7 November 2008 | $10

Science

Genetics of Behavior

AAAS

COVER

Honey bees (*Apis mellifera*), here shown on a honeycomb, form complex societies and interact with one another by means of stereotyped social behaviors. A special section beginning on page 891 explores what genetic approaches have taught us about behavior in bees and other species, including humans.

Image: Don Farrall, Getty Images

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SPECIAL SECTION

Genetics of Behavior

INTRODUCTION

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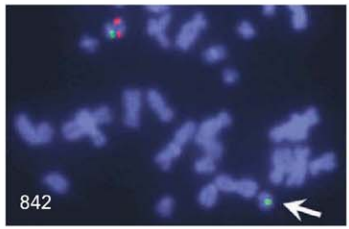
>> Editorial p. 821, News story p. 842, Policy Forum p. 861, Reviews pp. 876 and 881; Science Podcast



NEWS OF THE WEEK

NEWS FOCUS

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SCIENCE EXPRESS

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MOLECULAR BIOLOGY

The *Air* Noncoding RNA Epigenetically Silences Transcription by Targeting G9a to Chromatin

T. Nagano et al.

Air, a large noncoding RNA, interacts with chromatin at a particular promoter, recruiting a histone methyltransferase to silence gene expression in an allele-specific manner.

10.1126/science.1163802

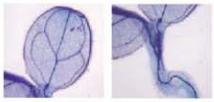
PLANETARY SCIENCE

Long-Lived Volcanism on the Lunar Farside Revealed by SELENE Terrain Camera

J. Haruyama et al.

Images of the Moon by the SELENE spacecraft and revised dates of lava flows by crater counts imply that episodic volcanism on the farside lasted to 2.5 billion years ago.

10.1126/science.1163382



MOLECULAR BIOLOGY

Photoexcited CRY2 Interacts with CIB1 to Regulate Transcription and Floral Initiation in *Arabidopsis*

H. Liu, X. Yu, K. Li, J. Klejnot, H. Yang, D. Lisiero, C. Lin

Blue light triggers the association of a photoreceptor, transcription factor, and DNA site, thus inducing expression of the gene *FT* (flowering time) and initiating flowering.

10.1126/science.1163927

LETTERS

TECHNICAL COMMENT ABSTRACTS

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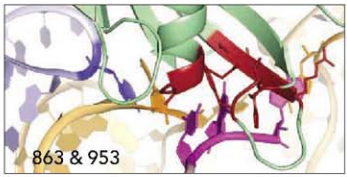

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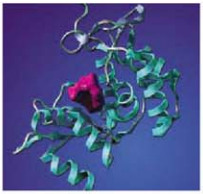
HIGHLIGHTS FROM OUR DAILY NEWS COVERAGE

River Dolphin Love Fetishes Not as Advertised
The boto has quite a reputation—but fortunately the body parts sold at Amazonian markets are fakes.

Diesel Fuel From a Tree Fungus?
Microbe's hydrocarbon stew could one day supplant fossil fuels.

Ancient Grave May Have Belonged to Shaman
Find hints at development of religion during crucial time in human history.



CD38, NAADP controller.

SCIENCE **SIGNALING**

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REVIEW: NAADP—A Universal Ca^{2+} Trigger
A. H. Guse and H. C. Lee
NAADP elicits an initial release of calcium, which is subsequently amplified through the action of other calcium messengers.

ST NETWATCH: The Nobel Prize in Chemistry 2008
This year's award went to the scientists who discovered green fluorescent protein and developed it as an experimental tool; in Awards and Announcements.

ST NETWATCH: ASBMB Interactive Features
View Awards Lectures and interviews with prominent cell biologists from the American Society for Biochemistry and Molecular Biology; in Web Broadcasts.

ST NETWATCH: AMBMR Webcasts
View seminars from the annual meeting of the American Society for Bone and Mineral Research; in Web Broadcasts.

Lessons for postdocs.

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FREE CAREER RESOURCES FOR SCIENTISTS

Taken for Granted: Postdocs and Joe the Plumber
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What early-career scientists can learn from the working class.

In Person: The Trick to a Rewarding Career
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Throughout his career, Marc Hermann has always done exactly what he wanted.

U.K. Visa Changes Mean Closer Scrutiny for Non-European Students
A. Saini
New U.K. immigration policies impose more rigid requirements than in the past.

November 2008 Funding News
J. Fernández
Learn about the latest in research funding, scholarships, fellowships, and internships.

SCIENCE**PODCAST**

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FREE WEEKLY SHOW

Download the 7 November *Science* Podcast to hear about genes and social behavior, switching memories on and off, chromosome 17 and mental disorders, and more.

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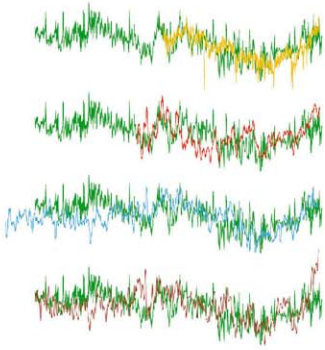


<< Tales of the Asian Monsoon

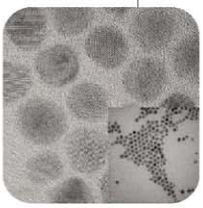
The Asian Monsoon is important for climate because it transports large amounts of heat and moisture from the ocean to the land. The monsoon is also important for human settlement because agriculture depends on monsoon rainwater. Using a record derived from a Chinese stalagmite, **Zhang *et al.*** (p. 940) present a detailed history of the Asian Monsoon over the past 1800 years that indicates connections between the monsoon, solar irradiation, Northern Hemispheric temperature, and glacial cycles in Europe. Shifts in the strength of the monsoon also correlate with the succession of Chinese dynasties, underscoring the importance that climate can have on human societies.

Stem Cells on Demand

Infection of adult mouse cells with viruses expressing genes of four transcription factors (Oct4, Sox2, c-myc, and Klf4) generates pluripotent stem cells (iPS) that resemble embryonic stem cells. Viruses commonly used for this procedure permanently alter the cells' genome and can cause tumors in animals, and thus these iPS cells cannot be used directly for cell therapy. **Stadtfeld *et al.*** (p. 945, published online 25 September) have produced mouse iPS cells by transiently exposing adult skin and liver cells to the four transcription factor genes using adenoviruses (that generally do not integrate into the genome). Thus, it is possible to make iPS cells without permanent genetic manipulation and it should be possible to make patient-specific cells not only to study disease but also for the future use of iPS cells in a clinical setting.

Sheltering Excitons in Quantum Dots

Quantum dots can exhibit long-lived fluorescence, but their excitonic states, which potentially are useful in photovoltaic and infrared detection applications, tend to decay very rapidly (in less than 1 picosecond). **Pandey and Guyot-Sionnest** (p. 929) report that the cooling of the two lowest energy excited states in cadmium-selenium quantum dots can be slowed by a thick coating of an electron insulator, in this case zinc-selenium. By using such insulation, the lifetimes of the excitonic states were extended to more than a nanosecond.



CREDITS (TOP TO BOTTOM): ZHANG *ET AL.*; PANDEY *ET AL.*

Going for the Burn

Fitness classes promote the idea that burning fat makes people healthier and perhaps live longer. **Wang *et al.*** (p. 957; see the Perspective by **Xie**) find that the *Caenorhabditis elegans* roundworm also adopts a fat-burning strategy to help them extend life. Up-regulation of a specific lipase, K04A8.5, decreases fat storage and increases life-span. The lipase level is low during adulthood but can be induced 10-fold when germline stem cells stop proliferating. In addition, the lipase contributes to longevity in worms by reducing insulin signaling. Thus, at least in *C. elegans*, fat metabolism and life-span control are directly linked.

Himalayan Graphite

Earth has an oxygen-rich atmosphere because, on a geological time scale, more organic material is created by photosynthesis than is respired back to carbon dioxide. Thus, knowing the particulars of how organic carbon is transformed by various geological processes, such as mountain-building, is essential for understanding the carbon and oxygen cycles. **Galy *et al.*** (p. 943) report that organic carbon is converted with surprising efficiency to graphite in the Himalayas, and subsequently buried in marine sediments after fluvial transport. During the erosion cycle up to half the carbon in the rocks was turned into graphite and sequestered in sediments, suggesting that the process could operate on a global scale to control carbon and oxygen cycles.

Moving Memories

The earliest phases of memory acquisition rely on the hippocampus, but growing evidence suggests that another area in the brain called the medial prefrontal cortex may take over in consolidated associative memories. **Takehara-Nishiuchi and McNaughton** (p. 960) found that following acquisition of an associative memory, neuronal activity in the rat medial prefrontal cortex became specific and necessary for the acquired memory. Selective activity patterns developed spontaneously during a consolidation period of about 6 weeks even without repetitive conditionings. Thus, a neural correlate of the memory gradually develops in the neocortex simultaneously with memory consolidation.

Mantle Flow

Seismic data provide an image of Earth's mantle today. Geologic data from mountain belts or sedimentary records in basins record the overall effects of mantle flow, but may not reveal the actual flow patterns. Starting with these observations, plus estimates of mantle properties, **Liu *et al.*** (p. 934; see the Perspective by **Steinberger**) have developed a model of the evolution of western North America during the past 100 million years. The model is consistent with flat subduction of the Farallon oceanic plate beneath the continent during much of this time, but shallow subduction extended over a larger area, which could explain a broad Cretaceous unconformity in sedimentary records.

Dry as a Bone Moon

Radar observations of the Moon from the Clementine spacecraft indicated water ice is present in the permanently shadowed Shackleton crater at the south pole. However, this finding has not been confirmed by Earth-based radar. Using a camera on board the SELENE (Kaguya) spacecraft, now orbiting the moon,

Continued on page 819

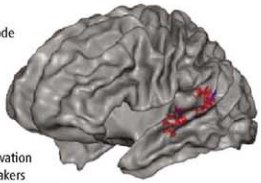
Continued from page 817

Haruyama *et al.* (p. 938) have been able to peer into this crater, and using the faint light reflected off the crater walls have measured the albedo and estimated surface temperatures across the interior. Although sufficiently cold (about 90 kelvin), the crater apparently lacks any large expanse of exposed ice. It is still possible that there are small amounts of ice beneath the surface, or mixed in the surface dust.

More Stem Cells on Demand

To rule out any risk of viral vectors integrating into the host genome and causing tumors, **Okita *et al.*** (p. 949, published online 9 October) used a plasmid transfection procedure to introduce transcription factor genes into mouse embryonic fibroblasts to make pluripotent cells. These cells show many features of embryonic stem cells, including the expression of pluripotency markers, as well as the capacity to develop teratomas and chimeras when transplanted into mice. Importantly, there was no evidence of plasmid integration and, although less efficient than other methods, this method looks like it will offer a safer way of inducing pluripotent stem cells.

Processing Speech and Voice



In everyday life, we automatically and effortlessly decode speech into language independently of who speaks. Similarly, we recognize a speaker's voice independently of what he says. **Formisano *et al.*** (p. 970) show that it is possible to decode the contents of speech and the identity of the speaker from measurements of the brain activity of a listener. They map and decode, trial-by-trial, the spatially distributed activation patterns evoked by listening to different vowels or speakers evoke in distinct patches of the listeners' auditory cortex. The pattern associated with a vowel does not change if the vowel is spoken by another speaker and the pattern associated with a speaker does not depend on what the person says.

CREDIT: FORMISANO ET AL.

Brain Repair

In mammals, a severed nerve in an arm or leg will eventually regrow and reestablish functional connections. A similar injury in the spinal cord or within the brain will not be repaired, resulting in permanent disability and paralysis. Poor regeneration in the central nervous system has been attributed to proteins embedded in brain myelin (the membranes that wrap each nerve axon), which interact with an inhibitory receptor on neurons called NgR. Two papers in this issue show that other inhibitory receptors recognize the myelin-embedded proteins (see the Perspective by **Kim and Snider**). **Atwal *et al.*** (p. 967) identified PirB, a mouse protein related to the immunoglobulins of the immune system, and if both PirB and NgR were blocked, regeneration resumed. **Park *et al.*** (p. 963) found that after injury to the optic nerve, the axons of the retinal ganglion cells in mice will regenerate if the growth-related signaling pathway mTOR is activated in these cells. When negative regulators of the mTOR pathway were deleted in the retinas of mice, within a few weeks, the axons of retinal ganglion cells would re-grow as far as the optic chiasm. Thus, to promote recovery from neural damage, a combination of therapeutic approaches is needed to remove inhibitory processes, as well as to stimulate the intrinsic growth pathways of the neurons.

Not Quite Sleep

Although thousands of people are made unresponsive under anesthesia, they are not always rendered unconscious, and stories of waking, eviscerated, on the operating table abound. **Alkire *et al.*** (p. 876) review what little we do know about the gap between behavioral unresponsiveness and oblivion. Although the relative role of the thalamus and cortical areas in switching consciousness on and off is not clear, despite their different mechanisms of action it does seem that most anesthetics hit a posterior corticothalamic complex centered around the inferior parietal lobe. As well as deactivating this region, anesthesia also causes functional disconnection between subregions of the complex. Understanding the effects of anesthesia could thus be a useful tool to understanding the neural correlates of consciousness.

Story Landis is director at the National Institute of Neurological Disorders and Stroke, National Institutes of Health.

Thomas R. Insel is director at the National Institute of Mental Health, National Institutes of Health.

The "Neuro" in Neurogenetics

THIS ISSUE OF *SCIENCE* FEATURES A SPECIAL SECTION (SEE PAGE 891) THAT FOCUSES ON AN emerging area of neurogenetics—the effort to link genomics and behavior. We are all intrigued by the notion that genomics may yield "simple" explanations for complex behaviors, including our own. The power of genomics has already revealed new insights into human disease and development. So what lessons has this new field taught us so far about behavior, and what can we look forward to in the coming decade?

One area of neurogenetics seeks the molecular basis for complex behaviors that range from mate choice in flies and social status in fish, to fidelity in voles and humans. Our intuition tells us that it should be easier to identify the mechanism underlying a simple reflex behavior (escape from threat) than a complex one (mate selection). But recent findings suggest that apparently simple genetic mechanisms may underlie some ostensibly complex behaviors. The field is just beginning to identify mechanisms for adaptive behaviors that are both parsimonious and profound. Although most research has investigated the genetics of behaviors in model organisms such as mice and flies, the diversity of the natural world is waiting to be mined. Behaviors that are unique to a species may be experiments of nature that can yield important insights into how genomic variation (inherited DNA sequence differences) relates to behavioral adaptation.

But perhaps most important in this burgeoning field is pursuit of the "neuro" in behavioral neurogenetics. Genes code for proteins, not for behaviors. By identifying how genomic variation modifies circuits of neurons, we will better understand both how and where behavior is instantiated. Most of the recently discovered variations are differences in the regulatory regions of genes that control gene expression. One important lesson from neurogenetics is that genomic variations in regulatory regions can account not only for how much of a protein is made, or when it is expressed, but exactly where in the brain a protein is expressed. Because brain function is specified by precise regional circuits, even small differences in the location of the brain cells that produce a particular receptor or an enzyme can result in large differences in function. Importantly, the link between genomic sequence and behavior is the brain: We cannot hope to understand how genomic variation influences behavior without understanding how genomic variation influences neural circuitry.

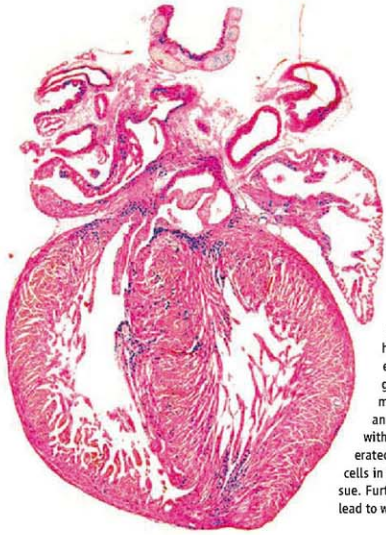
An early mainstay of neurogenetics was the identification of mutations in mice with abnormal behaviors. Here, discrete brain changes could be tied to regional molecular mechanisms once the genes were cloned. For human neurological disorders like Huntington's and Parkinson's disease, such obvious structural and functional changes can indeed explain how gene defects give rise to certain behaviors. For psychiatric diseases, where the neurobiological lesions are not known, the challenge will be greater. But genomics now promises to be the key to unlock the neurobiology of these complex disorders: There is real hope that genomic variation will lead us to neural mechanisms that can begin to explain such complex syndromes as schizophrenia or autism.

Behavioral phenotypes are the result of a complex interaction between nature (DNA) and nurture (experience). The developing brain is the stage for this drama, but we still know little about the details of how genes and experience interact within the developing brain to create something as complex as the phenotype we call human nature. In the coming decades, epigenomics—changes in gene expression due to alterations in protein-DNA interactions rather than DNA sequence—will be critical for understanding how experience alters the genome, complementing the current focus on how genomic variation affects behaviors.

Already it is clear that, for the study of behavior, genomics is not destiny. Indeed, if genomic sequence "determines" anything behaviorally, it determines diversity. It is important that we be wary about extrapolating from model organisms to humans. We must also avoid using small statistical associations to make grand claims about human nature. Obviously, we have much to discover before understanding how genes influence behavior—a discovery process that will closely involve the brain.

–Story Landis and Thomas R. Insel

10.1126/science.1167707



DEVELOPMENT

Healing a Broken Heart

The ability to regenerate damaged tissues and organs varies widely across animals. While mammals are able to repair ruptured muscles and to regrow fingertips, amphibia and fish have the more resilient tissues, being able to regenerate tails, fins, and even hearts. Although heart regeneration was thought to be restricted to a few species of amphibia, it is of particular interest to humans, because coronary heart disease remains a leading cause of death. Drenckhahn *et al.* have found that the fetal mouse heart is able to replace damaged tissue. The enzyme holocytochrome c synthase (Hccs) is involved in mitochondrial energy generation, and the authors inactivated the X-linked *Hccs* gene in female mice. At mid-gestation, heterozygous female hearts contained equal numbers of healthy and damaged cells; by the time of birth, these mice had fully functioning hearts, with less than 10% damaged cells. Thus, the mouse fetal heart appears to be regenerated predominantly from differentiated cardiac cells, suggesting that differentiated cells in the adult might retain an intrinsic capacity to expand and replace damaged tissue. Further studies aimed at understanding the molecular mechanisms involved could lead to ways of stimulating the regeneration of adult diseased hearts. — HP*

Dev. Cell **15**, 521 (2008).

IMMUNOLOGY

Lymphocyte Identity Cards

The determination of lineage, whether in genealogy, paleontology, or cell biology, can be very difficult. Schepers *et al.* have developed a retroviral tagging procedure by introducing a "bar code" into individual cells that persists in all of their progeny. The authors used a library of around 5000 tags, which can be identified by PCR amplification and microarray analysis, to monitor the life histories of T cells during the course of an infection.

A T cell population, specific for the antigen OVA, was transformed with the bar-code library and introduced into mice, which were subsequently injected with tumor cells and infected with influenza virus, both bearing the OVA antigen. At first, T cells in lymph nodes draining the two sites of invasion formed genetically distinct populations, distinguishable by their bar codes; however, the T cell populations in lung and tumor tissues had similar bar-code distributions, showing that they had originated from several lymph nodes. Over time, both lymph node T cell populations became similar as the infections stimulated the migration of T cells throughout the mouse. This technology has the potential to unravel lineage relationships in a wide range of cells, and the authors have already created a lentivirus library for use with quiescent cell types resistant to retroviral infection. — CS*

J. Exp. Med. **205,** 2309 (2008).

CREDITS (TOP TO BOTTOM): DRENCKHAHN *ET AL.*, *DEV. CELL* 15, 521 (2008); DEMETRIOU *ET AL.*, *PHYS. REV. LETT.* 101, 145702 (2008)

*Helen Pickersgill and Chris Surridge are locum editors in *Science*'s editorial department.

MATERIALS SCIENCE

Sizing Up the Foam

Bulk metallic glasses have high plastic yield strengths, and thus have the potential for making ultrastrong foams. However, the foam will only inherit the strength of the parent glassy material if it fails by plastic yielding, rather than by brittle fracture (which is associated with the solid fracture stress) or by elastic buckling (associated with the solid modulus). Demetriou *et al.* look at a number of critical structural scales that influence the failure mode and find that they can make ultrastrong glassy foams from a $Pd_{43}Ni_{10}Cu_{27}P_{20}$ alloy with up to 92% porosity. The foams were engineered against buckling and fracture though a process that limited membrane thickness and promoted cellular periodicity. Evaluation of compressed, collapsed specimens showed both crushed cells and shear banding, indicating that although the failure was due to fracture, the initial response of the foam involved plastic deformation. Thus, the foams inherited the best properties of the parent glassy material. The compressive strength of the glassy foams rivaled those obtained for highly engineered Ti-6Al-4V or ferrous metal foams. — MSL

Metallic-glass foam.

Phys. Rev. Lett. **101,** 145702 (2008).

SYSTEMS BIOLOGY

Network Failure

Models of metabolic and signalling networks have been characterized, perhaps unfairly, as reannotations of previously discovered interactions. To counter this concern (and the statistical issue of sorting through hundreds of correlations), Janes *et al.* describe an approach called "model breakpoint analysis" that stresses the network by using non-physiological inputs in a manner similar to that of

Continued on page 825

Continued from page 823

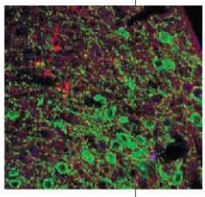
engineers performing failure analysis of bridges or cars. They began with their model of cytokine-induced apoptosis and proceeded to introduce implausible data that stretched the dynamic range of the cell (defined as the responsiveness of cell outcomes to incremental changes in cell activation). Surprisingly, network function did not degrade in parallel, but worked perfectly well until a threshold (or breakpoint) was reached, at which point the predictions were no longer useful. Pinpointing the signals and stimuli that were responsible for the system failure enabled them to distinguish epiphenomena from causal factors and to make predictions about the dynamic roles of three kinases (Akt, ERK, and Mk2) in cytokine-induced apoptosis. These predictions were then confirmed in inhibitor- and mutant-based experiments, suggesting that differences in dynamic range can be more important to cellular function than the strength of a particular signal. — BJ

Cell **135**, 343 (2008).

NEUROSCIENCE

Depotentiating via Dopamine

The capacity to associate events, in a neuronal context, is thought to rely on long-term potentiation (LTP), a mechanism that strengthens glutamatergic (excitatory) synaptic connections. Strong novel stimuli can selectively reverse or overwrite LTP by a mechanism known as depotentiation, which is thought to keep synapses from becoming saturated and thereby to maintain them in a dynamically responsive range. Neuregulin-1 is a factor expressed in brain and can effectively depotentiate LTP in the hippocampus. Kwon *et al.* found that neuregulin depotentiates LTP by recruiting a dopaminergic signaling pathway involving the dopamine D4 receptor (D4R), which is a target of the antipsychotic clozapine. Neuregulin acutely triggers dopamine release in the hippocampus, which in turn depotentiates LTP by activating D4Rs. The direct activation of D4Rs by selective agonists mimics the action of neuregulin in removing AMPA-type glutamate receptors from synapses. Mutant mice lacking D4Rs fail to depotentiate LTP in response either to neuregulin or to electrical stimuli. These observations thus functionally associate three signaling pathways (dopamine, glutamate, and neuregulin) in the regulation of synaptic plasticity. — PRS



Dopaminergic (green) neurons in the ventral tegmental area.

CREDIT: KWON *ET AL.*, *PROC. NATL. ACAD. SCI. U.S.A.* 105, 15587 (2008)

Proc. Natl. Acad. Sci. U.S.A. **105**, 15587 (2008).

CLIMATE SCIENCE

Warming Vapors

Water vapor is the atmospheric gas that collectively has the greatest greenhouse effect on climate, although it does not directly instigate warming or cooling trends, because the amount of water vapor in the atmosphere varies only in response to temperature change. Instead, water vapor only amplifies temperature trends being caused by other factors such as atmospheric CO_2 concentration or Earth's albedo. The extent to which humidity changes in response to temperature variation is therefore a key parameter in global climate models, because that quantity determines the strength of the associated warming or cooling. Dessler *et al.* present satellite data from 2003 to 2008 which show that models have gotten that relationship correct, and that relative humidity is effectively constant at any given temperature. Thus, the temperature increases predicted by global models are virtually guaranteed to be several degrees Celsius by the year 2100. Knowing the water vapor content of a warmer atmosphere is also important for predicting rainfall and storminess. — HJS

Geophys. Res. Lett. **35**, L20704 (2008).

CELL BIOLOGY

Curing Disease in Yeast

Batten disease is a neurodegenerative disorder linked to the pathological accumulation of material in lysosomes. In yeast the [URE3] phenotype is a prion (infectious protein) generated by the self-propagating amyloid form of the Ure2 protein, which regulates nitrogen catabolism. Yeast prions can arise and disappear spontaneously within populations, reflecting in part changes in the protein folding milieu. Kryndushkin *et al.* show that increased production of Btn2 protein or its homolog Cur1 can cure [URE3]. Conversely, deletion of *BTN2* and *CUR1* genes stabilizes the [URE3] phenotype. In cells expressing a fluorescently tagged version of Btn2p, fluorescence accumulated at a single point close to the nucleus and vacuole, where aggregates of Ure2p also accumulated. This accumulation of protein aggregates reduced the ability of the Ure2p amyloid seeds to enter budding daughter cells, explaining the cure of daughter cells. This accumulation of protein aggregates mirrors aggresome formation observed in mammalian cells, which may also function to remove potentially harmful protein aggregates. — SMH

EMBO J. **27**, 2725 (2008).

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Eyeing Balls

Useful news for tennis pros: Umpires are much more likely to make mistakes when calling balls out rather than in.

Scientists at the University of California, Davis, analyzed 4457 points from tennis matches played during the 2007 Wimbledon tournament in the U.K., including all challenges submitted by players. Of 83 recorded blunders, 70 were wrongly called out and only 13 wrongly called in. The skew is due to a perceptual bias toward the direction of movement of a bouncing ball, the authors reported in the 28 October issue of *Current Biology*. On top of that, says lead author David Whitney, umpires are more likely to "mislocalize" balls that are traveling toward them.

Tennis players can take advantage of this bias, he says, by concentrating their challenges on rulings that their own balls are "out"—rather than on rulings of "in" for an opponent.

Psychologist Alan Johnston of University College London says this perception bias "might have implications for other sports, such as soccer or rugby," for which player positions are at issue.

Gender and the Brain

The largest ever genetic study of male-to-female transsexuals has provided a hint—albeit a faint one—as to how gender is embedded in the brain. A team led by molecular geneticist Vincent Harley of the Monash Medical Centre in Melbourne, Australia, analyzed versions of

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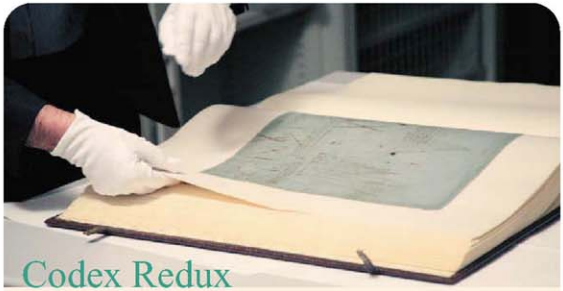
three hormone-related genes in 112 white male-to-female transsexuals recruited in Melbourne and Los Angeles, California. The findings were compared with DNA samples from 258 nontranssexual males. Categorizing the alleles as either "short" or "long," they found that the transsexuals had more long alleles for the androgen receptor gene, they reported online last week in *Biological Psychiatry*. Longer alleles, they explain, inhibit receptor activity, leading to less effective prenatal testosterone signaling. Although the effect is weak—55% of the transsexuals had the long allele, compared with 47% of the controls—the researchers suggest it could play a role in incomplete masculinization of the brain during early development.

Psychologist Kenneth Zucker, head of the Gender Identity Service at the Centre for Addiction and Mental Health in Toronto, Canada, says it's hard to see how prenatal hormones could affect brain development in that way without altering the sex organs as well. That's why "everybody is looking for some [other] type of marker," he says. Nonetheless, behavioral neuroendocrinologist Marc Breedlove of Michigan State University in East Lansing says "it will be exciting" if the finding is replicated.



Codex Redux

The 500-year-old Codex Atlanticus, a compilation of notes and drawings by Leonardo da Vinci, may be disassembled for better conservation, officials at Ambrosiana library in Milan, Italy, announced last week.

The Codex dates from the late 16th century, when an Italian sculptor gathered some 1120 pages of notes and drawings into a 402-page volume. In the early 1970s, restorers glued the notes onto blank sheets and split them into 12 books—a move that experts now say weakened the paper, altered edges, and made the pages awkward to display.

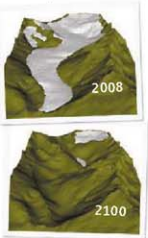
The Codex drew renewed attention last year when scholars noticed black stains on the support pages that they feared were from mold. After a year of research conducted at the Istituto Centrale di Patologia del Libro (ICPL), epidemiologist Gianfranco Tarsitani of the University of Rome "La Sapienza" announced last month that the stains were due not to mold but to mercury salts added as a preservative.

Leading da Vinci expert Carlo Pedretti, a professor emeritus at the University of California, Los Angeles, has given his blessing to the plan, which he says will help tailor conservation to the needs of individual pages. "Each time we have to study or display one drawing, we have to manipulate the whole volume," notes ICPL conservator Armida Batori.

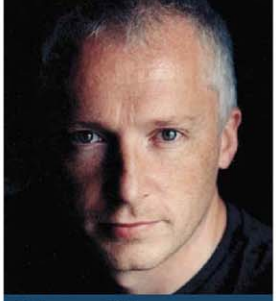
Running Out of Glacier Time

An iconic feature of the Swiss landscape may vanish within the century. Swiss researchers have developed a model simulating the retreat of the Rhône Glacier in southern Switzerland since 1874 that predicts the glacier's possible disappearance by 2100.

Mathematician Guillaume Jouvet of the Federal Polytechnic Institute in Lausanne, Switzerland, and colleagues tweaked a classic fluid-dynamics model to account for the viscosity of ice and accumulation of snow on the glacier, they report in an upcoming issue of the *Journal of Glaciology*. They also fed in more than a century of detailed temperature and precipitation data obtained from the Swiss Federal Institute of Technology Zurich (ETH).



If average global temperature goes up by 1°C by 2100, the glacier will lose about 35% of its volume, says ETH glaciologist Matthias Huss. Under the worst-case scenario, a nearly 4°C increase, the glacier will disappear completely by then. "In all possibilities, we have retreat," Huss says, with enormous consequences for water supplies and power generation as well as for ecology.



Three Q's >>

Acclaimed mathematician, best-selling author, newspaper columnist, and host of the current BBC television series *The Story of Maths*, **Marcus du Sautoy** has been appointed to the Simonyi Professorship Chair for the Public Understanding of Science at the University of Oxford in the U.K. He will succeed evolutionary biologist Richard Dawkins, who retired from the chair last month.

Q: Dawkins was a very high-profile holder of this professorship. What might you do differently?

I want to steer the position back to science rather than talking about religion, which is what I think it's been slightly concentrated on the past few years.

Q: Is communicating mathematics to the public more challenging than communicating evolution?

It is, partly because many of the things we study just exist in the mind and don't have a physical reality. But mathematics is fundamental to all the sciences. It is the language of nature.

Q: "Public understanding" is a difficult thing to quantify. How will you measure the success of your efforts?

Some indications [might be that] on [BBC] Radio 1, they're now quite happy to mention what a prime number is without batting an eye. That would not have been true 15 years ago. Once you see mathematics getting embedded into the public psyche and popular culture, that will be an indication that we're getting the message through. If we see fewer people saying "I hate maths" and actually choosing maths as a university subject, that will also be considered a success.

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MOVERS

NEW DIRECTION. DESY, Germany's particle physics lab near Hamburg, this week tapped a prominent solid-state physicist, Helmut Dosch of the Max Planck Institute for Metals Research in Stuttgart, to be its new director-general beginning in March 2009. This mismatch of disciplines reflects a shift in the lab itself. DESY's main accelerator, HERA, shut down in 2007, and the lab's main focus is now XFEL, an x-ray–free electron laser for studying the structure of matter that will be completed by 2013. "DESY will shed light on so-far-unexplored dimensions in nanospace," says Dosch.

WARM CASH. Lured by $15.7 million from the Alberta, Canada, government and the University of Lethbridge (UL), neuroscientist Bruce McNaughton is reestablishing his Canadian roots. Last month, the 60-year-old researcher at the University of Arizona, Tucson, joined UL's Canadian Centre for Behavioural Neuroscience and brought with him a talented former postdoc, David Euston, also from UA. More will follow, says McNaughton, who expects to provide a "kind of theoretical and computational perspective" for the center while steering younger scientists along promising avenues of research.

McNaughton, who left Canada in 1982 to do a postdoc in Norway, says he was attracted by the lack of strings attached to the prize, the first of three Polaris Investigator Awards that the province is offering to top-flight scientists from around the world (*Science*, 6 April 2007, p. 29).

McNaughton's only lament is the climate. "Ideally, one would live in Arizona at this time of year and come up here in the summertime," he says.

BACK TO THE LAB. J. Michael Bishop will step down in June 2009 as chancellor of the University of California, San Francisco (UCSF). The 72-year-old Nobelist will remain on the faculty as a professor of microbiology and immunology.

In his decade-long tenure as chancellor, Bishop oversaw both the construction of a second campus that will become one of the country's largest biomedical research centers and the establishment of an institute for research on stem cells and regenerative medicine. There were also some rough patches, among them lingering financial fallout from a failed hospital merger with Stanford University in Palo Alto in 1997 and the dismissal last year of medical school dean David Kessler over a dispute about the university's finances (*Science*, 21 December 2007, p. 1855).

Harold Varmus, who shared the 1989 Nobel Prize in physiology or medicine with Bishop, says Bishop has had a successful run as chancellor. "He enjoyed raising money and was enormously good at it at a time when UCSF was growing at a dramatic pace," says Varmus, adding that the university's reputation "just continues to improve."

PLUCKED. How often does a geologist have to be whisked off by helicopter in the middle of fieldwork? It happened to Greg Stock last month.

The staff geologist at Yosemite National Park in northern California was halfway into a 6-day climb to map the rock types on the face of the El Capitan mountain when he heard a loud rumble over his radio. A few kilometers away, a rockfall had sent nearly 6000 m^3 of stone tumbling down to Curry Village, a collection of rustic cabins and tent sites.

Slice of Life

The rockfall had slightly injured three people, and park managers wanted Stock to come over immediately to assess the chance of another incident. But he was several hundred meters up in the air, clinging to the world's most famous stone wall. So a rescue team landed a helicopter on top of the cliff, hauled Stock up with a long rope, and flew him to the accident site.

Ironically, Stock was climbing to learn more about why rockfalls happen. The previous night, he had heard of a much smaller rockfall at the accident site that "unsettled" him. Had he been able to check it out, it might have provided clues that the larger one was coming. "I wish that I wasn't up [on El Capitan] at the time," he says. The mapping effort, which Stock's guides completed, will help him locate the source of a mysterious 2.7-million-m^3 rockfall that came off El Cap 3600 years ago.

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NATIONAL INSTITUTES OF HEALTH

Zerhouni's Parting Message: Make Room for Young Scientists

An intractable problem faced Elias Zerhouni when he became director of the National Institutes of Health (NIH) 6 years ago: The agency's corps of more than 20,000 independent investigators was getting old. The average age at which researchers receive their first NIH research grant had been creeping up for decades. (It is now 42.) Zerhouni saw this as a crisis and tackled it head on. After probing the data, he launched an experiment. Instead of relying solely on peer review to apportion grants, he set a floor—a numerical quota—for the number of awards made to new investigators in 2007 and 2008.

Last week on his final day as director, Zerhouni made this a formal NIH policy. He hopes his successors will keep it: "I think anybody who thinks this is not the number-one issue in American science probably doesn't understand the long-term issues," he says. The notice states that NIH "intends to support new investigators at success rates comparable to those for established investigators submitting new applications." In 2009, that will mean at least 1650 awards to new investigators for R01s, NIH's most common research grant.

The quotas have meant pain for some institutes in a time when NIH's budget isn't growing. Many are trying to steer money to new grantees by setting funding cutoff points in peer-review scores at more generous levels for new investigators than for established ones. Although some scientists may see this as a kind of affirmative action, Zerhouni says it is not. To him, it is simply "leveling the playing field" by correcting peer reviewers' bias against the young.

In 1980, the average age of a first-time NIH grant recipient was 37. The 5-year rise in average age since then, observers say, can be blamed on longer time spent in training, including in postdocs, and the older age at which faculty are first hired at medical schools, where they begin independent careers. In 2003, when NIH's budget stopped growing, the situation "collapsed," Zerhouni says: The number of R01-like research grants (known as R01 equivalents) going to first-time investigators slipped to 1354 in 2006, the lowest level in 9 years.

Transfusion. Departing NIH Director Elias Zerhouni says it is urgent to bring new blood into U.S. biomedical research.

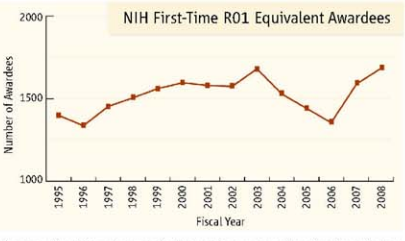
This is "detrimental for all sorts of reasons," says Jeremy Berg, director of the National Institute of General Medical Sciences. One concern is that scientists are not getting enough support when they're young, during their most creative years. Another is that the well may run dry. When Zerhouni asked his staff to model the age distribution of NIH-funded scientists over time, the results were startling. If trends continue, by 2020 there will be more investigators over 68 than under 38 (see p. 848). "If we don't fund the pipeline now, we will pay for it 20 years from now," Zerhouni says.

Zerhouni created special awards for young scientists but concluded that wasn't enough. In 2007, he set a target of funding 1500 new-investigator R01s, based on the previous 5 years' average. Some institutes struggled to reach their targets, NIH officials say. At the National Institute of Neurological Disorders and Stroke, for example, the shift to new grants meant that only 9% to 10% of established investigators with strong peer-review scores received funding, whereas 25% of comparable new investigators did, says NINDS Director Story Landis. She maintains, however, that "it's not as though a huge number of investigators lost out."

Some program directors grumbled at first, NIH officials say, but came on board when NIH noticed a change in behavior by peer reviewers. Told about the quotas, study sections began "punishing the young investigators with bad scores," says Zerhouni. That is, a previous slight gap in review scores for new grant applications from first-time and seasoned investigators widened in 2007 and 2008, Berg says. It revealed a bias against new investigators, Zerhouni says.

The 2007 target had an immediate effect: For the first time since 1995, new investigators and established ones submitting new grant applications had nearly the same success rate, about 19%. (Investigators renewing existing grants still do much better, however.) From now on, NIH will set award targets designed to equalize new grant success rates for the two groups.

NIH will also fine-tune its policy to tilt it in favor of early-career scientists. The goal is to adjust for the recently discovered fact that only about 55% of investigators who receive their first NIH grants are at an early stage of their career. The rest ▶



A leg up. After NIH set a numerical target for grants to first-time investigators in 2007, the number of awardees grew. Their success rates matched those of established investigators seeking new grants.

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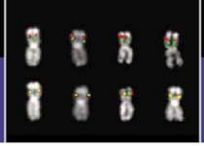

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are scientists who had been funded by other agencies or came from NIH's intramural program or from Europe after being forced to retire there. "It was embarrassing" to realize, for example, that the new investigators included two department chairs with Veterans Administration funding, Landis says. The targets will favor "early stage investigators," defined as researchers within 10 years of finishing their Ph.D. or residency.

Those outside NIH are generally supportive of the new-investigator targets, which were also endorsed earlier this year by an advisory committee reviewing NIH's peer-review policies (*Science*, 29 February, p. 1169). But at the same time, some scientists may be uneasy about the cost, says Howard Garrison, spokesperson for the Federation of American Societies for Experimental Biology in Bethesda, Maryland: "Every time you give a leg up to a young investigator, you're pushing someone off the edge of the cliff." Some observers say the real test will come when early stage investigators try to renew their grants: They may have trouble, and gains in creating a more youthful corps of investigators could be lost (*Science*, 26 September, p. 1776). NIH officials say they've looked at the data, and so far it seems that first-time investigators do just as well as established investigators who are renewing a new grant.

–JOCELYN KAISER

CLIMATE CHANGE

Rules for Ocean Fertilization Could Repel Companies

An international body has for the first time placed restrictions on experiments designed to fertilize large swaths of the world's oceans with a view to combating global warming. Meeting last week in London, delegates from 85 nations noted that such experiments "may offer a potential strategy for removing carbon dioxide from the atmosphere" by producing algal blooms that would absorb CO_2 and sink to the ocean floor. But they limited the experiments to "legitimate scientific research," a phrase not yet defined that could complicate plans to commercialize the approach.

Created in 1972 under the auspices of the United Nations' International Maritime Organization, the London Convention Treaty is supposed to regulate pollution in international waters. Members of the convention and the related London Protocol had been silent on ocean fertilization until several companies announced plans last year to carry out large-scale tests, setting off concern about environmental effects. The companies hope the technology will allow them to sell carbon credits on domestic and international markets.

On 31 October, delegates agreed unanimously to set scientific guidelines for proposed fertilization experiments, taking into account their expected carbon flux, impacts on oxygen levels and food webs, and the possibility that they will promote the growth of toxic species. Scientific bodies affiliated with the treaty will meet in May to hash out details.

"There was a widespread recognition among the delegates that there should not be a ban on legitimate research," says Henrik Enevoldsen, who observed the 5-day negotiations as a scientific staff member of UNESCO's International Oceanographic Commission. But the reference to "legitimate" studies was intended by some nations to exclude for-profit fertilization efforts, he says. "Most countries are looking to oppose something that's commercial research with an eye toward obtaining carbon credits."

Not ironed out. New global guidelines are being drawn up to govern experiments like this 2002 release of iron in the Southern Ocean.

CREDIT: MBARI

The experiments dump elements such as iron or nitrogen into the open ocean to stimulate the growth of plankton blooms (*Science*, 30 November 2007, p. 1368). Up to 3 tons of iron at a time have been released in a dozen small-scale fertilization experiments since 1993, and prominent scientists believe the technique, if scaled up, could sequester up to 1 billion tons of carbon dioxide per year as the blooms grow and die. But there are no international rules to regulate the practice, and researchers have identified myriad possible side effects, including local disruption of marine ecosystems or emissions of nitrous oxide, a potent greenhouse gas.

To quantify both the promise and perils of ocean fertilization, scientists want to launch experiments 10 to 30 times larger than earlier tests. Last week's vote implicitly supports such work, says geochemist Ken Buesseler of Woods Hole Oceanographic Institute in Massachusetts. But Buesseler worries that the upcoming rules, which will form the basis for permits to be issued by individual countries, "could preclude even legitimate science, if the [environmental] assessment needs to include measurement of all impacts on all time [and] space scales."

On the other hand, Greenpeace and other environmental activist groups are concerned about possible bias in reporting results among commercial companies looking to fight global warming by exploiting ocean fertilization for profit. But Dan Whaley, CEO of Climos, a San Francisco, California–based ocean fertilization start-up, defends his company's ethics and notes that the text of the resolution doesn't explicitly bar commercial projects. Climos still hopes to abide by the treaties and obtain permits for operations previously scheduled in 2010.

–ELI KINTISCH

CLIMATE CHANGE

Chinese Cave Speaks of a Fickle Sun Bringing Down Ancient Dynasties

A 1.2-meter-long chunk of stalagmite from a cave in northern China recorded the waning of Asian monsoon rains that helped bring down the Tang dynasty in 907 C.E., researchers report on page 940. A possible culprit, they conclude: a temporary weakening of the sun, which also seems to have contributed to the collapse of Maya civilization in Mesoamerica and the advance of glaciers in the Alps. "I think it's one of the coolest papers I've seen in a long time," says paleoclimatologist Gerald Haug of the Swiss Federal Institute of Technology in Zurich. This latest cave record also points to the potentially devastating effects that climate change—even change that's mild when averaged around the globe—can have on vulnerable local populations.

Although hardly the final word in such controversial fields, the cave record—which other researchers describe as "amazing," "fabulous," and "phenomenal"—provides the strongest evidence yet for a link among sun, climate, and culture. The key to obtaining it was "a really, really clean sample," says paleoclimatologist Lawrence Edwards of the University of Minnesota (UM), Twin Cities. Paleoclimatologists Pingzhong Zhang of Lanzhou University in China, Hai Cheng of UM, Edwards, and colleagues collected a stalagmite (a mound composed mostly of calcium carbonate slowly precipitated from dripping groundwater) from Wanxiang Cave in northern China at the far reach of the rains of the summer Asian monsoon.

Relatively high amounts of uranium and exceptionally low clay-borne thorium in this stalagmite enabled them to conduct uranium-thorium radiometric dating of the layered deposits to within an average of just 2.5 years. As a result, they could calculate precise dates for subtle variations in the stalagmite's oxygen isotope composition that reflect variations in rainfall near the cave. "They absolutely nailed the rainfall history of [northern] China over the past 1800 years," says Haug.

Comparing their rain record with Chinese historical records, Zhang and colleagues found that three of the five multicentury dynasties during that time—the Tang, the Yuan, and the Ming—ended after several decades of abruptly weaker and drier summer monsoons, possibly poor rice harvests, and social turmoil. In turn, decades that included the strongest, wettest monsoon of the past millennium coincided with the Northern Song Dynasty's golden age of rich harvests, exploding population, and social stability. "Our results really match the historical record," says Edwards. "You can't figure it's all climate, but when you see these nice correlations, you see that climate probably played an important role."

The group then looked farther afield. Critical parts of their monsoon rainfall record—in particular the dryness of the late Tang dynasty—match neatly with a previously published climate record from a lake on the southern coast of China, with the advances and retreats of Swiss alpine glaciers, and with records from within and near Central America. Most striking is the correlation between the Asian monsoon and the collapse at the end of the Maya Classic period under severe drought duress around 900 C.E. (*Science*, 18 May 2001, p. 1293), near the end of the drought-stricken Tang dynasty.

Previous research had linked changes in ▶

Good times. Monsoon rains were plentiful early in the Northern Song Dynasty of China, according to the isotopic record in a cave stalagmite (*top*). A cave-wall painting from the same province (*above*) recorded the bounty.

CREDITS: (TOP TO BOTTOM): COURTESY OF HAI CHENG; THE BRIDGEMAN ART LIBRARY

Call to Resume Nutrition Program

PARIS—After months of quiet diplomacy, Médécins Sans Frontières (MSF) has issued a public call to President Tandja Mamadou of Niger to let the humanitarian organization resume its nutrition programs in the country. The suspension by the Nigerien government "endangers the lives of thousands of children," MSF said in a statement last week. The French section of MSF operated a massive program in Niger's central region of Maradi, where malnourished children were given new, peanut-based products said to have revolutionized malnutrition treatment (*Science*, 3 October, p. 36). But the Nigerien government ended the program in mid-July, accusing MSF of breaking rules for nongovernmental organizations and insufficient coordination with the national health care system. Negotiations have been fruitless.

The suspension has also interrupted research into the efficacy of the peanut pastes and a large-scale study of infectious diseases in malnourished children for which subjects were recruited from an MSF hospital. Scientists are hoping they can resume the latter study by recruiting patients from a local hospital instead, says MSF's Philippe Guérin.

–MARTIN ENSERINK

Stalking Killers in Africa

BEIJING—Virus hunters in West Africa are banding together to better cope with emerging threats and old foes. At the International Consortium on Anti-Virals (ICAV) meeting here this week, researchers from Nigeria, Ghana, and other countries in the region agreed to establish a West African Viral Surveillance Network. "This is a neglected area of the world," says ICAV co-founder Jeremy Carver, a molecular biologist and professor emeritus at the University of Toronto in Canada.

Organizers have not decided on goals for fundraising, which has just begun, so the focus for now is on forging connections. "Scientists in the region weren't talking with each other," says ICAV Africa director Oyekanmi Nashiru of the National Biotechnology Development Agency in Abuja, Nigeria. There is plenty to share. Nigeria has virology expertise but poor infrastructure, Nashiru says, whereas nearby Ghana has top-notch labs at the Noguchi Memorial Institute for Medical Research at the University of Ghana in Legon. Key quarry include bird flu, HIV, and polio, which has yet to be eradicated from West Africa. When it comes to emerging viruses, says Noguchi Institute molecular biologist James Brandful, "now we'll be better prepared."

–RICHARD STONE

both the Asian monsoon and Mesoamerican climate to variations in the brightness of the sun (*Science*, 6 May 2005, p. 787). Checking their record, the group found an 11-year cycle in rainfall—the length of the shortest cycle of solar variability. In their record, rain tracked centuries-long trends in solar activity as measured in records of carbon and beryllium isotopes. And a climate model driven in part by solar variations broadly tracked the monsoon trends. "Solar variation is a player, but the sun is not everything," Edwards concludes. Internal jostlings of the climate system must also play a role, he says.

Climate modeler David Rind of NASA's Goddard Institute for Space Studies in New York City agrees. In a modeling study in press in the *Journal of Geophysical Research*, Rind and colleagues found that "the solar influence on the monsoon was more like a 'weighting of the dice'—it influenced the net result, but did not dominate," he writes in an e-mail.

De'er Zhang, chief scientist of the National Climate Center in Beijing, stresses that both climate and culture are too complex to be reduced to a simple cause-and-effect relationship. A single spot cannot properly represent such a vast area as encompassed by the monsoon, she writes in an e-mail, and numerous political factors influenced the Tang dynasty. "Climate might have played a role," she writes, but it was "far from playing 'a key role' as stated by [Pingzhong] Zhang *et al.*" Sorting out what "key" or "important" meant a millennium ago could require a lot more spelunking. **–RICHARD A. KERR**

PERSONAL GENOMICS

Number of Sequenced Human Genomes Doubles

Less than a decade ago, it took hundreds of millions of dollars and a large international community to sequence a single human genome. This week, three reports in the 6 November issue of *Nature* describe three more human genomes—the first African, the first Asian, and the first cancer patient to have their entire DNA deciphered. The sequences provide clues about genome variation and disease; they also demonstrate the potential of a relatively new sequencing technique to mass-produce human genomes. "The methods are extremely powerful," says geneticist James Lupski of Baylor College of Medicine in Houston, Texas. "Reading these papers, I think the personal genomes field is moving even faster than I anticipated."

Until now, four human genomes have been published: the reference human genome, derived from sequencing DNA from several anonymous individuals; one by Celera Genomics; and those of genome stars J. Craig Venter and James Watson. Efforts to date to identify differences among individuals have relied not on entire genome sequences but on surveys of single-base changes called SNPs and of structural variations in duplicated pieces of DNA (*Science*, 21 December 2007, p. 1842).

Even the broadest SNP surveys look at just a few million SNPs out of the 3 billion bases in the genome, leaving researchers in the dark about how much individual variation there is and how specific differences correlate with disease risks. Hence the push to drive down the cost of sequencing to $1000 per genome (*Science*, 17 March 2006, p. 1544). The newly published genomes came in with price tags of $250,000 to $500,000 each but would cost half that or less if done today. The three groups all used a technology developed by Solexa, now part of Illumina Inc. in San Diego, California, to speed and slash the cost of sequencing. It generates smaller pieces of sequence faster and cheaper than previous technologies. Such small pieces used to be difficult to stitch together, but this approach can work well now because the reference genome helps guide their assembly.

New genome on the block. The first genome sequence from a Chinese was on display last year at a technology fair in Shenzhen, China.

CREDIT: XINHUA/LANDOV

To explore the genetic underpinnings of cancer, Richard Wilson and colleagues at the Washington University School of Medicine in St. Louis, Missouri, sequenced genomes from both normal skin tissue and tumor tissue of a middle-aged woman who died of acute myelogenous leukemia (AML). They compared the DNA to determine what was different about the cancer cells. About 97% of the 2.65 million SNPs found in the tumor cells also existed in the normal skin cell, suggesting they were not critical to the cancer process. The researchers also eliminated SNPs that had been previously identified elsewhere as well as those that did not change the coding of a gene, ending up with 10 SNPs unique to the tumor cells. "I don't think we missed anything," says Wilson.

Two occurred in genes previously linked to this leukemia. Eight led the researchers to new candidate AML genes, including several tumor suppressor genes and genes possibly linked to cell immortality. By sequencing the whole cancer genome, "we capture what we don't know as well as what we do know [about cancer genes]," says Illumina's David Bentley. "That can really transform our ability to understand cancer."

Bentley and colleagues sequenced the genome of a Yoruba man from Nigeria whose DNA has already been extensively studied, enabling them to check the accuracy of their technology. In the third *Nature* paper, Jiang Wang of the Beijing Genomics Institute in Shenzhen, China, and colleagues sequenced the genome of a Han Chinese male. The Yoruba analysis uncovered almost 4 million SNPs, including 1 million novel ones. The Chinese genome had about 3 million, including 417,000 novel SNPs. As anticipated, the African genome had greater variation per kilobase than either the Chinese or sequenced Caucasian genomes, indicative of its ancestral status.

These new genomes were already significantly cheaper than their predecessors were; next year, Illumina expects the cost to drop to about $10,000. Other companies are promising even lower prices per genome. Nonetheless, geneticist Aravinda Chakravarti of Johns Hopkins University School of Medicine in Baltimore, Maryland, is cautious about how quickly genome sequencing should enter the clinic: "We still don't know how to interpret [the data]," he notes. Bentley agrees. Because of the uncertain applicability and utility of sequence data, "and possibly ethical barriers," he notes, saying the technology is poised to enter the clinic anytime soon is "pushing it." **–ELIZABETH PENNISI**

PERSONAL GENOMICS

The Touchy Subject of 'Race'

Nothing makes scientists more nervous than the topic of "race," so much so that they'd like to find a way not to talk about it at all. That was the core issue last week at a meeting* at the National Human Genome Research Institute (NHGRI) in Rockville, Maryland, where about 40 scientists and ethicists debated how to present the torrent of new findings from human gene sequencing studies to the public.

In different parts of the world, different gene mutations become advantageous and spread quickly through a population, making some variants more prevalent in particular ancestral groups. Some are innocuous enough—such as the emergence of lactose tolerance in farming populations. But there's already much debate over the use in medicine of findings of racial differences in the prevalence of genes associated with certain diseases. Many scientists predict that it won't be long before they have solid leads on much more controversial genes: genes that influence behavior—possibly including intelligence.

Everyone at the meeting agreed on the need for non-"fraught" terminology—"geographic ancestry," for example, instead of "race." But specifying such ancestries is also a minefield. "Amerindian," for example, is offensive to Native Americans, according to one speaker. "Caucasian" is also unacceptable because it implies racial rather than geographic ancestry. Some speakers even advised that it is inappropriate to refer to a "European allele" for lactose tolerance, because it also occurs in other groups.

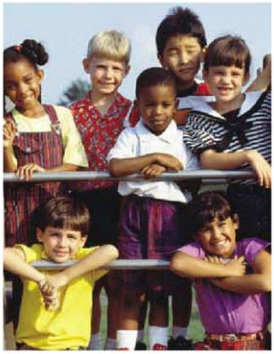
Participants acknowledged that however they characterize their findings, they can't control what the public makes of them. "When translated into popular culture, society reads whatever term we pick as 'race,'" said Timothy Caulfield, a health law professor at the University of Alberta in Edmonton, Canada. Carlos Bustamante, a population geneticist at Cornell University, said that when his group published a study in *Nature* this year indicating that European-Americans had more deleterious gene mutations than African-Americans, some publications touted the report as suggesting that blacks are fitter than whites.

Some tense moments came during a discussion of a paper on brain genes. In 2005, geneticist Bruce Lahn and colleagues at the University of Chicago in Illinois reported evidence for selection in mutations of two genes regulating brain development that are more common in Eurasians than in Africans (*Science*, 9 September 2005, pp. 1717 and 1720). They hypothesized that these mutations were related to the human cultural explosion some 40,000 years ago (*Science*, 22 December 2006, p. 1871). Celeste Condit, a professor of speech communication at the University of Georgia, Athens, criticized the way the papers were written, saying they could be seen as having a "political message embedded" in them: that the genes might contribute to racial differences in brain size and therefore perhaps to racial differences in IQ. Lahn denied any political message, telling her she was "putting words in [my] mouth."

Later, Lahn commented that some scientists "are almost like creationists" in their unwillingness to acknowledge that the brain is not exempt from selection pressures.

At the end of the day, Allen Buchanan, a philosophy professor at Duke University in Durham, North Carolina, warned the group against going overboard. "A visible, concerted effort to change vocabulary for moral reasons is likely to trigger a backlash," he said. There's "risk of … stifling freedom of expression in the name of political correctness," he said, and losing credibility in the process.

–CONSTANCE HOLDEN



CREDIT: PHOTOS.COM

Ancestry, not race. Researchers are grappling with how to communicate genetic data on differences among populations.

*Workshop on Ethical, Legal, and Social Issues in Natural Selection Research.

A Graduate Appetizer

The National Academies' eagerly awaited assessment of U.S. doctoral programs won't be released for another few months. But for the university administrators, faculty members, and graduate students whose lives are influenced by this mammoth undertaking, a description of what's new since the 1995 edition should be available in a few weeks. One wrinkle will be multiple ratings: In addition to a score from peers on overall quality, each of the 5000-plus programs at 212 universities will be ranked according to dimensions such as faculty productivity, diversity, and student outcomes. "They include factors the schools can influence and those that they can't really control," says study director Charlotte Kuh of the National Research Council. –JEFFREY MERVIS

Backing Up Hubble

The good news for NASA's Hubble Space Telescope is that controllers last week finally got a balky backup system to take over the job of sending images to Earth after the main system malfunctioned. The bad news is that managers have tacked on several months to the scheduled launch of a mission intended, among other things, to replace the faulty data system and avoid dependence on the backup. In a 31 October press conference, NASA officials said that preparing a replacement data system for launch and installation by astronauts will delay the repair mission, Hubble's last upgrade, until at least May 2009. –ANDREW LAWLER

A Basic Change for Korea

South Korea's academic researchers are smiling in anticipation of next year's budget. The Ministry of Education, Science, and Technology is seeking a 9.5% rise in its 2009 budget to $3.2 billion. "Korea has concentrated on applied science until now, but governmental policy is changing to increase support for basic research" to produce fundamental breakthroughs for technological development, explains Hang Sik Park, director of the ministry's Science and Technology Policy Planning Bureau. He says the proportion of governmental funding going to fundamental research could rise to roughly 28% of the total, up from about 25.6% this year. Other areas in line for big funding boosts include international collaborations, rising 75% to $34 million, and green technologies, with a 92% increase to $53 million. Other ministries have not yet announced their R&D requests, but the budget will go before the national assembly in December.

–DENNIS NORMILE

FOUNDATIONS

Economic Woes Threaten to Deflate Plans for 2009

Uncertainty has become the new norm for economic forecasters. But scientists planning next year's experiments want to know how the stock market turmoil, a credit crunch, and a recession will affect their research. It's an urgent question, especially with the U.S. government facing a yawning deficit and a likely squeeze on domestic spending. Among the first to feel the slowdown are charitable foundations and other philanthropies, which provide billions of dollars in funding to scientists each year, including support for innovative, risky research that the government may be reluctant to back. Some are scaling back; some say they're holding steady. Others say they cannot plan far ahead—not even to predict what the next 2 months, normally flush fundraising time, will bring.

"I've been in this business 30 years, and I've never seen an environment" like this, says Richard Mattingly, executive vice president and chief operating officer of the Cystic Fibrosis Foundation, which in 2008 gave out $199 million in research money. The foundation relies exclusively on fundraising. Mattingly, emerging from a board meeting last week, said he expects funding to drop next year, though he can't yet say how much.

One of the hardest-hit organizations so far is the Dr. Miriam and Sheldon G. Adelson Medical Research Foundation in Needham, Massachusetts, which has delayed $65 million in research funding to dozens of investigators for the second half of 2008 and 2009. Projects in melanoma, lymphoma, neurodegenerative diseases, inflammatory bowel disease, and others were ready to go, says Bruce Dobkin, the group's executive director and a neurologist at the University of California, Los Angeles. "Now, we're going to have to wait and see what happens." Dobkin says he doesn't know what, precisely, prompted such drastic action, and the foundation declined to comment further.

The Nature Conservancy, with more than 600 scientists on staff, decided 3 weeks ago to cut its current research budget by 10% and laid off some scientists. Peter Kareiva, the group's chief scientist, says international programs will be especially hard hit. The group is drawing up contingency plans in case further cuts are necessary.

Groups that rely mainly on contributions are nervously entering their peak fundraising season. Last week, the Multiple Myeloma Research Foundation (MMRF) in Norwalk, Connecticut, held its biggest gala of the year, at the Hyatt Regency Greenwich Hotel in Connecticut, with supermodel Cindy Crawford. Nine hundred people accepted; the event was expected to raise $1 million—impressive, but below the $1.5 million originally hoped for, says Scott Santarella, the group's chief operating officer. MMRF scaled back its research funding several months ago for 2008, cutting it from $17 million to $15 million, but expects to bring it back up to $17 million in 2009. The group, like many charities, typically raises 40% of its money in the last quarter of the year.

Similarly, the Michael J. Fox Foundation for Parkinson's Research held its star-studded gala this week in economically battered New York City, with the English rock band The Who performing. Leaders hope to raise a bit over $4 million from that event, down from last year's $5 million, says co-founder Debi Brooks.

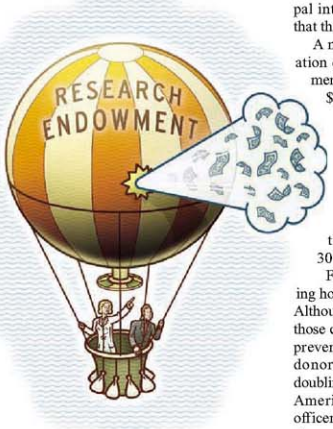


ILLUSTRATION: PETER HOEY

For organizations that live off endowment income, the drop in their value can be dizzying: The Burroughs Wellcome Fund fell from nearly $700 million at the end of July to $540 million last Friday, and the Bill and Melinda Gates Foundation lost $3.6 billion between the beginning of this year and the end of September, to end with $35.1 billion. The Howard Hughes Medical Institute's (HHMI's) worth fell from $18.7 billion in August 2007 to $17.4 billion at the end of August this year—and that was before the big drop in the stock market. (Neither the Gates Foundation nor HHMI would release current figures.) "Sometimes you go into a meeting and by the time you come out the endowment's gained $10 million, and by the end of the day it's lost $20 million," says Burroughs Wellcome spokesperson Russ Campbell, describing the wild gyrations in the market.

HHMI is required by law to distribute 3.5% of its assets each year, and foundations like Burroughs Wellcome must give out 5%. This is normally not a problem because these groups offset the outflow with investment gains, keeping their principal intact. Not all may be able to manage that this year.

A mid-September survey by the Association of Small Foundations (ASF), whose members have an average endowment of $20 million and give away $1 million each year, found that 84% said their endowments had dropped this year. But, responding days after the investment bank Lehman Brothers collapsed, 64% said they plan to maintain or increase grant budgets in 2009. That said, "I do get e-mails that say, 'Oh my gosh, we're down 30%,'" admits Tim Walter, ASF's CEO.

Fundraisers, meanwhile, are considering how to persuade donors to keep giving. Although many will continue to send checks, those checks may be smaller than before. To prevent that, and to stem the departure of donors altogether, many groups are redoubling their communication efforts. At the American Cancer Society, chief medical officer and oncologist Otis Brawley recently disseminated a list of 10 scientific discoveries funded with ACS dollars. "We have not made any plans right now to decrease our funding for cancer research," says Brawley, and in fact he says research funding is up about 5% this fiscal year, which began in September, over last. But although he doesn't work closely with ACS fundraisers, "I see those guys on the elevator, and they're not happy."

—JENNIFER COUZIN

With reporting by Jon Cohen.

17q21.31: Not Your Average Genomic Address

This one region of chromosome 17 has had a storied history, with changes in its DNA of import to human evolution and disease

For most of us, 17q21.31 is a meaningless alphanumeric. For geneticists, it's a genomic postal code identifying a region of chromosome 17. But for Tjitske Dansen, a Dutch mother of three, it's an answer for which she waited 17 years. From birth, her oldest daughter, Anne Zandee, had trouble. "She kept lagging in many respects: walking, talking, growing," Dansen recalls. For a while, the toddler had epileptic seizures. Weak jaw muscles cause Zandee to drool; weak back muscles may have contributed to her scoliosis. "But we never knew what was wrong with her."

Four years ago, an orthopedics doctor referred Zandee to Bert de Vries, a clinical geneticist at Radboud University Nijmegen Medical Centre (RUNMC) in the Netherlands, to try to find a genetic explanation for the scoliosis. "There had been so many studies, and they never found anything, so we didn't think anything would come of it," says Dansen. "We didn't hear anything from De Vries for a year and a half, when suddenly he called us." He told them Zandee was missing a piece of chromosome 17; to be exact, a piece of 17q21.31. Zandee is now one of 22 documented cases of a new genomic disorder. "We were happy to find out," says Dansen. But, "of course we had never heard of 17q21.31 before."

Among geneticists, however, 17q21.31 has been gaining notoriety for almost 20 years. Its half-dozen genes include one controversially implicated in Alzheimer's disease and firmly tied to other dementias. More recently, researchers excavating this single chromosomal address, located about 19 million bases down the "q," or longer arm, of chromosome 17, have uncovered a tumultuous past. Here, vulnerable DNA has gone astray to cause mental retardation, learning disabilities, and even cancer. Genes hide within genes, and variation in this sequence even suggests to a few researchers that our species interbred with Neandertals. "It's probably one of the most bizarre and fascinating regions of the human genome," says Evan Eichler, a geneticist at the University of Washington, Seattle.

Zoom, zoom

The most famous gene that lives at this address is *MAPT* (*microtubule-associated protein tau*). Tau first drew neuroscientists here because it is the protein that gets jumbled together to form

DNA locator. Under a microscope, gene-rich and gene-poor regions stain differently, creating readily defined and labeled genomic addresses. 17q21.31 is in red.

CREDITS: COURTESY OF ROB ZANDEE; SOURCE: GENE CARDS

Short on DNA. From birth, Anne Zandee's development lagged. A deleted piece of chromosome 17 is to blame.

neurofibrillary tangles in the brains of patients with Alzheimer's disease. But even though Athena Andreadis, now at the University of Massachusetts Medical School's Eunice Kennedy Shriver Center in Waltham, and her colleagues cloned *MAPT* in humans in 1992, neither they nor others have been able to find mutations that could explain Alzheimer's. Most considered further investigations a waste of time and lost interest in 17q21.31.

> *"It's probably one of the most bizarre and fascinating regions of the human genome."*
>
> —EVAN EICHLER, UNIVERSITY OF WASHINGTON, SEATTLE

But John van Swieten of Erasmus University Medical Center in Rotterdam, the Netherlands, was eyeing that gene region with another disorder in mind: Pick's disease, a neurodegenerative condition in which individuals become increasingly bored, listless, and incapable of relating to others. Personal hygiene fails, emotions falter, and symptoms become progressively worse until full-time care and supervision are required. In this disease, also called frontotemporal dementia (FTD), the frontal lobe of the brain shrinks and tangles form.

In 1994, Kirk Wilhelmsen and Timothy Lynch of Columbia-Presbyterian Medical Center in New York City established a link between FTD and 17q21.31 by evaluating how the disease was inherited in one large family. Four years later, Van Swieten, Erasmus geneticist Peter Heutink, and Michael Hutton, now at Merck Research Laboratories in Boston, pinpointed mutations in *MAPT* responsible for 10% of the cases of this disease.

Suddenly, the gene had sex appeal. "It provided a rationale for why tau was important in Alzheimer's," and it became possible to develop mouse models to study tau's effects, recalls Hutton. As a result, "a lot of people moved to the field," says Van Swieten.

Hutton, who now devotes his career to looking for potential Alzheimer's disease therapies that target tau tangles, was investigating yet another tau-related disease. In 1999, while sequencing the *MAPT* gene from patients with progressive supranuclear palsy, he and his colleagues noticed something odd. "We got interested in it almost as a piece of DNA rather than its relationship with the tangles," recalls Hutton's collaborator, John Hardy of University College London.

Most chromosomes undergo recombination: During cell division, bits of one chromosome swap places with comparable bits of the matching chromosome, introducing small differences in the DNA sequence from one generation to the next and between one individual and another. The pattern of those differences is called the haplotype. What struck Hutton, Hardy, and their colleagues was that there seemed to be two very distinct haplotypes in the *MAPT* region. One, dubbed H1, seemed to be slightly variable, indicative of some recombination. But the sequence of the other, H2, was nearly identical across about 1.3 million bases in everyone with that haplotype, at least at all of the bases they examined. "It was inherited as one long lump of DNA," Hardy explains.

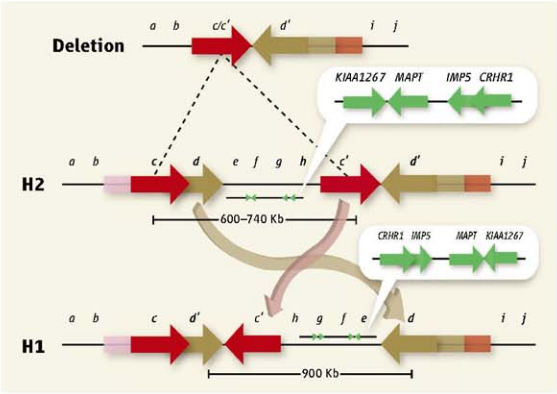
Hutton and Hardy realized there was something very odd about H2. "There were clearly unusual structures in or close to the boundary of the haplotype block," Hutton recalls. Researchers in Iceland were coming to a similar realization, and eventually they scooped the British group in making a startling determination: Almost a million bases in H2 were pointed in the wrong direction.

Kári Stefánsson and his colleagues at deCODE Genetics in Reykjavik, Iceland, had also noticed the lack of variability along 17q21.31 in some individuals. When Stefánsson's group took a close look at the reference human genome sequence at this location, they realized that the sequence, which had involved deciphering DNA from multiple individuals to come up with a consensus genome, contained bits of both H1 and H2. So, they went back to the drawing board to sort out the differences between the two.

A comparison of separate H1 and H2 sequences revealed that H2 has a 900,000-base stretch of 17q21.31 that is inverted relative to H1, the deCODE group reported in 2005. The boundaries, or breakpoints, of the inverted region consist of low-copy repeats, blocks of DNA duplicated multiple times. Based on a comparison with chimpanzee DNA from the same region, the researchers concluded that the second haplotype emerged at least 2 million years ago.

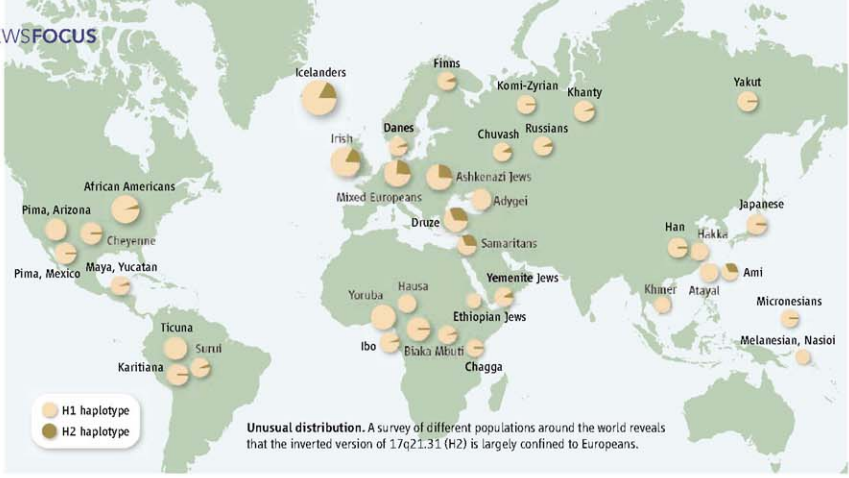
The haplotypes were not evenly distributed, however. Most people are H1. Stefánsson and, independently, Hardy's group found H2 almost exclusively in Europeans, at a frequency of about one in five. "Since the inversion is largely restricted to Caucasians, we all thought the ancestral state would be the H1 orientation," says Eichler. Indeed, the deCODE data suggest that once the inversion occurred, H2 spread because it provided a reproductive edge, says Stefánsson: Women with H2 had more children than women with H1, they reported in 2005. They saw a similar, but less clear-cut, trend for men. These results implied that H2 was under positive selection and should be on the rise.

There was a problem with this scenario, though: Some data indicated that H2 predated H1. In August, Eichler and his colleagues showed that was indeed the case. Eichler's group sequenced both H1 and H2 and carried out a detailed comparison among



Flip and fall. The H2 version of this genomic region has genes (green) and duplicated regions (thick arrows) facing the wrong way compared to H1. This orientation predisposes H2 to losing a gene-rich section of DNA (Deletion).

CREDIT: ADAPTED FROM LUPSKI, *NATURE GENETICS* 38, 1141 (2006)



Unusual distribution. A survey of different populations around the world reveals that the inverted version of 17q21.31 (H2) is largely confined to Europeans.

the two human versions of the region and the same stretch of DNA in chimpanzees, macaques, and orangutans. All three macaque species they examined and the Sumatran orangutan carried only the inverted version. The two chimp species carried a mix of inverted and non-inverted copies, with the inverted version predominating, and the Bornean orangutan has both as well. H2 is the more ancient haplotype, Eichler and his colleagues concluded in a paper published online by *Nature Genetics* on 10 August. "It's an amazing result," says Hutton.

The sequence comparisons also reveal that independently in humans, chimps, and orangutans, this 900,000-base region has reoriented itself into the H1 orientation, which explains why Eichler found both orientations in these primates. "This bit of DNA has been flip-flopping up and down. There must be an evolutionary reason for that, but we don't know what it is," says Hardy.

Eichler suspects that when H1 appeared, it somehow provided a strong fitness bonus and became much more common over time at the expense of H2. In Africans, H2 almost disappeared, except in the relatively few people who migrated to Europe 50,000 to 100,000 years ago. Then, for as-yet-unknown reasons, H2 provided its own advantage in the European population—as Stefánsson's data show—and the pendulum has begun to swing in the other direction.

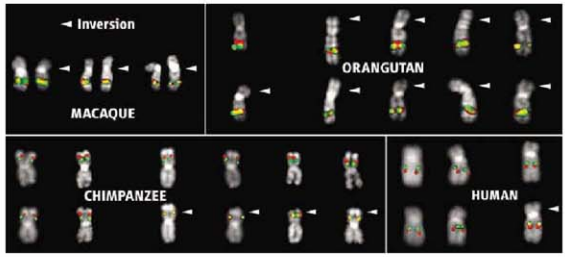
Hardy and, to a lesser extent, Stefánsson give credence to a more extreme explanation for the distribution of H2. Hardy thinks that H2 had disappeared from the modern humans moving out of Africa to populate the Northern Hemisphere but not from Neandertals, who reintroduced the inversion into the European gene pool through interbreeding with *Homo sapiens* 28,000 to 40,000 years ago. This view is not supported by the genetic evidence emerging from sequencing Neandertal DNA, and "I realize it's an off-the-wall idea," says Hardy. But he nonetheless thinks it's plausible.

Whatever happened, about 50,000 years ago, H2 went haywire, with duplicated regions begetting ever more duplicated regions. Low-copy repeats can destabilize a chromosome by confusing the DNA recombination machinery and causing the repeat regions to be copied extra times. Repeats can also cause skips, resulting in DNA between repeats getting left out. This had happened in H2 but not as much in H1. H2 has 441,000 bases' worth of repeats at the boundaries of the inverted DNA, compared with 169,000 bases in H1. H2 also carries extra duplications within its boundaries and is organized in such a way as to predispose the sequence to further rearrangement.

Lost DNA

As Dansen and her daughter Zandee know all too well, those extra duplications can spell trouble. They were the tip-off, not just for De Vries but also for other researchers trying to understand mental retardation, that drew them to the microdeletion responsible for Zandee's syndrome.

In 2002, Eichler and his colleagues were cruising the genome in search of repeats, or segmental duplications—nearly identical stretches of genome at least 10,000 bases long, each separated by 50,000 to 10 million bases—thinking they might mark places where the genome was in disarray and causing



Which came first? Readily distinguishable red and green tags merge and look yellow in chromosome 17 containing inverted DNA. Labeled macaque, chimp, orangutan, and human chromosomes reveal that the inversion dates deeper in the primate tree than the noninverted version.

CREDITS: ADAPTED FROM HREINN STEFANSSON, ET AL., *NATURE GENETICS* 37, 129 (2005); MICHAEL ZODY ET AL., *NATURE GENETICS* ADVANCE ONLINE PUBLICATION; DOI 10.1038/NG.193

disease. They came up with 130 possible problematic spots, then investigated those spots in 290 people with mental retardation. They found 16 rearrangements, including four people with a piece of 17q21.31 missing. Using microarrays, they figured out that when the missing DNA dropped out, it took a half-dozen genes with it, including *MAPT*. The breakpoints are two 38,000-base low-copy repeats flanking the DNA deleted in these individuals.

Parents have the inversion, which is necessary to set up the repeats in such a way that deletions become more likely. "Some think it's the inversion itself that's the culprit, but it's not," says Eichler. It's the large number of repeats and their orientation that make 17q21.31 vulnerable.

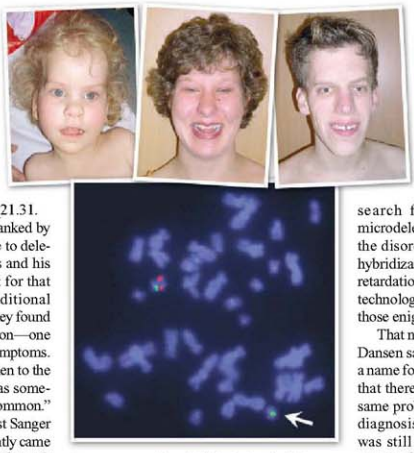
De Vries came to this microdeletion by a different route. Eager to help parents understand the basis of unexplained mental retardation in their children, De Vries and his colleagues initially screened 340 patients using a technique called microarray-based comparative genomic hybridization to detect genomic rearrangements too small to see by simply staining the chromosomes. In one, they detected a missing piece of 17q21.31.

Because the missing piece was flanked by low-copy repeats that might give rise to deletions in other individuals, De Vries and his colleagues designed a probe to test for that missing piece and screened an additional 840 mentally retarded individuals. They found two more people with the same deletion—one was Zandee—and the same set of symptoms. "We went first to the genotype and then to the phenotype," says De Vries. "This was something new, but it will become more common."

Nigel Carter of the Wellcome Trust Sanger Institute in Hinxton, U.K., independently came across this microdeletion syndrome through queries to a database called DECIPHER. Entries include comparative genomic hybridization results, along with clinical descriptions of the symptoms of the people tested. "Many of us as clinicians may see one of these kids in our lives, but [these researchers] got the same descriptions with the same array findings from three [entries]," says James Lupski, a geneticist at Baylor College of Medicine in Houston, Texas.

The three teams published independent reports back to back in 2006 in *Nature Genetics*. Now they have joined forces to describe 22 patients in molecular and clinical detail in a paper published online 15 July by the *Journal of Medical Genetics*. They calculate the prevalence of this new genomic disorder to be 1 in 16,000 newborns, and it may account for up to 0.64% of unexplained mental retardation in Europeans. "This is the first novel microdeletion syndrome identified and one of the most frequent ones," says collaborator Joris Veltman, a molecular geneticist at RUNMC.

The deleted region contains six genes, and at this point, they don't know which loss matters the most. Even so, "we've gone from 2 years ago not even knowing the syndrome existed to having [dozens of] kids [diagnosed]," says Lupski. "We're going to see that more and more and more." Last year, Danish clinical geneticists came across a patient with unexplained mental retardation whose abnormality was an extra copy of what was deleted in De Vries's patients.



Common cause. These individuals share facial features indicative of a DNA deletion, visualized by the absence of a red tag in a patient's stained chromosomes.

CREDITS: DAVID KOOLEN *ET AL.*, *NATURE GENETICS* **38**, 999 (2006); SHARP *ET AL.*, *NATURE GENETICS* **38**, 1038 (2006)

Still a puzzler

Despite this quick success, 17q21.31 is still slow to give up its secrets. It is clear that both haplotypes have their pitfalls: H1 increases the risk of progressive supranuclear palsy and other neurodegenerative diseases, likely by increasing the production of *MAPT*, and H2 increases the chances that offspring will have mental retardation because of a microdeletion. But at every turn, this genomic address proves a little more complicated.

Consider the elusive Alzheimer's connection, where no causative *MAPT* mutations have yet been found. Frustrated, Christopher Conrad, a neurogeneticist at Columbia University, began looking for other undiscovered genes in that region. In 2001, he found a very tiny one inside *MAPT* that bears no resemblance to any known gene. "It's one of the few examples of a gene within a gene," says Conrad. He named it *Saitohin*, after the deceased adviser who helped get him started on the project, and has spent the past several years trying to figure out its role. The gene seems to have appeared first in primates, and Andreadis, who is collaborating with Conrad, has determined that it interacts with a protein involved in antioxidation. It seems to lead to alternative splicing of *MAPT*, which may result in a version of tau that is more likely to aggregate into tangles. "Given the appearance only in primates, it's tempting to say the gene could have something to do with brain development," says Conrad.

Likewise, Stefánsson is frustrated by 17q21.31's enigmatic connection to psychiatric disorders. "We've done a lot of work to see what the risk [of the inversion] is to schizophrenia, but we have not succeeded yet," says Stefánsson.

De Vries is continuing to search for more individuals with the microdeletion syndrome and to characterize the disorder. Before comparative genomic hybridization, about half the cases of mental retardation went unexplained. Now, this new technology is making sense of about 10% of those enigmatic cases.

That makes a big difference to the parents. Dansen says her family was just glad to have a name for their daughter's disorder and to see that there were others just like her with the same problems. For at least one mother, the diagnosis brought good news. Her toddler was still not walking, but De Vries could reassure her that the others had also been slow to walk but did so eventually. "When I explained that to the mother, she was very relieved," says De Vries.

Now almost 20, Zandee plays in a special band, works in a canteen, and paints. Eventually, she will move from her parents' home to a group house with others with mental handicaps. "I will keep following the research," says her mother, although she's not sure what more it will tell her. But she knows that by tracking Zandee's progress, De Vries will learn a lot about adult diseases associated with the syndrome and even about life expectancy. "My son recently asked, 'How long can she live anyway?'" says Dansen. "We have no idea. Nobody does." **–ELIZABETH PENNISI**

With reporting by Martin Enserink.

NEUROTECHNOLOGY

Engineering a Fix for Broken Nervous Systems

A recent meeting on neural prosthetics provided an update on progress and some interesting digressions

PALO ALTO, CALIFORNIA— "I believe we're at the beginning of a new age of neurotechnology," Brown University neuroscientist John Donoghue told researchers who gathered here recently to discuss the state of the art in neural prosthetics, surgically implanted devices designed to restore sight to the blind, hearing to the deaf, and movement to paralyzed people. The idea of engineering a fix for nervous systems that can't heal themselves continues to spur both hope and hype; the meeting here at Bio-X, Stanford University's interdisciplinary research center, provided a glimpse of where the technology really stands. It also prompted frank discussions of current challenges and some fascinating, if slightly tangential, dinner conversations.

If the age of neurotech is indeed upon us, Donoghue is one of those ushering it in. In 2001, he co-founded a company (Cyberkinetics) to develop and commercialize brain-computer interfaces. He and colleagues made headlines with a 2006 *Nature* report describing their work with Matthew Nagel, a young man paralyzed by a knife attack that severed his spinal cord. Surgeons implanted a 4 × 4–millimeter chip studded with 100 hair-thin electrodes into the part of Nagel's motor cortex responsible for planning arm movements. Now, as Nagel imagines moving his arm, a computer infers his intentions from the neural chatter. Videos accompanying the paper showed Nagel moving a cursor to operate an e-mail program and moving the fingers of a prosthetic arm. *Nature* apparently bleeped out Nagel's candid reaction when he first saw the hand respond to his thoughts: "Whoa, holy shit!" he says in an uncensored version Donoghue played at the meeting.

Three more patients, including one suffering from amyotrophic lateral sclerosis, have now received implants. All have been able to use the thought-controlled cursor without any training, Donoghue said. But video clips of their efforts showed that the cursor's movement is plodding and wobbly. When Nagel attempts to draw a circle onscreen, the result is subpar. "We're asking him to draw a circle with 24 neurons," Donoghue explains. "When we do something like that, we're using millions." Brown computer scientist Michael Black has developed algorithms to reduce the wobble—but so far the tradeoff is an even slower cursor.

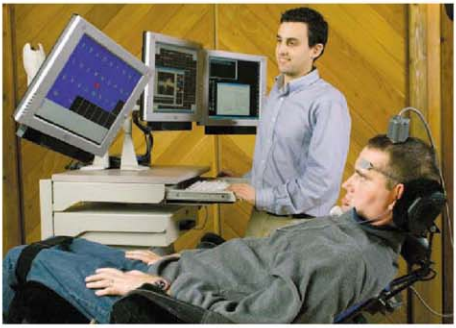
Other presenters described the potential for prosthetic devices for people deprived of hearing or sight. Stanford University Medical School otolaryngologist and surgeon Nikolas Blevins gave a brief history of research on cochlear implants, beginning with a seminal, if ill-advised, experiment by Italian physiologist Alessandro Volta circa 1790. Volta connected two metal rods to a battery and stuck them into his ear canals. Apparently unharmed, he reported hearing something like water boiling, thereby demonstrating that electrical stimulation could produce the sensation of sound.

Today's cochlear implants have restored hearing to tens of thousands of people but still have drawbacks. One of Blevins's patients, an articulate middle-aged woman with a trace of a British accent, said her implant "gave me back my life." But she still struggles to follow a conversation in a noisy restaurant and can't appreciate music. "It's just terrible, like honky-tonk piano or just bass and no melody," she said. The likely problem, Blevins said, is that individual nerve fibers in the cochlea normally respond to a narrow range of frequencies, but the electrodes in the implants stimulate many fibers at once.

Even so, cochlear implants are far ahead of retinal prosthetics, neuro-ophthalmologist Joseph Rizzo of Harvard Medical School in Boston told the audience. So far, about 50 people have received retinal implants, which transmit signals from a tiny camera to an array of electrodes attached to the retina. Patients tolerate the implants well, but exactly what they're able to see is difficult to know because the companies making the implants have been reluctant to release their data.

One of the most surprising exchanges occurred over dinner. Vilayanur Ramachandran of the University of California, San Diego, who had captivated the audience earlier with case studies of neurological curiosities, was about to tuck into his salad when he was interrupted by a tap on the shoulder. "Are you the guy who did that transgender study?" asked Stanford neurobiologist Ben Barres. He was. In a paper last year, Ramachandran hypothesized that transgendered people who have reassignment surgery might be immune to the "phantom penis" phenomenon. Just as many people who have had an arm amputated retain a vivid sense that the arm is still there, he explained, about 60% of men who have their penis amputated for cancer experience a phantom penis. He believes such sensations arise because the brain's representation of the body still has a place for the missing appendage. But does the brain's body representation include a penis for a woman born into a man's body? Ramachandran thought not, and a preliminary survey backed him up: Transgendered people were far less likely to report phantom penises (or breasts, in the case of female-to-male operations).

"That fits my experience exactly," said Barres, who is transgendered, adding that he'd heard similar stories from other transgendered people. Ramachandran seemed relieved. He said he'd gotten flak from some psychologist colleagues who didn't like his suggestion that some aspects of transsexuality could be explained by innate differences in the brain's body map. "I have a name for that," he said. "I call it neuron envy." **–GREG MILLER**



Think about it. Researchers are testing neural prosthetics that would enable paralyzed people like this man with ALS to control a cursor with their thoughts.

CREDIT: PHOTO BY MCKEEPHOTOGRAPHY.COM

BIOMEDICAL RESEARCH

The Graying of NIH Research

Many scientists who got their first grant in the 1950s or 1960s are still going strong. How do they view affirmative action for first-time grantees?

Roger Unger found himself drawn to research as a young internal medicine resident sometime around 1950, when he was treating diabetes patients in New York City. He had a controversial idea—that glucagon, a biomolecule then thought to be a contaminant in insulin made from ground-up beef and pork pancreases, might actually be a key hormone affecting blood sugar. Unger and colleagues in Texas had no direct evidence for this, but "we had the tools to answer the question, and we needed some money," Unger says. So at age 32, Unger applied for and won a research grant from the U.S. National Institutes of Health (NIH).

It didn't seem hard, "because I didn't know what I was doing back then," says Unger, now at the University of Texas (UT) Southwestern Medical Center in Dallas. Several years later, Unger's group published a landmark paper pinning down glucagon's role as a counter to insulin in regulating blood glucose levels: Glucagon tells cells to make more glucose, whereas insulin brings excess amounts down.

Today, at 84, Unger still runs a lab that enjoys NIH support. Now he's motivated by a new public health problem—the "meltdown" in Americans' health due to rising rates of obesity, he says. He's deep into exploring a concept his lab put forward: that a surfeit of lipids in obese people contributes to diabetes and heart disease. "I always decided I would retire when I ran out of ideas. But I didn't. The ideas got more exciting," says Unger.

That researchers such as Unger are still going strong in their 70s and 80s—and pulling down grants—would have been unheard of 3 decades ago. Because the biomedical enterprise was young and most universities had mandatory faculty retirement until 1994, there were few NIH-funded principal investigators older than 70 in 1980. But in 2007, there were at least 400 of them, according to NIH data. Indeed, NIH projections indicate that grantees over 68 could outnumber scientists under 38 by 2020 (see graph). The average age for obtaining a first NIH research grant is now 42. These data worry some research leaders, who have called on the community to reverse the trend. They have also contributed to a sense of crisis at NIH, which is taking steps to bolster the number of new investigators and slow the rising age of the average NIH-funded scientist, now 51 (see p. 834).

NIH officials say they do not mean to discourage very senior investigators from continuing in research. "It's not young against old," says NIH Director Elias Zerhouni. The number of investigators over 70 among those funded by NIH is a tiny fraction of the total, and some of them are incredibly productive into their later years—for example, Nobel laureates Eric Kandel and Paul Greengard are both around 80. Furthermore, peer review is supposed to winnow out any whose productivity has decreased. Scientists who have served on study sections generally say they haven't noticed a bias in favor of keeping older scientists' labs running, even if many of the reviewers are the applicants' former students and postdocs.

At the same time, concerns about the aging biomedical work force have prompted NIH to deploy what amounts to an affirmative action plan, setting numerical targets at each institute for grants to newcomers. To sample the community's views of this plan, particularly among those who won't benefit from the initiative, *Science* interviewed a score of researchers 70 or older. Most were drawn from a list of NIH investigators who have had the same basic NIH research grant, known as an R01, for at least 35 years, nearly all of them men. We asked: How does a very senior scientist decide when to shut down his or her lab? And does the current plight of young investigators influence their thinking? Most praised the idea of introducing fresh blood, but only about half said that they're ready to relinquish their own lab.

No time to quit

One strong theme—a sense that the review process was more interested in originality in the past—emerged in comments from this generation of scientists who applied for their first grants in the 1960s or earlier, often in their 20s or early 30s. It was a different game, they say. Not only did NIH have plenty of money to go around, but peer reviewers wanted ideas, not preliminary data. Microbiologist Samuel Kaplan, 74, of the University of Texas Medical School in Houston says he proposed studying a "newish" bacterium that he had never cultured. "If I submitted a proposal like that now, the study session couldn't stop laughing," he says. Peter von Hippel, 77, who earned a Ph.D. from the Massachusetts Institute of Technology in Cambridge at age 24 and then moved on to a postdoc there, found his grant waiting for him when he joined the Dartmouth Medical School faculty at age 28. "There was less to learn, and if you got on to a good project, things moved along pretty fast," says Von Hippel, now a professor emeritus and researcher at the University of Oregon, Eugene.

Some of these scientists were part of a

CREDITS: LEFT TO RIGHT: JASON KOSKI/CORNELL UNIVERSITY; KALMON ZABARSKY/BOSTON UNIVERSITY; UT SOUTHWESTERN MEDICAL CENTER

Lifelong passion. Harold Scheraga, 87, Phillips Robbins, 78, and Roger Unger, 84, are active researchers with NIH funding.

cadre who created the field of molecular biology. Others were pioneers in areas such as spectroscopy and protein chemistry. Forty or more years later, most have published hundreds of papers and trained scores of graduate students and postdocs. Many are members of the National Academy of Sciences. Some of those interviewed edit journals. (NIH intramural researcher Herbert Tabor, the editor of the *Journal of Biological Chemistry*, is nearly 90.) And many are still publishing in high-profile journals such as the *Proceedings of the National Academy of Sciences* and *Science*.

Most of those over 75 said they have cut back their research in recent years and stopped taking graduate students, who might be left in the lurch if their mentor developed health problems. Some have retired and are now emeriti, so their university no longer pays their salaries. Most say they are sympathetic to the funding difficulties faced by young investigators and support NIH's plans to target more grants to this group. "I couldn't agree more that we have to bring down the age of investigators," says Unger.

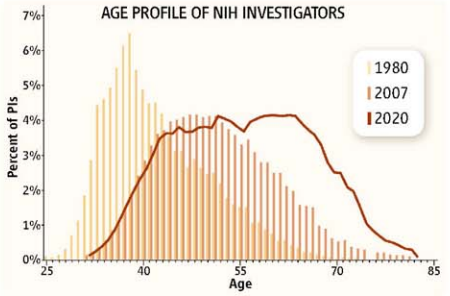
Representative of the nonretiring group is Cornell University protein chemist Harold Scheraga, 87, who may be the oldest NIH investigator. Since 1947, he has published more than 1200 papers, 20 of them in 2008. Scheraga is winding down an NIH grant for experimental work that expires in March 2009, which will free up lab space for a new faculty member, he points out. But he plans to continue with 10 workers on another NIH grant, the one that funds his theoretical study of protein folding, which he's had for 52 years.

"I'm very productive and making good progress," Scheraga says. "I'll keep going as long as I'm sane and my health is holding up. Only when somebody—my peers or myself—says that my science is washed up will I quit."

Some say that, like Unger, they're motivated by finding new research directions. The University of Pennsylvania's Robin Hochstrasser, 77, has a 14-person lab that is using lasers to study how protein structures change with time. "These techniques were only created 8 years ago. Close to 100 people are using them, and they started here," he says. But he praises NIH's new grants for young investigators and thinks setting targets for newcomer R01s is "reasonable … to ensure the future of medical research." John Dietschy of UT Southwestern, 76, says he has no plans to give up his R01 of 44 years on cholesterol metabolism, which ranked in the top 1% of proposals when it was last reviewed. "We're ahead of everybody in our field at the moment," says Dietschy. "As long as I'm having fun in the lab, we'll probably keep going."

The passion for doing research doesn't correlate with youth, some point out. "I think the people who are my age and continue to work in science have a certain amount of tenacity and they have a passion for it. I see the flame extinguishing in people in their 40s or 50s as much as people in their 70s," says molecular biologist E. Peter Geiduschek, 80, of the University of California (UC), San Diego. He says he will "keep doing research until somebody stops me from doing it." Like many others interviewed by *Science*, he says he can't imagine doing anything else.

Biochemist Carl Frieden, 79, of Washington University in St. Louis, Missouri, also says he will let peer reviewers tell him when it's time to close his lab. He says that although he's sympathetic to the struggles of young scientists, funding should be based strictly on scientific merit, not age. "We're the only profession judged by our peers every 3 to 5 years. If older scientists can pass that trial, I'm comfortable with that," he says.



Graying work force. NIH investigators are aging, and those over 68 could outnumber those under 38 by 2020.

SOURCE: NIH

Moving on

Others have decided to wind down. For molecular geneticist Robert Wells of Texas A&M University in College Station, who is just 70 but gave up his NIH grant and has been closing his lab for the past 2 years, the difficulties young investigators face were foremost in his thoughts. "If I and other old birds continue to land the grants, the [young scientists] are not going to get them," he says. He worries that the budget won't be able to support the 100 people "I've trained … to replace me." He will stay involved in science through advocacy.

Boston University biochemist Phillips Robbins, 78, has mixed feelings about his plans not to seek renewal of his grant when it ends in 3 years. He recently teamed up with a parasitologist to study glycosylation patterns in human parasites such as *Giardia*. "It's almost as though I've opened up a brand-new career," he says. But it's time, he says. "I think the folks who want to go out the door feet first, that that mindset is wrong. Once I reach 81, 82, it would be a poor decision for myself, for my university, and for students."

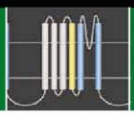
"It depends on what you're working on," suggests UC Berkeley biochemist Howard Schachman, 89, famous for fighting forced retirement at UC schools (*Science*, 14 September 1990, p. 1235). He says he let his last R01 lapse a few years ago only because his work studying a bacterial enzyme is out of date. "To what extent do you keep working and depriving young faculty of space in your department? I asked myself that question at 80 and decided I should keep going. But I couldn't do that today," he says. But Schachman, now emeritus, teaches the main biomedical research ethics course at Berkeley. "It's something that was interesting and important to me," he says.

For those researchers who do decide to leave the lab, the transition should be easier, says Harvard University molecular biologist Richard Losick, 65. He wishes there was more recognition for teaching and mentoring junior faculty members. "I don't think the culture of science fosters a graceful transition for aging scientists," says Losick, who says his own thoughts are to teach more in a few years. Others support the idea of giving retired faculty a small lab and encouraging them to keep up other activities.

Whatever their individual choices, the dilemma of how and when aging scientists should hang up their lab coats is only going to become more urgent. As Frieden points out, "It's rare to be as old as I, but there are going to be more of us."

–JOCELYN KAISER

With reporting by Rachel Zelkowitz.



LETTERS

edited by Jennifer Sills

Epigenomics: A Roadmap to Chromatin

IN THEIR LETTER "EPIGENOMICS: A ROADMAP, BUT TO WHERE?" (3 October, p. 43), H. D. Madhani *et al.* applaud the NIH for directing funds towards chromatin research, but argue that the Epigenomics Roadmap initiative (*1*) is ill-conceived and diverts funds from investigator-initiated proposals. However, their criticisms are more semantic than scientific, and they ignore the role that technology development has played in driving chromatin research. As recipients of grants awarded in this program, we would like to set the record straight.

We agree with Madhani *et al.* that epigenetic regulation is driven by transcription factor binding. However, studies of such regulatory processes have traditionally received strong NIH support, whereas the Epigenomics Roadmap aims to characterize the chromatin landscape that transcription factors act upon. Unlike transcription factors, which are diverse and often differ between eukaryotic taxa, chromatin components include histone variants and modifications that are essentially universal. Ultimately, transcription factors must act upon DNA packaged by histones, and essentially all eukaryotes use a common set of histone and DNA modifying enzymes, nucleosome remodelers, histone chaperones, and chromatin-binding proteins to facilitate transcription factor and polymerase action. We think that the NIH is justified in limiting this initiative to chromatin, and had some other term than "epigenomics" been used, there would be no basis for this complaint.

A more substantive concern is that this initiative diverts funds from investigator-initiated grants, corralling individual scientists "to work together under a more rigid, directed framework." However, 17 of the 22 grantees aim to develop novel tools and markers for chromatin research. Our three grants are high-risk, high-gain R21s; at $175,000 to $200,000 per year for 2 years, they are among the smallest NIH awards. Although we recognize that these funds might have been diverted from traditional programs of the NIH institutes that fund us (the National Institute on Drug Abuse, the National Institute of Diabetes and Digestive and Kidney Diseases, and the National Institute of Environmental Health Sciences), we believe that they deserve credit, not criticism, for investing in novel technologies for understanding chromatin.

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Reference

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Bacteria by the Book

THE NEWS STORY "THE BACTERIA FIGHT back" (Special Section on Drug Resistance, G. Taubes, 18 July, p. 356) clearly describes the current resistance of bacteria to antibiotics and the diminishing pipeline of new products to treat them. However, Louis Rice mistakenly attributes the cause of the problem to physicians in past decades treating patients for "7 days, 10 days, 21 days, with no real reason other than making the doctor more comfortable," when the pneumonias "get better after 2 or 3 days."

In fact, physicians who treated pneumonias for longer periods were following established good medical practice. Medical textbooks from 30 years ago (*1*) recommended treatment of pneumonias for up to 3 to 4 weeks. Even today's medical textbooks (*2*) emphasize the need to treat patients with most bacterial pneumonias for 2 to 3 weeks. *Streptococcus pneumoniae* pneumonia should be treated for 1 to 2 weeks, *Mycoplasma pneumoniae* pneumonia for up to 3 weeks to avoid relapse, and Gram-negative bacilli pneumonia for "a minimum of 1 to 2 weeks" (*2*).

In addition, it was standard teaching in past decades that the administration of an antibiotic for fewer days than the full course would lead to the development of antibiotic resistance, since the surviving organisms of a partially treated infection would be selected for the presence of resistance.

EDWARD TABOR

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Response

TABOR CITES RECOMMENDATIONS IN RESPECTED textbooks of medicine and pediatrics regarding durations of antimicrobial therapy for common infections. There is no dispute regarding the existence of the recommendations. The issue is the evidence upon which these recommendations are based. In the News story, "The bacteria fight back" (Special Section on Drug Resistance, G. Taubes, 18 July, p. 356), I intended to point out that the available evidence actually supports the administration of short courses of antimicrobial agents for the treatment of pneumonia. Studies in the 1940s documented the excellent response of pneumococcal pneumonia to 2 to 3 days of therapy (*1*, *2*).

More recently, a European study compared 3 days with 8 days of amoxicillin therapy for community-acquired pneumonia and found that the results were excellent and equivalent for the two treatment durations (*3*).

Many current recommendations on therapy durations for common illnesses arose without experimental basis and during a time when antimicrobial agents were considered, at worst, a therapeutically neutral choice. We now recognize that there is no free lunch—administration of antimicrobial agents always comes at a cost of increased resistance and superinfections with serious pathogens such as *Clostridium difficile*. Given the ample data indicating that the risk of resistance increases with the duration of therapy (*4*, *5*), we as scientific and medical communities have an obligation to determine, in a scientifically credible way, minimal durations of therapy for common illnesses. The National Institutes of Health has acknowledged this reality by issuing a Broad Agency Announcement to support studies to look at optimal antimicrobial use (*6*).

The concept that shortened courses of therapy promote the emergence of resistance is a curious one. In vitro, susceptible organisms almost always out-compete resistant ones when there are no antibiotics around to provide a selective advantage (*7*). I suspect that this concept became established early in the antimicrobial era, as an explanation for relapses of resistant tuberculosis after short-course streptomycin therapy. The reality of the relapses was clear. The cause, however, was not the short duration of streptomycin therapy, but rather the existence of streptomycin-resistant subpopulations at the start of therapy that became the predominant population (*8*). We acknowledge this reality today by our use of combinations of antimicrobial agents, rather than longer courses of single agents, to treat tuberculosis. The concept that continued administration of an antibiotic will prevent emergence of a pathogen that is resistant to it simply makes no sense.

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Environmental Agencies: Lessons Learned

PREVIOUS ATTEMPTS TO ESTABLISH AN INDEPENDENT, science-based, environmentally focused federal research agency, including the National Biological Survey and the National Institute for the Environment, have ended in failure. Now we are treated to calls for "An Earth systems science agency" (M. Schaefer *et al.*, Policy Forum, 4 July, p. 44). Not surprisingly, the same objectives are being discussed: the need for a response-driven, flexible, interdisciplinary agency and the current poor organization, collaboration, and funding among existing agencies. This is undoubtedly true, but creating an umbrella superagency will not fix federal research programs.

In the U.S. Geological Survey (USGS), biological research has been treated as a poor stepchild to the earth sciences, and there is little doubt this will continue in the Earth Systems Science Agency (ESSA). Funding has been cut or shunted to administration; talented researchers have been drowned in paperwork, micromanaged, politicized, and subject to inept and incompetent leadership; and collaboration has become more difficult. It is ironic that some authors of the ESSA proposal oversaw procedures that have crippled biological research in USGS.

Changing the name and organization will not correct problems in federal natural science and environmental research. Unless the command and control mindset is lifted to free the creative energies of its scientists, federal science agencies will continue to lose their most valuable assets, scientists, as frustration and lack of support take a toll. Until scientists are recognized as valuable assets rather than full-time equivalents, the ESSA will be outmoded before the 10 years it takes to quell the administrative bickering.

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Response

THERE MAY BE SOME TRUTH IN WHAT C. K. DODD writes, but history gives us important counter-examples. The creation of the National Oceanic and Atmospheric Administration (NOAA) in 1970 from existing agencies has led to better and stronger oceanic and atmospheric science, more applications, the sharing of a Nobel Prize, and numerous scientific awards. Today, there is a much stronger public and congressional awareness of environmental issues than at the time of the reorganizations he mentions.

Of course, not all of the bureaucracy, micromanagement, and command and control issues can be solved at once, and it is important to note that biology has been an equal partner in the problem faced by the entire U.S. Geological Survey (USGS)—a science organization in a budget-challenged management organization that has priorities other than science. We prefer to look on the positive side. The creation of an Earth Systems Science Agency (ESSA) provides the context to bring together synergistic subjects and researchers in an agency with a mission to provide societal benefits. We believe that this new context allows many, if not all, of the issues Dodd raises to be dealt with in an effective way so that researchers can prosper.

We have also emphasized the need for at least 25% of the agency's budget to be provided to grants, contracts, and cooperative agreements with academic and nonprofit institutions, in coordination with the National Science Foundation. It will be important that grant funding decisions are made in a forum where considerations from all parts of earth system science can be balanced. Outreach and links with outside institutions should also help the internal structure.

With respect to the biological sciences, ESSA would allow biodiversity and related issues to be examined in the context of both terrestrial and marine systems. Furthermore, ecosystem-based research and monitoring would be advanced by integrating atmospheric, oceanic, terrestrial, and freshwater biological and physical science programs.

Finally, although Dodd focuses on research, we note that our Policy Forum proposed a broader range for the new institution, reflecting the missions of both NOAA and USGS in research, monitoring, communication, and decision support systems that