

edited by Gilbert Chin

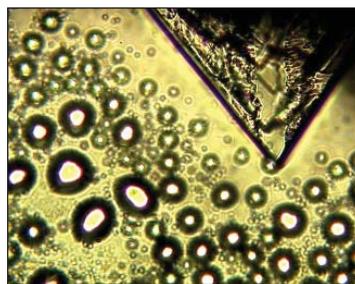
## CHEMISTRY

## Crystals via Liquids

Crystallization is used widely to isolate and purify molecules, but the early stages of nucleation and growth are not completely understood. Molecular dynamics simulations have suggested that a liquid-like state precedes crystal formation. A liquid phase has been observed to appear during crystallization of macromolecules, but evidence that small molecules behave similarly has been limited. Bonnett *et al.* observed liquid phase separation during crystallization of a methoxyacrylate from a water-methanol mixture as it cooled. Small drops of solute-rich liquid formed, and then crystals began to grow at the expense of the drops. This behavior is due not to kinetic effects but to a feature of the phase diagram that allows liquid-liquid phase separation before the onset of crystallization. — JFU

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Solute-rich droplets and growing crystals.



*Chem. Commun.* 2003, 698 (2003).

Asia since the first reported outbreak in Japan in the 1870s. All five genotypes identified occur simultaneously in Indonesia and Malaysia, whereas only evolutionarily more recent strains have spread out of this region. The Japanese epidemic was devastating and affected people of all ages, as flaviviruses do when they reach an immunologically naïve population. By contrast, in Malaysia, it is rarely epidemic, suggesting a long-standing association with humans here and pointing to the Indonesia-Malaysia region as the nidus of JEV. — CA

*J. Virol.* 77, 3091 (2003).

## ASTROPHYSICS

## A Star is Born

The first billion years of the universe [redshift ( $z$ ) greater than 6] was a time of great darkness and commotion. After inflation, there was mostly hydrogen and helium gas expanding into darkness. Residual ionization and primordial density fluctuations from the Big Bang led to clumping of this molecular gas and dark matter. The first sources of light, probably stars or quasi-stellar objects (QSOs), began to form around  $z \sim 30$ , and most of the hydrogen was reionized by  $z \sim 7$ . Observers are beginning to discover some of the earliest QSOs ( $z \sim 6$ ), and these ancient objects provide the most luminous markers for checking models of the formation of the early universe.

Using the Hubble Space Telescope, Freudling *et al.* have obtained near-infrared spectra of three QSOs ( $5.7 < z < 6.3$ ). The Fe/Mg abundance ratios are similar to or greater than that of the Sun, suggesting that massive galaxies (as opposed to galaxy mergers) with solar or supersolar Fe/Mg appeared within the first billion years. If the QSOs were triggered by supernovae, then

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## GEOPHYSICS

## Snow Job

The largest source of year-to-year variability of winter weather in the extratropical Northern Hemisphere is an oscillating pattern of atmospheric pressure that has poles near Iceland and in the subtropical North Atlantic, commonly called the Arctic Oscillation/North Atlantic Oscillation (AO/NAO). The AO/NAO directs the tracks of storms crossing the Atlantic, affecting temperature and rainfall in North America, Europe, and northern Asia. It has been thought that the pattern of interannual variability of the AO/NAO is random and a consequence of the internal dynamics of the climate system. However, it also has been noted that, over the past 30 years, the AO/NAO has exhibited a trend; this has led to the proposal that it is modulated by soil moisture, secular changes of atmospheric greenhouse gas concentrations, sea-surface temperatures, the stratosphere, or sea-ice cover. Saito

and Cohen add another ingredient to this olio by showing that continental-scale snow cover in North America and Eurasia varies with the atmosphere, leading the atmosphere by several months and influencing the AO/NAO on annual to decadal time scales. — HJS

*Geophys. Res. Lett.* 30, 1302 (2003).

## CHEMISTRY

## Quick Decisions on Catalysts

The development of new polymerization catalysts, especially for specific copolymerizations of two distinct monomers, can be an expensive trial-and-error process. Bousсие *et al.* use microscale, high-throughput

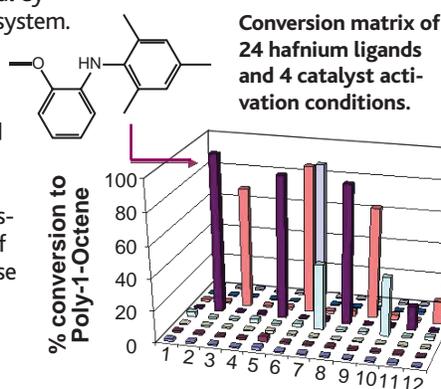
primary screening methods to identify 10 candidate catalysts from about 400 trials. Analysis of these screens was carried out by rapid gel permeation chromatography and Fourier-transform infrared spectroscopy methods. From these leads, a hafnium(IV) complex was found to polymerize 1-octene to high conversions. Secondary screens of a 96-member focus library identified a high-temperature ethylene-1-octene copolymerization catalyst. — PDS

*J. Am. Chem. Soc.* 10.1021/ja020868k (2003).

## VIROLOGY

## Mapping Virus History

Southeast Asia is attracting attention as a source of potentially dangerous emerging infections, not least influenza, but also dengue, Nipah, and possibly the causative agent of severe acute respiratory syndrome (SARS). The most important cause of epidemic encephalitis worldwide is the mosquito-borne Japanese encephalitis virus (JEV), a flavivirus allied to West Nile virus. Solomon *et al.* have probed the geographical distribution of JEV strains across



it would have taken 0.5 to 0.8 billion years from the formation of the supernovae progenitors for the gas to become enriched enough to supply solar or super-solar Fe/Mg. Formation of the progenitors at  $z \sim 30$  to 10 would be consistent with recent results from the Wilkinson Microwave Anisotropy Probe, indicating that star formation began about 0.2 billion years after the Big Bang. — LR

*Astrophys. J.* **587** Rapid Release 21 March 2003 (astro-ph/0303424).

## BIOTECHNOLOGY

### Step-by-Step

Rather than trying to sample all of chemical space in searching for drug leads, designers have deconstructed the problem and compiled combinatorial libraries of fragments. This approach facilitates synthesis, especially when the target can be used as a template to favor some fragments over others. Braisted *et al.* have selected for weakly binding fragments by capturing them via disulfide tethering to the target. In one such instance, joining a fragment to a previously identified lead improved the inhibitory potency of an interleukin-2 antagonist by 50-fold. Erlanson *et al.* have extended this approach by screening for two weakly binding fragments that together conform to the linear active sites of caspases, the enzymes of apoptosis. — GJC

*J. Am. Chem. Soc.* 10.1021/ja034247i (2003);  
*Nature Biotechnol.* **21**, 308 (2003).

## BIOMEDICINE

### The Genetics of Overeating

While it is generally accepted that genetics plays a role in obesity, the culprit genes have been difficult to identify because this disorder typically arises from the combined effects of multiple genes and environmental factors. The *MC4R* gene, which encodes the melanocortin 4 receptor, is one of the few genes causally linked to rare, monogenic forms of obesity. New work reinforces the idea that *MC4R* mutations are strong contributors to the development of morbid obesity induced by hyperphagia (overeating) and suggests that these mutations may be more common than previously thought.

In a study of 500 patients with severe childhood obesity, Farooqi *et al.* found that

nearly 6% had mutations in *MC4R* and that the severity of their clinical phenotype correlated with impairment of receptor function. Independently, Branson *et al.* found that sequence changes in *MC4R* were especially prevalent in obese subjects who engaged in binge eating, although the functional effects of the sequence changes were not tested. Recent mouse data from Weide *et al.* support the hypothesis that hyperphagia, rather than reduced metabolism, is the primary disturbance leading to early-onset obesity in the *MC4R*-deficient state. — PAK

*N. Engl. J. Med.* **348**, 1085; 1096 (2003);  
*Physiol. Genomics* **13**, 47 (2003).

## BIOCHEMISTRY

### A Copper Economy

Copper is an essential element, but free copper is toxic, so bacteria have developed regulatory systems, such as the *pco* system in *Escherichia coli* and the homologous *cop* system in *Pseudomonas syringae*. Four proteins, *Pco/CopA*, *B*, *C*, and *D*, are expressed under the control of a copper-inducible promoter. Recently, Peariso *et al.* used x-ray absorption spectroscopy (XAS) to show that the small periplasmic protein *PcoC* binds both Cu(I) and Cu(II), using different sets of ligands.

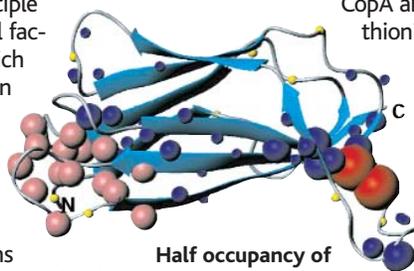
Arnesano *et al.* have determined the solution structure of *CopC* bound to Cu(I), and show that the binding sites for Cu(I) and Cu(II) in *CopC* are 30 angstroms apart. Cu(II) is bound by two histidines, an aspartic acid, and a glutamic acid, whereas Cu(I) is bound by a histidine and three methionines. A shift in redox state causes the copper ion to migrate between the sites.

How does *CopC* contribute to copper homeostasis? *CopA* is a periplasmic copper oxidase, and *CopB* and *CopD* are outer- and inner-membrane proteins, respectively.

*CopA* and *CopB* contain methionine-rich repeats that, on the basis of the *CopC* structure, are likely to bind Cu(I). *CopC* may act as a molecular switch that facilitates either Cu(II) import to the cytoplasm via *CopD*, or Cu(I) export via *CopB*.

Conversely, *CopA* may oxidize Cu(I) bound to *CopC*, or Cu(I) delivered from *CopC* might catalyze the oxidase activity of *CopA*. — VV

*J. Am. Chem. Soc.* **125**, 342 (2003);  
*Proc. Natl. Acad. Sci. U.S.A.* **100**, 3814 (2003).



Half occupancy of the Cu(I) and Cu(II) sites in *CopC*.

## Crystals via Liquids

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DOI: 10.1126/science.300.5616.19a

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