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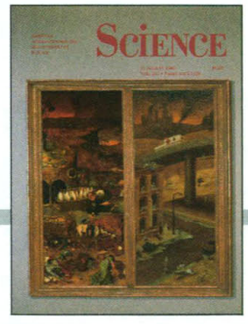
COVER

A view of our past and our possible future: plagues have been part of our history but could once again become a reality with the rise of drug-resistant microorganisms. On the left of the diptych, detail from Pieter Bruegel's *Triumph of Death* (1556) highlights the horrors of the bubonic plague. On the right, Brent Watkinson depicts some of the social problems that are contributing to modern epidemics. Articles on current difficulties with drug-resistant strains begin on page 1050; also see the News story on page 1036. [Left panel: Scala/Art Resource. Right panel: Brent Wakinson, Merriam, Kansas. Frame: Richard Kozak]





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edited by PHIL SZUROMI

## Mouse model for cystic fibrosis

The defects associated with the cystic fibrosis (CF) gene manifest themselves in epithelial cells of the respiratory, digestive, and reproductive tracts. For example, mucous secretions can block the airway and can cause respiratory infections. Snouwaert *et al.* (p. 1083) have developed a mouse model of CF (see news story by Barinaga, p. 1046). Many of the physiological effects of CF in these mice, such as intestinal obstruction and alterations in mucous secretion, are similar to those observed in humans. Clarke *et al.* (p. 1125) present data on the chloride channel transport of the CF transmembrane conductance gene in these mice.

■

## Homeodomain specificity

Homeodomain proteins are highly specific developmental signals that help establish the identity of differentiating cells, yet they often bind DNA in a weak and nonspecific fashion. Gruneberg *et al.* (p. 1089) used expression cloning in yeast to identify a human homeodomain protein, Phox1, that interacts with the yeast protein MCM1. This latter protein is a MADS box protein, a family of proteins involved in signal transduction, and is related to the serum response factor (SRF), the principal target of growth factor regulation of the proto-oncogene c-*fos*. In vitro, Phox1 and related homeodomain proteins from *Drosophila* enhanced SRF binding to its DNA binding sequence. This activity was preserved in a Phox1 mutant that does not bind DNA. The results suggest that the specificity of homeodomain proteins can be attributed in part to interactions with MADS box proteins.

## Mixed message from meteorites

Mesosiderites are meteorites composed of both metal and silicate clasts that were apparently mixed as a result of large impacts on a parent body. Mittlefehldt *et al.* (p. 1096) report that some of the silicate clasts in these meteorites show extreme fractionation of europium from the rest of the rare earth elements—greater than that of any other known rock. Simple igneous processes on the parent body of the meteorite cannot likely account for the observed enrichment. Instead, the authors suggest that the history of such mesosiderites may have involved complex processes such as melting produced by large impacts or melting of metal-iron impact breccias by electromagnetic induction from a dense primordial solar wind.

■

## Mantle model

The proportion of $(Mg,Fe)SiO_3$ in the perovskite structure and (Mg,Fe)O in the magnesiowüstite structure in the lower mantle is uncertain but central to the questions of whether the lower and upper mantle have different compositions and whether convection in Earth's mantle is layered. Stixrude *et al.* (p. 1099) addressed this problem by developing an equation of state for these minerals. They used this model to then compare the calculated density and elastic properties for different proportions of these minerals, iron contents, and temperatures to seismic observations of density and bulk sound velocity in the lower mantle. The results are most consistent if the lower mantle is composed mostly of perovskite and thus has a different composition from that of the upper mantle.

■

## Glass from the past

Glassy spherules (tektites) found at the Cretaceous-Tertiary (K-T) boundary (65 million years ago) in Caribbean sections are thought to derive from a nearby large impact. Blum and Chamberlain (p. 1104) analyzed the oxygen isotopic composition of the two types of tektites observed. The impact probably occurred in a mixture of predominantly carbonate and silicate rocks; sulfate-rich evaporites were likely only a minor component, ruling out a volcanic origin. Claeys *et al.* (p. 1102) found similar but much older glass spherules from Belgian rocks near the Frasnian-Famennian boundary (367 million years ago), also a major extinction. The relation of these tektites to similar-aged spherules from China or to the nearby Siljan ring impact structure in Sweden is unclear.

■

## Hormone deficiency

In humans, the combined pituitary hormone deficiency syndrome is associated with a loss of growth hormone (GH), prolactin (Prl), and thyroid-stimulating hormone (TSH) production and also with short stature and mental retardation. Two groups report that point mutations in the pituitary-specific transcription factor, Pit-1, correlate with this disease in humans. These mutations are located in two regions of Pit-1 necessary for DNA binding, in the POU-homeodomain [reported by Radovick *et al.* (p. 1115)] and in the POU-specific domain [reported by Pfäffle *et al.* (p. 1118)]. When assayed in vitro, the mutant Pit-1 proteins were unable to activate the transcription of the Pit-1 target genes, GH and Prl, but still retained DNA binding activity.

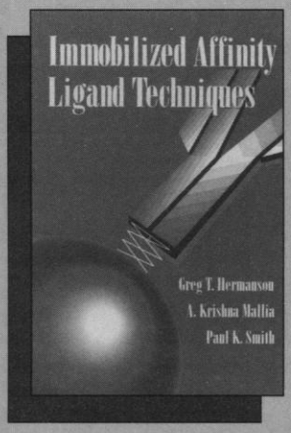
■

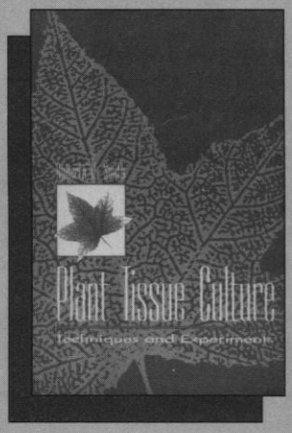
## Unstable network

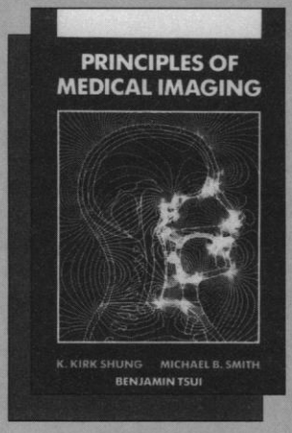
The skin, or epidermis, helps prevent the entry of infective organisms. If the skin cells (keratinocytes) do not function well, these protective aspects can be lost. Rothnagel *et al.* (p. 1128) study the causes of a hereditary skin disorder that leads to blistering and thickened skin. These patients carry mutations in the keratin proteins, which normally assemble into polymers to form the intermediate filament network within the cell. The mutated keratins are unable to form a stable filament network, and the keratinocytes lyse too easily.

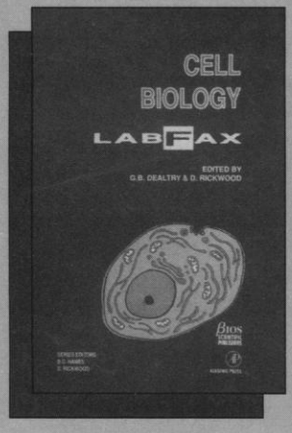
## Anergy origins

How T cells maintain anergy, a state in which they do not respond to antigen presentation, is the subject of two reports. Mature T cells that bind to self antigens are normally deleted or else are maintained in an anergic state. Ramsdell and Fowlkes (p. 1130) show that the antigen must be present in the body to maintain this anergy. Adoptive transfer of T cells from one mouse strain into a mouse strain that lacked the same antigens restored responsiveness. A T cell can become nonresponsive to a foreign antigen if it does not receive appropriate accessory signals simultaneously with antigen binding to the receptor; such cells produce little interleukin-2 (IL-2). Kang *et al.* (p. 1134) show that in such anergic T cells the AP-1 transcription factor element of the IL-2 gene is down-regulated. Exposure of anergic T cells to IL-2, which is known to restore antigen responsiveness, also restored the activity of the AP-1 region of the IL-2 promoter.

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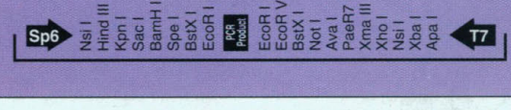


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| September 25–28 | October 2–5 | October 23-26 |
|---|---|---|
| **GTP Binding Proteins and Vesicular Transport in Eukaryotic Cells** | **MOLECULAR CHAPERONES: Functions in Protein Folding and Cellular Metabolism** | **Structure and Function of Proteins Kinases and Phosphatases** |

## KEYNOTE SPEAKERS AND TOPICS

Henry R. Bourne
*University of California, SF*

**GTPases Everywhere**

Peter S. Kim
*MIT*

**Protein Folding in the Test Tube**

Edmond H. Fischer
*University of Washington*

**Cellular Processes by Protein Phosphorylation: An Historical Overview**

## ORGANIZERS

Philip Stahl, *Washington University*
Peter Novick, *Yale University*
William Balch, *Scripps Clinic and Research Foundation*

Roger McMacken, *Johns Hopkins University*
Elizabeth Craig, *University of Wisconsin*
George Lorimer, *Dupont Corporation*

Jack Dixon, *University of Michigan*
Susan Taylor, *University of California, San Diego*

*Registration information is available from:* **ASBMB Symposia Office,** Room 3206, 9650 Rockville Pike, Bethesda, MD 20814-3998 Tel: 301-530-7010, Fax: 301-530-7014

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CELL ADHESION

SmithKline Beecham Pharmaceuticals
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## *Cellular Adhesion: Molecular Definition to Therapeutic Potential*

October 19-21, 1992

Valley Forge Hilton Valley Forge, Pennsylvania
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**Topics:**

Adhesion Molecule Structure & Function
Leukocyte Endothelial Cell Adhesion
T-Cell Adhesion Cascades
Lymphocyte Homing
Therapeutic Approaches

Adhesion Molecules in:
Inflammation & Development
Bone Remodeling
Infectious Disease
Cardiovascular Disease

**Registration Deadline: September 1st. For Additional Information and Registration Forms, Contact:**

Ms Dee Brooks, Symposium Coordinator Symposium Office (UW2109) SmithKline Beecham Pharmaceuticals
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*Synthesize over 10 times the amount of RNA as conventional* in vitro *transcription reactions.*

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MEGASCRIPT KITS utilize novel reaction conditions which allow the synthesis of over 10 times the amount of RNA as conventional transcription reactions (patent pending). 1 µg of control template DNA yields 50-100 µg of RNA in a 20 µl reaction. Kits contain complete reagents and controls for synthesis and purification of RNA. Cap analog (Cat. #8050) is available separately for synthesis of capped RNAs.

Kits include reagents for 40 reactions. This is sufficient to synthesize up to 5 mg of RNA using the control template supplied with the T7 kit and up to 3.2 mg with the SP6 and T3 kits. Kits include polymerase, nucleotide solutions, reaction buffer, placental ribonuclease inhibitor, RNase-free DNase, control template and a comprehensive manual.

FOR USE IN

- Microinjection of Capped mRNAs
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*SP6 KIT, CAT. #1330; T7 KIT, CAT. #1334; T3 KIT, CAT. #1338*

Comparison of MEGAscript with conventional *in vitro* transcription reactions.

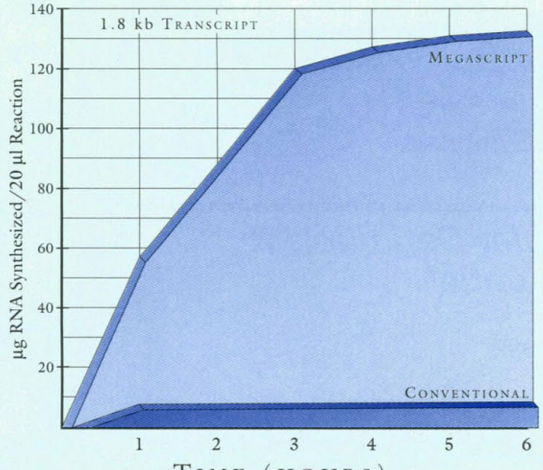


FIGURE 1. 20 µl transcription reactions containing 1 µg template DNA (1.8 kb transcript size), 40 U of T7 RNA polymerase, buffer, NTPs and $^{32}$P-UTP were incubated at 37°. 1 µl aliquots were removed at 1 hour intervals and acid precipitable cpm determined by scintillation counting.

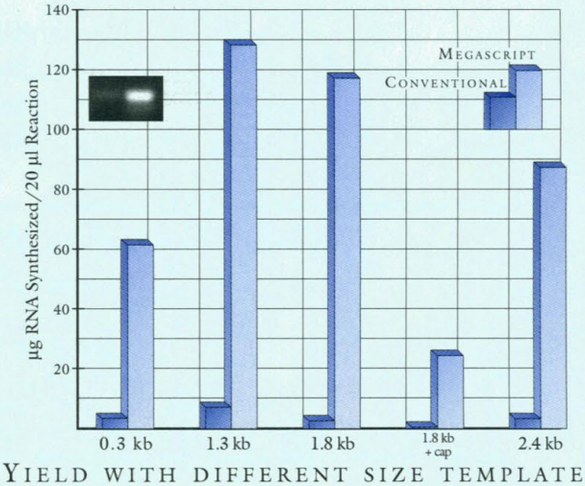


FIGURE 2. Transcription reactions were as described in Figure 1 with 1 µg of different DNA templates coding for the indicated sized transcripts added to each reaction. Inset shows 0.25 µl aliquots of both conventional and MEGAscript reactions transcribing a 0.3 kb transcript separated on a 2% agarose gel and ethidium bromide stained.


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