

## EDITORS' CHOICE

edited by Gilbert Chin

## BIOMEDICINE

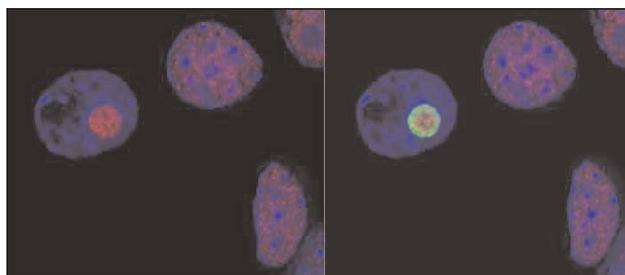
Neurodegeneration:  
Expanding on a Theme

At least nine neurodegenerative diseases are caused by mutant proteins containing expanded polyglutamine (PG) repeats, which form intracellular aggregates and are neurotoxic. Recent investigations have indicated that the source of this neurotoxicity may lie in the capacity of the PG repeats to disrupt the transcriptional machinery.

Additional support for this hypothesis is provided by new research with fruit fly, yeast, and mammalian cell culture models of neurodegeneration, which shows that expanded PG repeats alter histone acetylation, a protein modification that plays a key role in transcriptional regulation. Experiments by Steffan *et al.* revealed that, through direct binding, the expanded PG repeats inhibit the enzymatic activity of acetyltransferases involved in histone acetylation, and that when expressed in a neuronal cell line, these repeats reduce the level of histone acetylation. Consistent with this, Hughes *et al.* found that expression of expanded PG repeats in yeast shifted the pattern of transcribed genes to a pattern characteristic of mutant yeast strains with defects in histone acetylation. Finally, in a study of cultured mammalian neurons, McCampbell *et al.* found that targeting of expanded PG repeats to the nucleus caused cell death that was associated with decreased histone acetylation and that could be mitigated by overexpression of the histone acetyltransferase CBP.

In all cases—and most significantly in the fruit fly models of neurodegeneration studied by Steffan *et al.*—PG toxicity could be slowed or prevented by treatment with small-molecule histone deacetylase inhibitors. Thus, these drugs, which already are in clinical trials for other disorders, could have therapeutic potential for neurodegenerative diseases. — PAK

*Nature* 413, 739 (2001); *Proc. Natl. Acad. Sci. U.S.A.* 98, 13201; 15179 (2001).



Nuclear-targeted PG repeats (green) sequester CBP (red).

only a few hundred years. Recent studies have begun making a more explicit connection between solar activity and Earth's climate by linking accurately dated changes in the production of cosmogenic nuclides, such as  $^{14}\text{C}$  or  $^{10}\text{Be}$ , which are produced by cosmic rays in Earth's upper atmosphere, to distinct climate events. Björck *et al.* present an intriguing example from the early Holocene. A number of climate records throughout the Northern Hemisphere show a dramatic cooling episode about 10,300 years ago. This event can be calibrated precisely using tree ring and other high-resolution records and corresponds with the beginning of a marked change in the  $^{10}\text{Be}$  flux. — BH

*Geology* 29, 1107 (2001).

## APPLIED PHYSICS

## Consistent at Tap

Several proposals have been put forward for ultrahigh density memories in which reading or writing operations involve the use of an atomic force microscope (AFM), which can map surface topography with high resolution when operated in the "tapping mode." One drawback, however, is that the tip tends to take a somewhat chaotic path during imaging, and many scans need to be averaged to achieve consistent resolution. Fein *et al.* evaluate the ability of an AFM with an all-metal conducting tip operating in tapping mode to inject current pulses into a conducting gold substrate. Currents pulses up to 10 microamperes per square centimeter can be injected each time the tip comes into contact with the surface, which is sufficiently high to modify the surface by heating or to reverse the magnetization in a ferromagnetic region. These pulses were almost identical in shape even when tapping at the same position.

CONTINUED ON PAGE 17

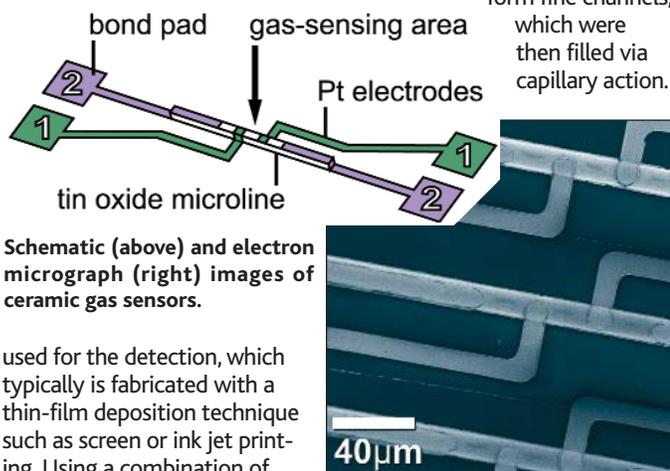
## MATERIALS SCIENCE

## Tiny Gas Sensors

One aspect of the development of smaller microelectromechanical systems has been the creation of low-powered chemical sensors. For solid-state gas sensors, an active ceramic layer is

soft lithography and photolithography and a suspension of tin oxide particles, Heule and Gauckler create a sensor element on the micrometer scale, which is about two orders of magnitude smaller than current designs. The polymer template was placed on the substrate to

form fine channels, which were then filled via capillary action.



Schematic (above) and electron micrograph (right) images of ceramic gas sensors.

used for the detection, which typically is fabricated with a thin-film deposition technique such as screen or ink jet printing. Using a combination of

The ceramic particles were sintered and then connected to the device via platinum contacts. The tin oxide device showed sensitivity to both hydrogen and carbon monoxide down to 100 and 600 parts per million, respectively. It is envisioned that a variety of doped and undoped ceramics can be placed onto a single device to create a sensor array that would replace single gas sensors. — MSL

*Adv. Mater.* 13, 1791 (2001).

## CLIMATOLOGY

## Is the Crux Solar Flux?

Changes in solar activity may have significantly affected Earth's recent climate, but recent solar changes are thought to be small, and accurate irradiance measurements extend back only a few decades. Even sunspot records extend back

Such reproducibility should decrease the need for averaging and thus boost the bit rate of associated processes. — ISO

*Appl. Phys. Lett.* **79**, 3935 (2001).

## BIOCHEMISTRY

### Construction Sites

Enzymes that contain iron-sulfur clusters participate in diverse and essential cellular processes such as electron transfer and nitrogen fixation. In the cube-shaped [4Fe-4S] cluster, the iron atoms exist as mixed valence Fe(II)/Fe(III) pairs, and the sulfur atoms are in the sulfide ( $S^{2-}$ ) oxidation state. The fact that both  $Fe^{2+}$  and  $S^{2-}$  are metabolically toxic has led to the appreciation that assembly of this cluster likely involves multiple oxidation-reduction steps.

Krebs *et al.*, working on the nitrogen-fixing (Nif) system in *Azotobacter vinelandii*, show that sulfane sulfur ( $S^0$ ), which is produced by the cysteine desulfurase NifS, is combined with ferrous ion ( $Fe^{2+}$ ) to build first a [2Fe-2S] cluster and then a [4Fe-4S] cluster, which can be inserted into an apoenzyme. Assembly takes place on a dimeric protein designated NifIscA, which is the homolog of *Escherichia coli* IscA (iron-sulfur cluster), and these authors propose that sulfur reduction is coupled to iron oxidation. This use of NifIscA as a construction scaffold is reminiscent of the interaction between IscS, a cysteine desulfurase and the *E. coli* homolog of NifS, and IscU, the homolog of NifU. Smith *et al.* and Urbina *et al.* have shown that sulfane sulfur is transferred directly from the active site of IscS to cysteine residues of IscU in a parallel pathway for making [Fe-S] clusters. What distinguishes the scaffolding roles of IscA and IscU is not yet clear, but recent work by Schwartz *et al.* has revealed that the gene cluster *iscSUA* is regulated by the product of an upstream open reading frame *iscR*; the IscR protein itself binds a [2Fe-2S] cluster. — GJC

*Biochemistry* **40**, 14069 (2001); *J. Am. Chem. Soc.* **123**, 11103 (2001); *J. Biol. Chem.* **276**, 44521 (2001); *Proc. Natl. Acad. Sci. U.S.A.* **98**, 14895 (2001).

## MICROBIOLOGY

### Life in a Melting Pot

The pathogen *Helicobacter pylori* resides in the human stomach and can induce lifelong infections that cause gastric irritation, ulcers, and cancer. The long-term character of its tenacity enables a resident strain to benefit from genetic exchange

with recent arrivals. Falush *et al.* have collected 22 paired isolates taken an average of 2 years apart from patients in New Orleans and the Colombian Andes. Approximately 5 kilobases of sequence from each isolate were analyzed with a mathematical model in order to estimate the frequency and extent of recombination. The average size of the acquired DNA was relatively small, about 400 base pairs, and raises the possibility that *H. pylori* may be nonspecifically importing fragments of partially digested DNA, unlike bacterial recipients that discriminate between related and unrelated donors. Each pair of isolates was found to differ as a consequence of about 100 recombination events, or by about 3% of the genome. From the mutation rate, they calculate that *H. pylori* has colonized humans for 2500 to 11,000 years. The age of the human malaria parasite *Plasmodium falciparum*, as estimated by Tiskoff *et al.* and Volkman *et al.* (Reports, 20 July 2001, p. 455 and 482), lies within this range, as does the date for the origin of agriculture. — GJC

*Proc. Natl. Acad. Sci. U.S.A.* **98**, 15056 (2001).

## EVOLUTION

### Computer Dating

In many animal species, females select mates according to visual signals—showy plumage, courtship displays, etc. The detailed study of the mechanisms of such



A real male stickleback.

sexual selection is often hindered by the difficulty of obtaining sufficient sample sizes or by the compound ef-

fects of several signals operating simultaneously. Künzler and Bakker have developed computer animations of male stickleback fish to study female responses. In virtual males, a single trait can be varied while others are held constant, and the experiment can be repeated indefinitely. Female three-spined sticklebacks were exposed to virtual males that varied in size, throat coloration, and courtship display, revealing which of the traits—in isolation and in combination—elicited the most enthusiastic response. Sexual selection is a powerful evolutionary force, and virtual-imaging technology promises to open new channels for its investigation. — AMS

*Behav. Ecol.* **12**, 681 (2001).