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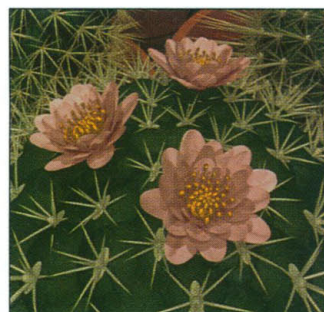
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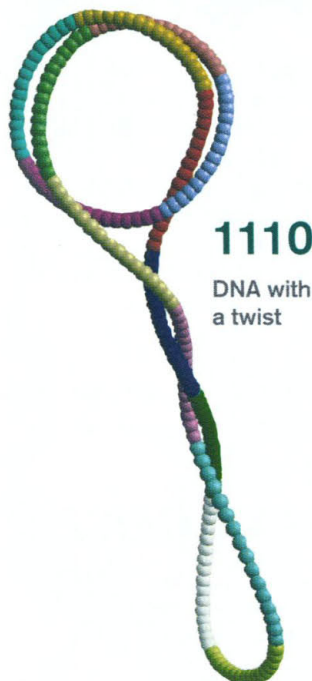
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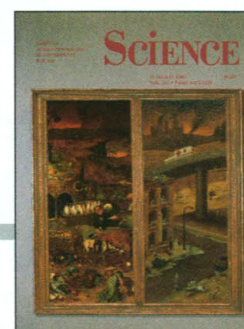
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COVER

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 Watkinson, Merriam, Kansas. Frame: Richard Kozak]



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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. Gruenberg *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 $(\text{Mg,Fe})\text{SiO}_3$ in the perovskite structure and $(\text{Mg,Fe})\text{O}$ 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 lay-

ered. 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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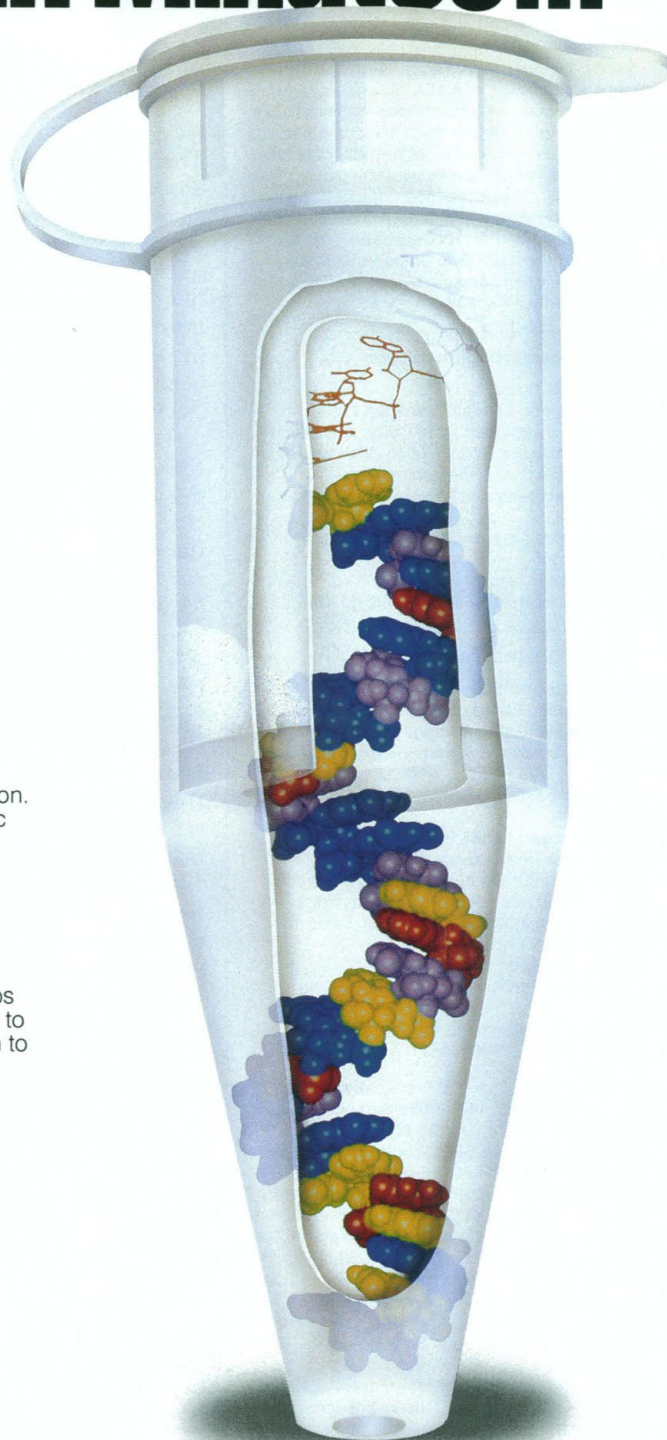
*patent pending. mRNA model courtesy of BIOSYM

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EQUIPMENT SPECIFICATIONS

The microscope must have a vertically adjustable, centerable condenser and iris diaphragm.

PROCEDURE

1. Rack up condenser with top lens swung in.
2. Focus on specimen with 10X or 16X objective.
3. Close down lamp field stop (diaphragm in base) while viewing.
4. Lower condenser slightly until diaphragm image is in focus.
5. Center image using condenser centering screws.
6. Open diaphragm to edge of field, fine focus and open further to just clear field.
7. Adjust contrast using condenser diaphragm.
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Drug Prohibition in the United States: Costs, Consequences, and Alternatives

An Article Reprinted from *Science* (1 September 1989)

ETHAN A. NADELMANN

FROM THE ABSTRACT:

"Drug legalization" increasingly merits serious consideration as both an analytical model and a policy option for addressing the "drug problem." Criminal justice approaches to the drug problem have proven limited in their capacity to curtail drug abuse. They also have proven increasingly costly and counterproductive. Drug legalization policies that are wisely implemented can minimize the risks of legalization, dramatically reduce the costs of current policies, and directly address the problems of drug abuse. Twelve pages.



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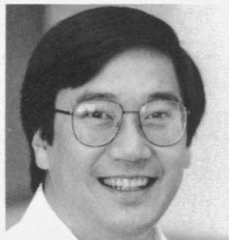
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KEYNOTE SPEAKERS AND TOPICS



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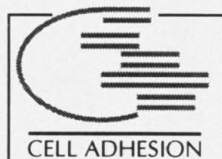
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Comparison of MEGAScript with conventional *in vitro* transcription reactions.

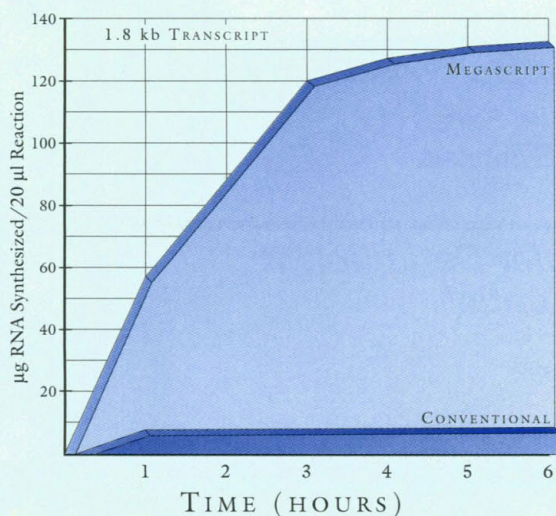
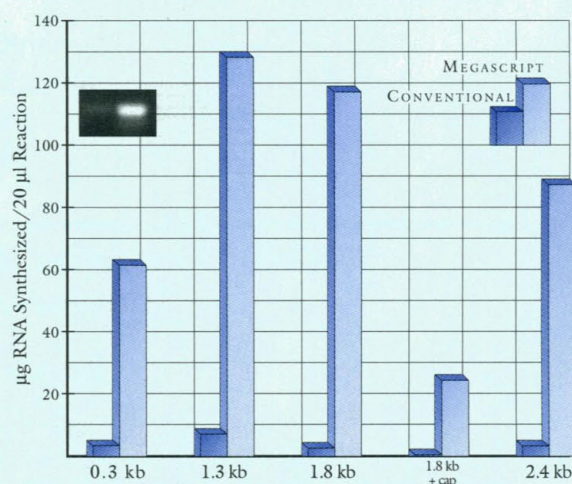


FIGURE 1. 20 µl transcription reactions containing 1 µg template DNA (1.8 kb transcript size), 40 U of T7 RNA polymerase, buffer, NTPs and ³²P-UTP were incubated at 37°. 1 µl aliquots were removed at 1 hour intervals and acid precipitable cpm determined by scintillation counting.



YIELD WITH DIFFERENT SIZE TEMPLATES

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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