws that govern how fast a bit can move from place to place, how much information can be transferred back and forth over a given communications channel, and how much energy it takes to erase a bit from memory. All classical information-processing machines are subject to these laws—and because information seems to be rattling back and forth in our brains, do the laws of information mean that our thoughts are reducible to bits and bytes? Are we merely computers? It's an unsettling thought.

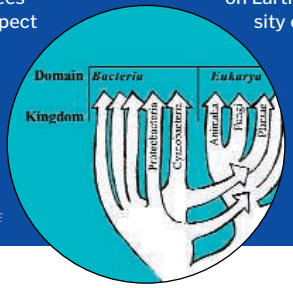
But there is a realm beyond the classical computer: the quantum. The probabilistic nature of quantum theory allows atoms and other quantum objects to store information that's not restricted to only the binary 0 or 1 of information theory, but can also be 0 and 1 at the same time. Physicists around the world are building rudimentary quantum computers that exploit this and other quantum effects to do things that are provably impossible for ordinary computers, such as finding a target record in a database with too few queries. But scientists are still trying to figure out what quantum-mechanical properties make quantum computers so powerful and to engineer quantum computers big enough to do something useful.

By learning the strange logic of the quantum world and using it to do computing, scientists are delving deep into the laws of the subatomic world. Perhaps something as seemingly mundane as the quest for computing power might lead to a newfound understanding of the quantum realm.

—CHARLES SEIFE

CREDIT: JUPITER IMAGES

Will there ever be a tree of life that systematists can agree on?
Despite better morphological, molecular, and statistical methods, researchers' trees don't agree. Expect greater, but not complete, consensus.



W. F. DOOLITTLE, *SCIENCE* **284,** 2124 (1999)

How many species are there on Earth?
Count all the stars in the sky? Impossible. Count all the species on Earth? Ditto. But the biodiversity crisis demands that we try.

What is a species?
A "simple" concept that's been muddied by evolutionary data; a clear definition may be a long time in coming.

Why does lateral transfer occur in so many species and how?
Once considered rare, gene swapping, particularly among microbes, is proving quite common. But why and how genes are so mobile—and the effect on fitness—remains to be determined.

M. DWORKIN, *MICROBIOL. REVS.* **60,** 70 (1996)

Who was LUCA (the last universal common ancestor)?
Ideas about the origin of the 1.5-billion-year-old "mother" of all complex organisms abound. The continued discovery of primitive microbes, along with comparative genomics, should help resolve life's deep past.

Published by AAAS

Can We Selectively Shut Off Immune Responses

In the past few decades, organ transplantation has gone from experimental to routine. In the United States alone, more than 20,000 heart, liver, and kidney transplants are performed every year. But for transplant recipients, one prospect has remained unchanged: a lifetime of taking powerful drugs to suppress the immune system, a treatment that can have serious side effects. Researchers have long sought ways to induce the immune system to tolerate a transplant without blunting the body's entire defenses, but so far, they have had limited success.

They face formidable challenges. Although immune tolerance can occur—in rare cases, transplant recipients who stop taking immunosuppressants have not rejected their foreign organs—researchers don't have a clear picture of what is happening at the molecular and cellular levels to allow this to happen. Tinkering with the immune system is also a bit like tinkering with a mechanical watch: Fiddle with one part, and you may disrupt the whole mechanism. And there is a big roadblock to testing drugs designed to induce tolerance: It is hard to know if they work unless immunosuppressant drugs are withdrawn, and that would risk rejection of the transplant. But if researchers can figure out how to train the immune system to tolerate transplants, the knowledge could have implications for the treatment of autoimmune diseases, which also result from unwanted immune attack—in these cases on some of the body's own tissues.

A report in *Science* 60 years ago fired the starting gun in the race to induce transplant tolerance—a race that has turned into a marathon. Ray Owen of the University of Wisconsin, Madison, reported that fraternal twin cattle sometimes share a placenta and are born with each other's red blood cells, a state referred to as mixed chimerism. The cattle tolerated the foreign cells with no apparent problems.

A few years later, Peter Medawar and his team at the University of Birmingham, U.K., showed that fraternal twin cattle with mixed chimerism readily accept skin grafts from each other. Medawar did not immediately appreciate the link to Owen's work, but when he saw the connection, he decided to inject fetal mice in utero with tissue from mice of a different strain. In a publication in *Nature* in 1953, the researchers showed that, after birth, some of these mice tolerated skin grafts from different strains. This influential experiment led many to devote their careers to transplantation and also raised hopes that the work would lead to cures for autoimmune diseases.

Immunologists, many of them working with mice, have since spelled out several detailed mechanisms behind tolerance. The immune system can, for example, dispatch "regulatory" cells that suppress immune attacks against self. Or the system can force harmful immune cells to commit suicide or to go into a dysfunctional stupor called anergy. Researchers indeed now know fine details about the genes, receptors, and cell-to-cell communications that drive these processes.

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Yet it's one matter to unravel how the immune system works and another to figure out safe ways to manipulate it. Transplant researchers are pursuing three main strategies to induce tolerance. One builds on Medawar's experiments by trying to exploit chimerism. Researchers infuse the patient with the organ donor's bone marrow in hopes that the donor's immune cells will teach the host to tolerate the transplant; donor immune cells that come along with the transplanted organ also, some contend, can teach tolerance. A second strategy uses drugs to train T cells to become anergic or commit suicide when they see the foreign antigens on the transplanted tissue. The third approach turns up production of T regulatory cells, which prevent specific immune cells from copying themselves and can also suppress rejection by secreting biochemicals called cytokines that direct the immune orchestra to change its tune.

All these strategies face a common problem: It is maddeningly difficult to judge whether the approach has failed or succeeded because there are no reliable "biomarkers" that indicate whether a person has become tolerant to a transplant. So the only way to assess tolerance is to stop drug treatment, which puts the patient at risk of rejecting the organ. Similarly, ethical concerns often require researchers to test drugs aimed at inducing tolerance in concert with immunosuppressive therapy. This, in turn, can undermine the drugs' effectiveness because they need a fully functioning immune system to do their job.

If researchers can complete their 50-year quest to induce immune tolerance safely and selectively, the prospects for hundreds of thousands of transplant recipients would be greatly improved, and so, too, might the prospects for controlling autoimmune diseases.

–JON COHEN

How did flowers evolve?
Darwin called this question an "abominable mystery." Flowers arose in the cycads and conifers, but the details of their evolution remain obscure.

How do plants make cell walls?
Cellulose and pectin walls surround cells, keeping water in and supporting tall trees. The biochemistry holds the secrets to turning its biomass into fuel.

J. MOGLIA/*SCIENCE*

How is plant growth controlled?
Redwoods grow to be hundreds of meters tall, Arctic willows barely 10 centimeters. Understanding the difference could lead to higher-yielding crops.

Why aren't all plants immune to all diseases?
Plants can mount a general immune response, but they also maintain molecular snipers that take out specific pathogens. Plant pathologists are asking why different species, even closely related ones, have different sets of defenders. The answer could result in hardier crops.

ARS

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What is the basis of variation in stress tolerance in plants?
We need crops that better withstand drought, cold, and other stresses. But there are so many genes involved, in complex interactions, that no one has yet figured out which ones work how.

Published by AAAS

Special Section

Do Deeper Principles Underlie Quantum Uncertainty and Nonlocality

"Quantum mechanics is very impressive," Albert Einstein wrote in 1926. "But an inner voice tells me that it is not yet the real thing." As quantum theory matured over the years, that voice has gotten quieter—but it has not been silenced. There is a relentless murmur of confusion underneath the chorus of praise for quantum theory.

Quantum theory was born at the very end of the 19th century and soon became one of the pillars of modern physics. It describes, with incredible precision, the bizarre and counterintuitive behavior of the very small: atoms and electrons and other wee beasties of the submicroscopic world. But that success came with the price of discomfort. The equations of quantum mechanics work very well; they just don't seem to make sense.

No matter how you look at the equations of quantum theory, they allow a tiny object to behave in ways that defy intuition. For example, such an object can be in "superposition": It can have two mutually exclusive properties at the same time. The mathematics of quantum theory says that an atom, for example, can be on the left side of a box and the right side of the box at the very same instant, as long as the atom is undisturbed and unobserved. But as soon as an observer opens the box and tries to spot where the atom is, the superposition collapses and the atom instantly "chooses" whether to be on the right or the left.

This idea is almost as unsettling today as it was 80 years ago, when Erwin Schrödinger ridiculed superposition by describing a half-living, half-dead cat. That is because quantum theory changes what the meaning of "is" is. In the classical world, an object has a solid reality: Even a cloud of gas is well described by hard little billiard ball–like pieces, each of which has a well-defined position and velocity. Quantum theory seems to undermine that solid reality. Indeed, the famous Uncertainty Principle, which arises directly from the mathematics of quantum theory, says that objects' positions and momenta are smeary and ill defined, and gaining knowledge about one implies losing knowledge about the other.

The early quantum physicists dealt with this unreality by saying that the "is"—the fundamental objects handled by the equations of quantum theory—were not actually particles that had an extrinsic reality but "probability

waves" that merely had the capability of becoming "real" when an observer makes a measurement. This so-called Copenhagen Interpretation makes sense, if you're willing to accept that reality is probability waves and not solid objects. Even so, it still doesn't sufficiently explain another weirdness of quantum theory: nonlocality.

In 1935, Einstein came up with a scenario that still defies common sense. In his thought experiment, two particles fly away from each other and wind up at opposite ends of the galaxy. But the two particles happen to be "entangled"—linked in a quantum-mechanical sense—so that one particle instantly "feels" what happens to its twin. Measure one, and the other is instantly transformed by that measurement as well; it's as if the twins mystically communicate, instantly, over vast regions of space. This "nonlocality" is a mathematical consequence of quantum theory and has been measured in the lab. The spooky action apparently ignores distance and the flow of time; in theory, particles can be entangled *after* their entanglement has already been measured.

On one level, the weirdness of quantum theory isn't a problem at all. The mathematical framework is sound and describes all these bizarre phenomena well. If we humans can't imagine a physical reality that corresponds to our equations, so what? That attitude has been called the "shut up and calculate" interpretation of quantum mechanics. But to others, our difficulties in wrapping our heads around quantum theory hint at greater truths yet to be understood.

Some physicists in the second group are busy trying to design experiments that can get to the heart of the weirdness of quantum theory. They are slowly testing what causes quantum superpositions to "collapse"—research that may gain insight into the role of measurement in quantum theory as well as into why big objects behave so differently from small ones. Others are looking for ways to test various explanations for the weirdnesses of quantum theory, such as the "many worlds" interpretation, which explains superposition, entanglement, and other quantum phenomena by positing the existence of parallel universes. Through such efforts, scientists might hope to get beyond the discomfort that led Einstein to declare that "[God] does not play dice."

—CHARLES SEIFE

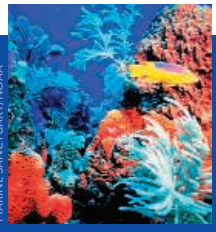
CREDIT: RIMMA GERLOVINA AND VALERIY GERLOVIN "TWO EGGS" © 2002, C-PRINT. COURTESY ROBERT BROWN GALLERY, WASHINGTON, D.C.

What caused mass extinctions?
A huge impact did in the dinosaurs, but the search for other catastrophic triggers of extinction has had no luck so far. If more subtle or stealthy culprits are to blame, they will take considerably longer to find.

Can we prevent extinction?
Finding cost-effective and politically feasible ways to save many endangered species requires creative thinking.

Why were some dinosaurs so large?
Dinosaurs reached almost unimaginable sizes, some in less than 20 years. But how did the long-necked sauropods, for instance, eat enough to pack on up to 100 tons without denuding their world?

LOUIE PSIHOYOS/CORBIS



FLORIDA KEYS NATIONAL MARINE SANCTUARY/NOAA

How will ecosystems respond to global warming?
To anticipate the effects of the intensifying greenhouse, climate modelers will have to focus on regional changes and ecologists on the right combination of environmental changes.

Published by AAAS

Is an Effective HIV Vaccine Feasible

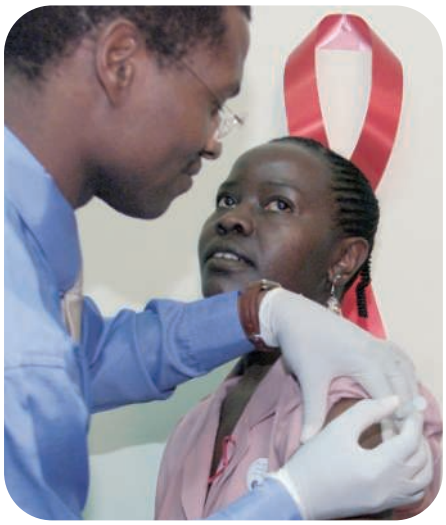
In the 2 decades since researchers identified HIV as the cause of AIDS, more money has been spent on the search for a vaccine against the virus than on any vaccine effort in history. The U.S. National Institutes of Health alone invests nearly $500 million each year, and more than 50 different preparations have entered clinical trials. Yet an effective AIDS vaccine, which potentially could thwart millions of new HIV infections each year, remains a distant dream.

Although AIDS researchers have turned the virus inside-out and carefully detailed how it destroys the immune system, they have yet to unravel which immune responses can fend off an infection. That means, as one AIDS vaccine researcher famously put it more than a decade ago, the field is "flying without a compass."

Some skeptics contend that no vaccine will ever stop HIV. They argue that the virus replicates so quickly and makes so many mistakes during the process that vaccines can't possibly fend off all the types of HIV that exist. HIV also has developed sophisticated mechanisms to dodge immune attack, shrouding its surface protein in sugars to hide vulnerable sites from antibodies and producing proteins that thwart production of other immune warriors. And the skeptics point out that vaccine developers have had little success against pathogens like HIV that routinely outwit the immune system—the malaria parasite, hepatitis C virus, and the tuberculosis bacillus are prime examples.

Yet AIDS vaccine researchers have solid reasons to believe they can succeed. Monkey experiments have shown that vaccines can protect animals from SIV, a simian relative of HIV. Several studies have identified people who repeatedly expose themselves to HIV but remain uninfected, suggesting that something is stopping the virus. A small percentage of people who do become infected never seem to suffer any harm, and others hold the virus at bay for a decade or more before showing damage to their immune systems. Scientists also have found that some rare antibodies do work powerfully against the virus in test tube experiments.

At the start, researchers pinned their hopes on vaccines designed to trigger production of antibodies against HIV's surface protein. The approach seemed promising because HIV uses the surface protein to latch onto white blood cells and establish an infection. But vaccines that only contained HIV's surface protein looked lackluster in animal and test tube studies, and then proved worthless in large-scale clinical trials.



CREDIT: REUTERS/CORBIS

Now, researchers are intensely investigating other approaches. When HIV manages to thwart antibodies and establish an infection, a second line of defense, cellular immunity, specifically targets and eliminates HIV-infected cells. Several vaccines which are now being tested aim to stimulate production of killer cells, the storm troopers of the cellular immune system. But cellular immunity involves other players—such as macrophages, the network of chemical messengers called cytokines, and so-called natural killer cells—that have received scant attention.

The hunt for an antibody-based vaccine also is going through something of a renaissance, although it's requiring researchers to think backward. Vaccine researchers typically start with antigens—in this case, pieces of HIV—and then evaluate the antibodies they elicit. But now researchers have isolated more than a dozen antibodies from infected people that have blocked HIV infection in test tube experiments. The trick will be to figure out which specific antigens triggered their production.

It could well be that a successful AIDS vaccine will need to stimulate both the production of antibodies and cellular immunity, a strategy many are attempting to exploit. Perhaps the key will be stimulating immunity at mucosal surfaces, where HIV typically enters. It's even possible that researchers will discover an immune response that no one knows about today. Or perhaps the answer lies in the interplay between the immune system and human genetic variability: Studies have highlighted genes that strongly influence who is most susceptible—and who is most resistant—to HIV infection and disease.

Wherever the answer lies, the insights could help in the development of vaccines against other diseases that, like HIV, don't easily succumb to immune attack and that kill millions of people. Vaccine developers for these diseases will probably also have to look in unusual places for answers. The maps created by AIDS vaccine researchers currently exploring uncharted immunologic terrain could prove invaluable. —JON COHEN

How many kinds of humans coexisted in the recent past, and how did they relate?
The new dwarf human species fossil from Indonesia suggests that at least four kinds of humans thrived in the past 100,000 years. Better dates and additional material will help confirm or revise this picture.

NSF

What gave rise to modern human behavior?
Did *Homo sapiens* acquire abstract thought, language, and art gradually or in a cultural "big bang," which in Europe occurred about 40,000 years ago? Data from Africa, where our species arose, may hold the key to the answer.

What are the roots of human culture?
No animal comes close to having humans' ability to build on previous discoveries and pass the improvements on. What determines those differences could help us understand how human culture evolved.

JUPITER IMAGES

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What are the evolutionary roots of language and music?
Neuroscientists exploring how we speak and make music are just beginning to find clues as to how these prized abilities arose.

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How Hot Will The Greenhouse World Be

Scientists know that the world has warmed lately, and they believe humankind is behind most of that warming. But how far might we push the planet in coming decades and centuries? That depends on just how sensitively the climate system—air, oceans, ice, land, and life—responds to the greenhouse gases we're pumping into the atmosphere. For a quarter-century, expert opinion was vague about climate sensitivity. Experts allowed that climate might be quite touchy, warming sharply when shoved by one climate driver or another, such as the carbon dioxide from fossil fuel burning, volcanic debris, or dimming of the sun. On the other hand, the same experts conceded that climate might be relatively unresponsive, warming only modestly despite a hard push toward the warm side.

A harbinger? Coffins being lined up during the record-breaking 2003 heat wave in Europe.

The problem with climate sensitivity is that you can't just go out and directly measure it. Sooner or later a climate model must enter the picture. Every model has its own sensitivity, but each is subject to all the uncertainties inherent in building a hugely simplified facsimile of the real-world climate system. As a result, climate scientists have long quoted the same vague range for sensitivity: A doubling of the greenhouse gas carbon dioxide, which is expected to occur this century, would eventually warm the world between a modest 1.5°C and a whopping 4.5°C. This range—based on just two early climate models—first appeared in 1979 and has been quoted by every major climate assessment since.

Researchers are finally beginning to tighten up the range of possible sensitivities, at least at one end. For one, the sensitivities of the available models (5% to 95% confidence range) are now falling within the canonical range of 1.5°C to 4.5°C; some had gone considerably beyond the high end. And the first try at a new approach—running a single model while varying a number of model parameters such as cloud behavior—has produced a sensitivity range of 2.4°C to 5.4°C with a most probable value of 3.2°C.

Models are only models, however. How much better if nature ran the experiment? Enter paleoclimatologists, who sort out how climate drivers such as greenhouse gases have varied naturally in the distant past and how the climate system of the time responded. Nature, of course, has never run the perfect analog for the coming greenhouse warming. And estimating how much carbon dioxide concentrations fell during the depths of the last ice age or how much sunlight debris from the eruption of Mount Pinatubo in the Philippines blocked will always have lingering uncertainties. But paleoclimate estimates of climate sensitivity generally fall in the canonical range, with a best estimate in the region of 3°C.

The lower end at least of likely climate sensitivity does seem to be firming up; it's not likely below 1.5°C, say researchers. That would rule out the negligible warmings proposed by some greenhouse contrarians. But climate sensitivity calculations still put a fuzzy boundary on the high end. Studies drawing on the past century's observed climate change plus estimates of natural and anthropogenic climate drivers yield up to 30% probabilities of sensitivities above 4.5°C, ranging as high as 9°C. The latest study that varies model parameters allows sensitivities up to 11°C, with the authors contending that they can't yet say what the chances of such extremes are. Others are pointing to times of extreme warmth in the geologic past that climate models fail to replicate, suggesting that there's a dangerous element to the climate system that the models do not yet contain.

Climate researchers have their work cut out for them. They must inject a better understanding of clouds and aerosols—the biggest sources of uncertainty—into their modeling. Ten or 15 years ago, scientists said that would take 10 or 15 years; there's no sign of it happening anytime soon. They must increase the fidelity of models, a realistic goal given the continued acceleration of affordable computing power. And they must retrieve more and better records of past climate changes and their drivers. Meanwhile, unless a rapid shift away from fossil fuel use occurs worldwide, a doubling of carbon dioxide—and more—will be inevitable.

–RICHARD A. KERR

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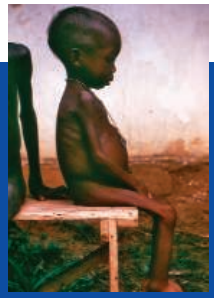
What are human races, and how did they develop?
Anthropologists have long argued that race lacks biological reality. But our genetic makeup does vary with geographic origin and as such raises political and ethical as well as scientific questions.

JUPITER IMAGES

Why do some countries grow and others stagnate?
From Norway to Nigeria, living standards across countries vary enormously, and they're not becoming more equal.

What impact do large government deficits have on a country's interest rates and economic growth rate?
The United States could provide a test case.



LYLE CONRAD/CDC

Are political and economic freedom closely tied?
China may provide one answer.

Why has poverty increased and life expectancy declined in sub-Saharan Africa?
Almost all efforts to reduce poverty in sub-Saharan Africa have failed. Figuring out what will work is crucial to alleviating massive human suffering.

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What Can Replace Cheap Oil—and When

The road from old to new energy sources can be bumpy, but the transitions have gone pretty smoothly in the past. After millennia of dependence on wood, society added coal and gravity-driven water to the energy mix. Industrialization took off. Oil arrived, and transportation by land and air soared, with hardly a worry about where the next log or lump of coal was coming from, or what the explosive growth in energy production might be doing to the world.

Times have changed. The price of oil has been climbing, and ice is melting around both poles as the mercury in the global thermometer rises. Whether the next big energy transition will be as smooth as past ones will depend in large part on three sets of questions: When will world oil production peak? How sensitive is Earth's climate to the carbon dioxide we are pouring into the atmosphere by burning fossil fuels? And will alternative energy sources be available at reasonable costs? The answers rest on science and technology, but how society responds will be firmly in the realm of politics.

There is little disagreement that the world will soon be running short of oil. The debate is over how soon. Global demand for oil has been rising at 1% or 2% each year, and we are now sucking almost 1000 barrels of oil from the ground every second. Pessimists—mostly former oil company geologists—expect oil production to peak very soon. They point to American geologist M. King Hubbert's successful 1956 prediction of the 1970 peak in U.S. production. Using the same method involving records of past production and discoveries, they predict a world oil peak by the end of the decade. Optimists—mostly resource economists—argue that oil production depends more on economics and politics than on how much happens to be in the ground. Technological innovation will intervene, and production will continue to rise, they say. Even so, midcentury is about as far as anyone is willing to push the peak. That's still "soon" considering that the United States, for one, will need to begin replacing oil's 40% contribution to its energy consumption by then. And as concerns about climate change intensify, the transition to nonfossil fuels could become even more urgent (see p. 100).

If oil supplies do peak soon or climate concerns prompt a major shift away from fossil fuels, plenty of alternative energy supplies are waiting in the wings. The sun bathes Earth's surface with 86,000 trillion watts, or terawatts, of energy at all times, about 6600 times the amount used by all humans on the planet each year. Wind, biomass, and nuclear power are also plentiful. And there is no shortage of opportunities for using energy more efficiently.

Of course, alternative energy sources have their issues. Nuclear fission supporters have never found a noncontroversial solution for disposing of long-lived radioactive wastes, and concerns over liability and capital costs are scaring utility companies off. Renewable energy sources are diffuse, making it difficult and expensive to corral enough power from them at cheap prices. So far, wind is leading the way with a global installed capacity of more than 40 billion watts, or gigawatts, providing electricity for about 4.5 cents per kilowatt hour.

That sounds good, but the scale of renewable energy is still very small when compared to fossil fuel use. In the United States, renewables account for just 6% of overall energy production. And, with global energy demand expected to grow from approximately 13 terawatts a year now to somewhere between 30 and 60 terawatts by the middle of this century, use of renewables will have to expand enormously to displace current sources and have a significant impact on the world's future energy needs.

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What needs to happen for that to take place? Using energy more efficiently is likely to be the sine qua non of energy planning—not least to buy time for efficiency improvements in alternative energy. The cost of solar electric power modules has already dropped two orders of magnitude over the last 30 years. And most experts figure the price needs to drop 100-fold again before solar energy systems will be widely adopted. Advances in nanotechnology may help by providing novel semiconductor systems to boost the efficiency of solar energy collectors and perhaps produce chemical fuels directly from sunlight, CO_2, and water.

But whether these will come in time to avoid an energy crunch depends in part on how high a priority we give energy research and development. And it will require a global political consensus on what the science is telling us.

–RICHARD A. KERR AND ROBERT F. SERVICE

The following six mathematics questions are drawn from a list of seven outstanding problems selected by the Clay Mathematics Institute. (The seventh problem is discussed on p. 96.) For more details, go to www.claymath.org/millennium.

Is there a simple test for determining whether an elliptic curve has an infinite number of rational solutions?
Equations of the form $y^2 = x^3 + ax + b$ are powerful mathematical tools. The Birch and Swinnerton-Dyer conjecture tells how to determine how many solutions they have in the realm of rational numbers—information that could solve a host of problems, if the conjecture is true.

continued >>

Can a Hodge cycle be written as a sum of algebraic cycles?
Two useful mathematical structures arose independently in geometry and in abstract algebra. The Hodge conjecture posits a surprising link between them, but the bridge remains to be built.

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Will Malthus Continue to Be Wrong

In 1798, a 32-year-old curate at a small parish church in Albury, England, published a sobering pamphlet entitled *An Essay on the Principle of Population*. As a grim rebuttal of the utopian philosophers of his day, Thomas Malthus argued that human populations will always tend to grow and, eventually, they will always be checked—either by foresight, such as birth control, or as a result of famine, war, or disease. Those speculations have inspired many a dire warning from environmentalists.

Since Malthus's time, world population has risen sixfold to more than 6 billion. Yet happily, apocalyptic collapses have mostly been prevented by the advent of cheap energy, the rise of science and technology, and the green revolution. Most demographers predict that by 2100, global population will level off at about 10 billion.

The urgent question is whether current standards of living can be sustained while improving the plight of those in need. Consumption of resources—not just food but also water, fossil fuels, timber, and other essentials—has grown enormously in the developed world. In addition, humans have compounded the direct threats to those resources in many ways, including by changing climate (see p. 100), polluting land and water, and spreading invasive species.

How can humans live sustainably on the planet and do so in a way that manages to preserve some biodiversity? Tackling that question involves a broad range of research for natural and social scientists. It's abundantly clear, for example, that humans are degrading many ecosystems and hindering their ability to provide clean water and other "goods and services" (*Science*, 1 April, p. 41). But exactly how bad is the situation? Researchers need better information on the status and trends of wetlands, forests, and other areas. To set priorities, they'd also like a better understanding of what makes ecosystems more resistant or vulnerable and whether stressed ecosystems, such as marine fisheries, have a threshold at which they won't recover.

Out of balance. Sustaining a growing world population is threatened by inefficient consumption of resources—and by poverty.

Agronomists face the task of feeding 4 billion more mouths. Yields may be maxing out in the developed world, but much can still be done in the developing world, particularly sub-Saharan Africa, which desperately needs more nitrogen. Although agricultural biotechnology clearly has potential to boost yields and lessen the environmental impact of farming, it has its own risks, and winning over skeptics has proven difficult.

There's no shortage of work for social scientists either. Perverse subsidies that encourage overuse of resources—tax loopholes for luxury Hummers and other inefficient vehicles, for example—remain a chronic problem. A new area of activity is the attempt to place values on ecosystems' services, so that the price of clear-cut lumber, for instance, covers the loss of a forest's ability to provide clean water. Incorporating those "externalities" into pricing is a daunting challenge that demands much more knowledge of ecosystems. In addition, economic decisions often consider only net present value and discount the future value of resources—soil erosion, slash-and-burn agriculture, and the mining of groundwater for cities and farming are prime examples. All this complicates the process of transforming industries so that they provide jobs, goods, and services while damaging the environment less.

Researchers must also grapple with the changing demographics of housing and how it will impact human well-being: In the next 35 to 50 years, the number of people living in cities will double. Much of the growth will likely happen in the developing world in cities that currently have 30,000 to 3 million residents. Coping with that huge urban influx will require everything from energy-efficient ways to make concrete to simple ways to purify drinking water.

And in an age of global television and relentless advertising, what will happen to patterns of consumption? The world clearly can't support 10 billion people living like Americans do today. Whether science—both the natural and social sciences—and technology can crank up efficiency and solve the problems we've created is perhaps the most critical question the world faces. Mustering the political will to make hard choices is, however, likely to be an even bigger challenge. **–ERIK STOKSTAD**

CREDIT: VIVIANE MOOS/CORBIS

Will mathematicians unleash the power of the Navier-Stokes equations?
First written down in the 1840s, the equations hold the keys to understanding both smooth and turbulent flow. To harness them, though, theorists must find out exactly when they work and under what conditions they break down.

Does Poincaré's test identify spheres in four-dimensional space?
You can tie a string around a doughnut, but it will slide right off a sphere. The mathematical principle behind that observation can reliably spot every spherelike object in 3D space. Henri Poincaré conjectured that it should also work in the next dimension up, but no one has proved it yet.

Do mathematically interesting zero-value solutions of the Riemann zeta function all have the form a + bi?
Don't sweat the details. Since the mid-19th century, the "Riemann hypothesis" has been *the* monster catfish in mathematicians' pond. If true, it will give them a wealth of information about the distribution of prime numbers and other long-standing mysteries.

Does the Standard Model of particle physics rest on solid mathematical foundations?
For almost 50 years, the model has rested on "quantum Yang-Mills theory," which links the behavior of particles to structures found in geometry. The theory is breathtakingly elegant and useful—but no one has proved that it's sound.

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