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SCIENCE

1 December 1989
Vol. 246 ■ Pages 1089–1212

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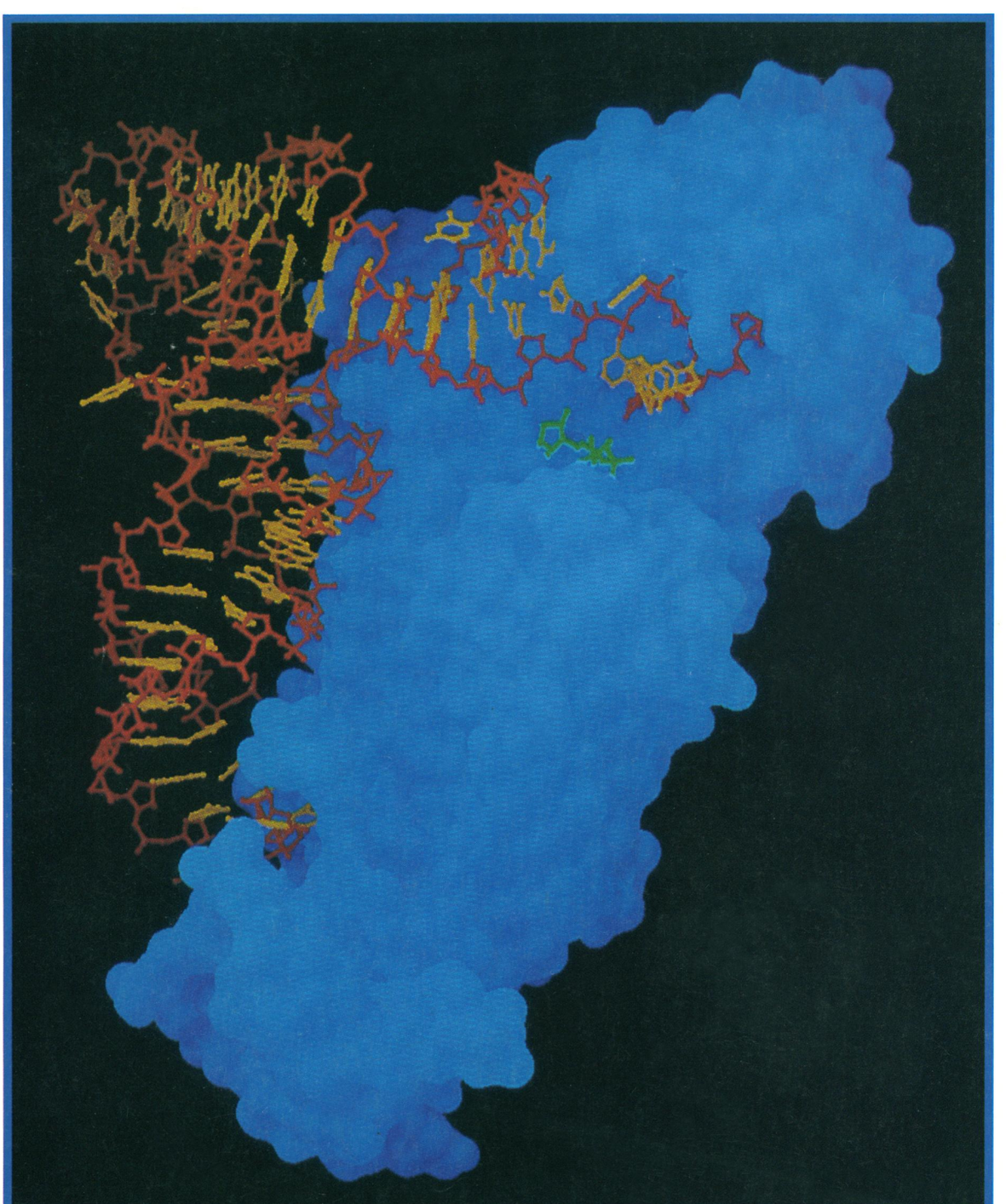

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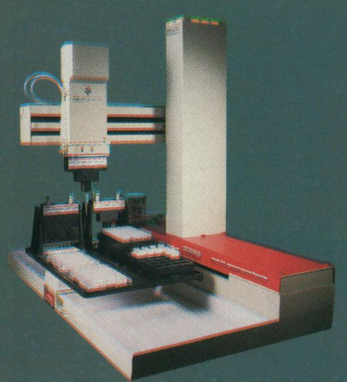
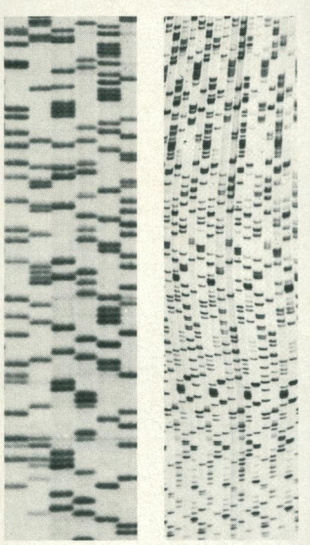


Figure 1 Figure 2



1 18

Figure 1. Autoradiogram of sequence analyses accomplished on the Biomek 1000 using GemSeq K/RT double-stranded DNA sequencing system and Riboprobe Gemini pGEM-3 vector, containing an insert of a known cDNA.

Figure 2. Autoradiogram of sequence analyses using M13mp18. Lanes 1-9 were performed manually, lanes 10-18 were performed on the Biomek 1000.

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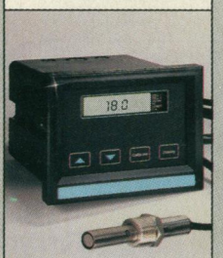

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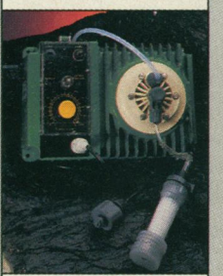

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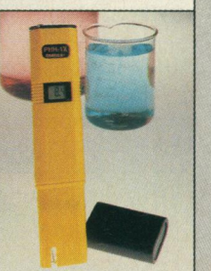

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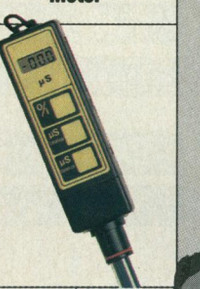

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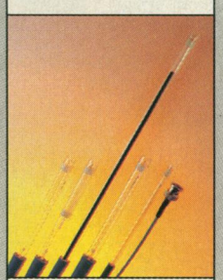

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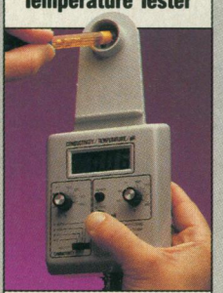

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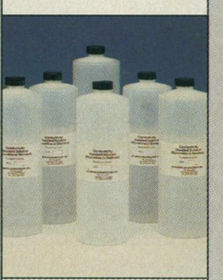

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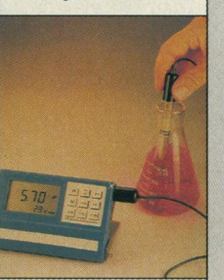

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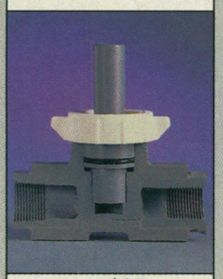

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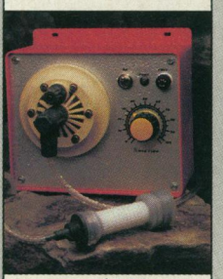

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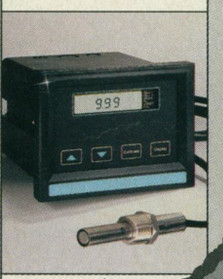

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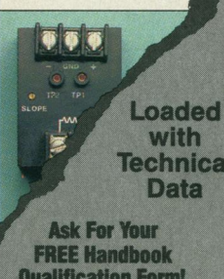

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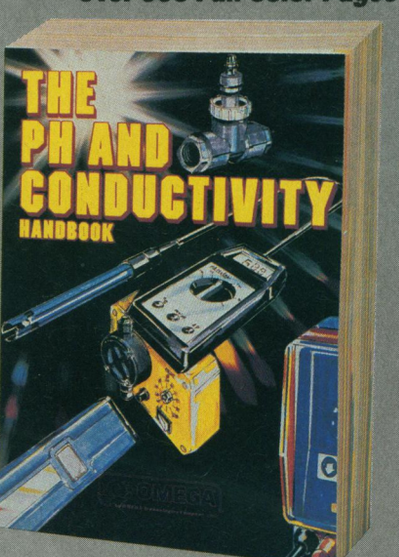

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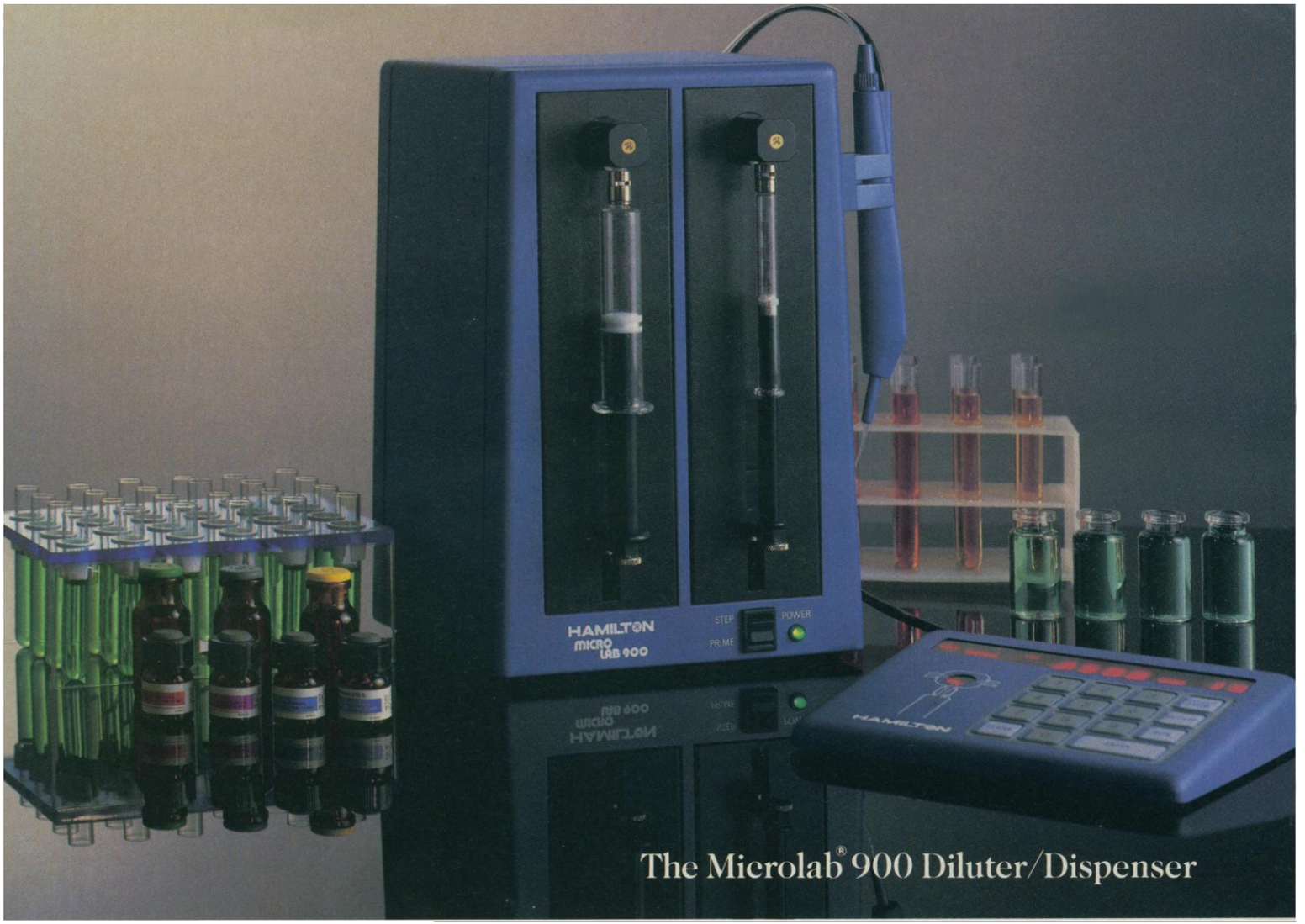
COVER The crystal structure of *Escherichia coli* glutaminyl-tRNA synthetase (in blue) complexed with $tRNA^{Gln}$ (in red and yellow) and adenosine triphosphate (ATP, in green). The structure shows that this enzyme recognizes this specific tRNA and discriminates against the other sixty through extensive interactions with the acceptor stem and anticodon of the tRNA. See pages 1135 and 1152. [Graphics by M. A. Rould, J. J. Perona, P. Vgt, and T. A. Steitz, Yale University, New Haven, Connecticut]



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This Week in
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Theory acceptance

TRUE or false? A theory that can make a prediction is more readily accepted than one that can only explain known facts. False, is Brush's conclusion, after considering an historic case—the acceptance of Einstein's general theory of relativity; and, he notes further, because prediction is not a requirement for theory acceptance, "soft" science theories—for example, those in psychoanalysis and evolutionary biology—that explain but do not predict should not categorically be dismissed as inadequate (page 1124). Two phenomena—one that was predicted in advance and one a prior observation—were central to acceptance of general relativity. Einstein predicted that light would be bent in the sun's gravitational field; in 1919 this prediction was borne out by measurements of light bending during an eclipse. It gained the theory "favorable publicity," bringing it to the attention of other scientists and the public, but not acceptance. Stronger support came from observations of the advance of Mercury's perihelion, a gradual shift in the planet's orbit; even though this phenomenon was known before the theory was formulated, it turned out to be the more important factor for the theory's acceptance.

Complex's complexity simplified

ONE of the puzzling phenomena of protein synthesis is how synthetase enzymes discriminate among physically similar but functionally different molecules of transfer RNA (tRNA). New x-ray crystallographic data for a complex (cover) of glutaminyl-tRNA synthetase (one of the 20 synthetases that assist in translation of the genetic code into protein), the specific tRNA molecule that the enzyme recognizes, and the power supplier ATP bring this puzzle closer to solution (page 1135). Synthetases facilitate the "charging" of tRNA molecules with the appropriate amino acid; after being charged, tRNA molecules go to the ribosome and present passenger amino acids for addition to growing protein chains. Rould *et al.* describe the complex's features and discuss how certain chemical interactions can account for the synthetase's ability to recognize the "right" tRNA molecule to charge. Perona *et al.* use the crystal-structure data to explain how simple mutations affecting just one amino acid in the enzyme result in a reduced ability of the enzyme to make this discrimination (page 1152). Waldrop explains the significance of these data for understanding the workings of the cell's synthetic machinery (page 1122).

Ship tracks

THE effects of pollutants on cloud structure and function have been assessed by comparing conditions in pristine clouds over the oceans with those of "ship tracks," clouds that are modified by emissions from ships. Radke *et al.* combined measurements made from above (by satellites) and from within (by aircraft flying through the clouds) to study features of ship tracks in stratocumulus clouds off the California coast (page 1146). The tracks appear to have been generated both by particulate emissions and by emitted gases that were converted to particles. The ship tracks altered reflectivity, upwelling radiance, the sizes and concentration of cloud droplets, and the liquid-water content of clouds. These ship track perturbations, which affect the scattering and absorption of sunlight and precipitation, are indicators of what atmospheric pollutants can do.

AZT resistance and mutant enzymes

AZT may only serve as a stopgap for the treatment of AIDS: after about 6 months of AZT therapy, many patients harbor viruses that show decreased sensitivity to the drug; whether these resistant viruses have clinical significance remains to be seen. The molecular basis for AZT resistance appears to be accumulation of three or four specific point mutations in the gene that encodes the enzyme reverse transcriptase (RT) (page 1155). This enzyme is central to the multiplication and spread of the AIDS virus in infected hosts; when RT is rendered nonfunctional by AZT, the virus can be contained. Base changes leading to four amino acid substitutions were regularly found in AZT-resistant viruses; a viral clone made to express these replacements showed strong resistance to AZT. RT normally has many mutations, and six months seems long for mutations to accumulate. Larder and Kemp suggest that the grace period may reflect the fact that for one of the substituted amino acids two base changes are required. Rapid tests for identifying AZT resistant strains can now be designed and used for evaluating whether the clinical status of patients and the emergence of AZT-resistant viruses are correlated.

Cell-death receptor?

ONE way to determine the function of a surface receptor is to see what happens to the cell when the receptor is missing. Such an approach has been taken for deducing functions of T cell receptors that have heterodimers of ζ and η chains (page 1162). (Other T cell receptors have homodimers of ζ chains.) Two common consequences of T cell activation—interleukin 2 production and blocking of the cell cycle—occurred as usual for properly stimulated T hybridoma cells that lacked $\zeta\eta$ molecules. In contrast, antigen activation of these cells did not cause cells to die; under the same conditions, their $\zeta\eta$-bearing counterparts die rapidly. Mercćep *et al.* conclude that the T cell receptor complex consists of a number of different functional subunits that induce different responses in and by the cells. The $\zeta\eta$ receptors appear to have a role in programmed cell death after activation; perhaps in vivo these receptors take part in the elimination of self-reactive T cells. ■ RUTH LEVY GUYER

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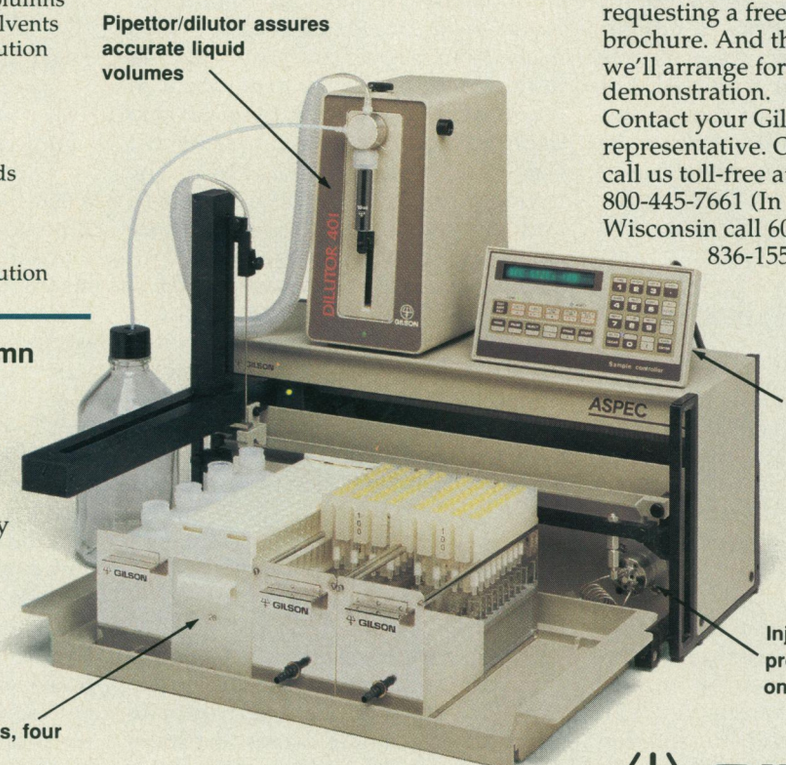

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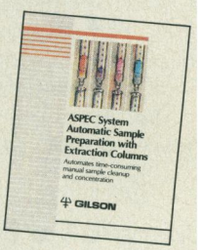

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SCIENCE

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Cleaning Hazardous Waste Sites

Since the inception of the Superfund program, there has been a paucity of completed clean-ups. But the pace of action is likely to accelerate, leading to requirements for training and employment of scientists and engineers. Remediation activities could last 30 years or more and cost as much as $500 billion. About half of this would be furnished by the government and the remainder by private parties who had disposed of their wastes in common dumps.

The major cost will be incurred in treating abandoned or inactive sites (Superfund program). Another substantial sum will be spent at government-owned facilities. (Costs of remediation for the Department of Energy alone have been estimated at $130 billion.) In the private sector, as many as 375,000 leaking underground tanks have contaminated, or will contaminate, ground water. Remediation will be difficult and costly.

The Environmental Protection Agency has been ineffective in fulfilling its role as the key government agency in clean-up matters. Since 1980 more than 31,000 abandoned or inactive waste sites have been identified. Of these, 1224 have been placed on a National Priority List. As of early 1989, EPA had initiated studies of approximately 70% of the NPL sites. Actual remedial action had been begun on only 20% (about 250) of the NPL sites, and clean-ups had been completed on only 43 of them. The time from site identification to start of clean-up has averaged 7 to 9 years. Actual clean-ups have required an additional 2 to 3 years. At sites with contaminated ground water, 20 to 40 years more may be spent in treatment of ground water.

The poor performance of EPA has been due to lack of money and technical expertise plus an excess of willingness to respond to the headlines of the day. Costs of clean-ups range up to $1 million an acre, and some sites contain more than a hundred acres. No sites are identical, and within a given site variable conditions prevail. To conduct cost-effective remediation requires a highly expert interdisciplinary team, including earth scientists, chemical engineers, and bioscientists. During the current 5-year Superfund program, EPA has about $2 billion per year to spend. Responding to criticism, the new EPA administrator has spurred the formulation of a plan that will provide more money from private parties and an increase in EPA personnel.

The best hope for a vigorous, innovative program lies in the Department of Energy. Secretary James D. Watkins, a retired admiral, has the technical and managerial expertise to make things happen. His organization contains the necessary scientific and engineering expertise to devise or choose cost-effective means of remediation. Their tasks are demanding. The DOE is responsible for a total of 3700 sites of which many are no longer active. The problems at the sites include leaking storage tanks at Hanford that contain high-level radioactive waste. They also include soil and ground water contaminated by mixtures of heavy metals, radioactive substances, and hazardous organic liquids. Some of the sites have been active for more than 40 years, during which the various contaminants were dumped locally. The pollutants have migrated deep into the soil. Cubic miles of earth have been contaminated. A recent draft of a DOE report is impressive in its outline of problems and its mode of organizing to deal with them.*

Contamination of ground water is common to the majority of all waste sites. Insofar as there have been or will be health effects related to waste sites or leaky tanks, the largest fraction of them will be due to ingestion of polluted waters. The principal organic compounds found in leachates are small chlorinated hydrocarbons, benzene, toluene, and xylenes. Since World War II, more than 40 billion pounds of small chlorinated hydrocarbons have been distributed, of which 4 billion pounds or more have been incorporated into waste sites. Much of that has already been leached. Vast sums of money will be spent in removing contaminants from ground water. The costs will be determined by the effectiveness of the technologies employed. Particularly promising is bio-remediation. The costs will also be determined by answers to the questions, "At what level of contamination is toxicity negligible? How clean is clean?" —PHILIP H. ABELSON

*"Applied research, development, demonstration, testing, and evaluation plan for environmental restoration and waste management" (Department of Energy, Washington, DC, 1989).

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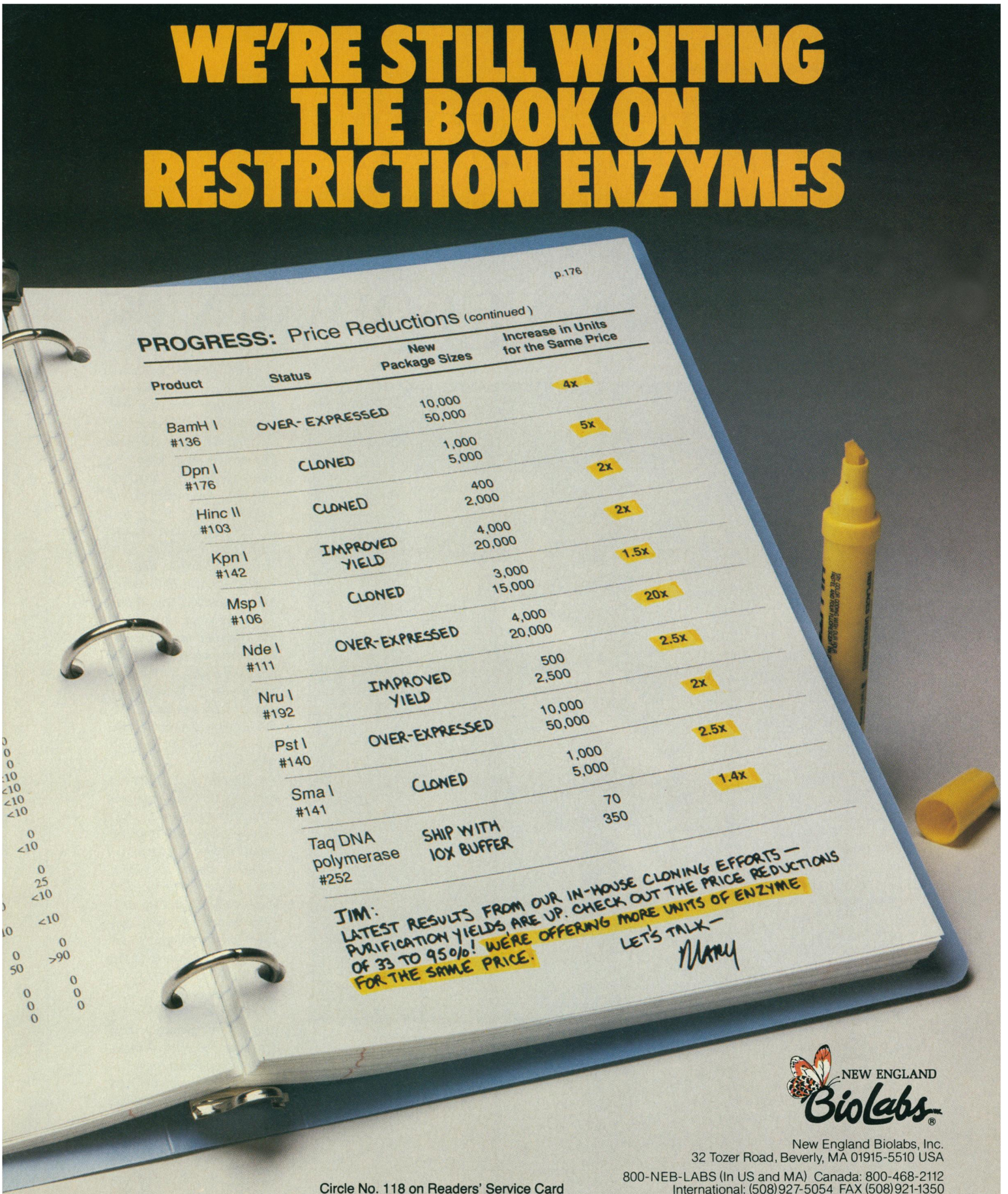

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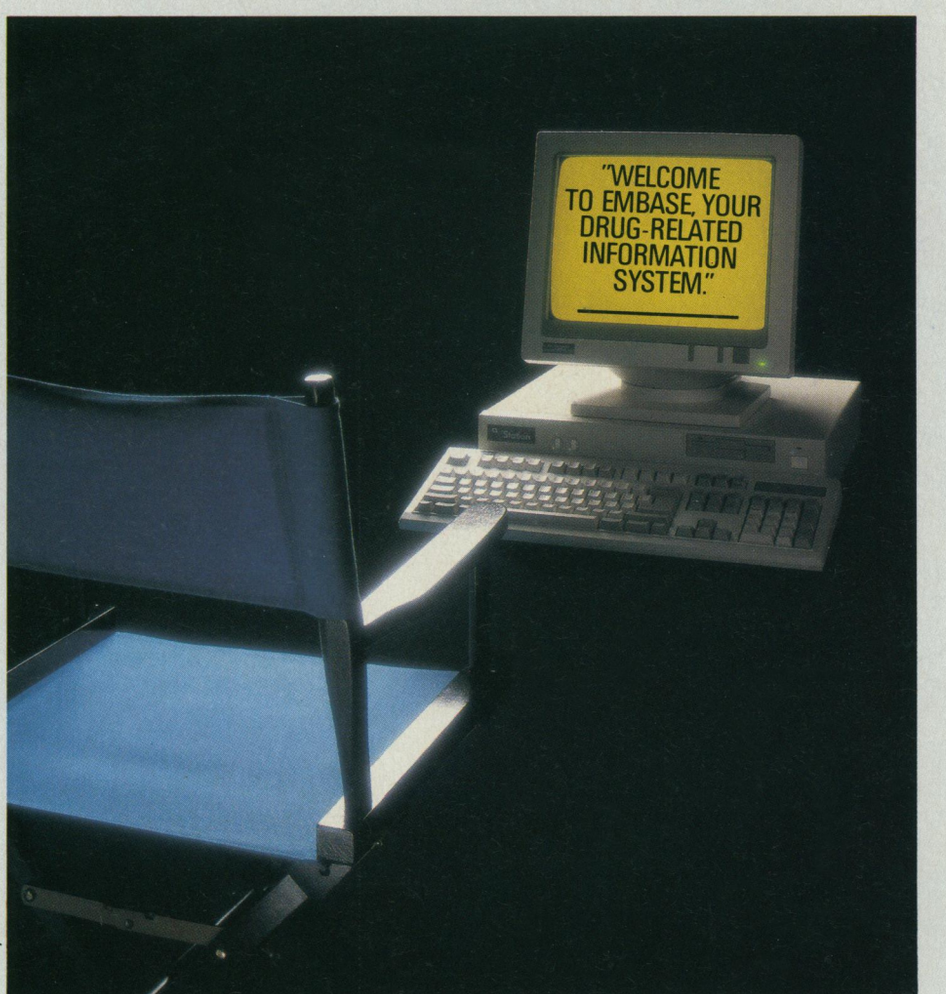

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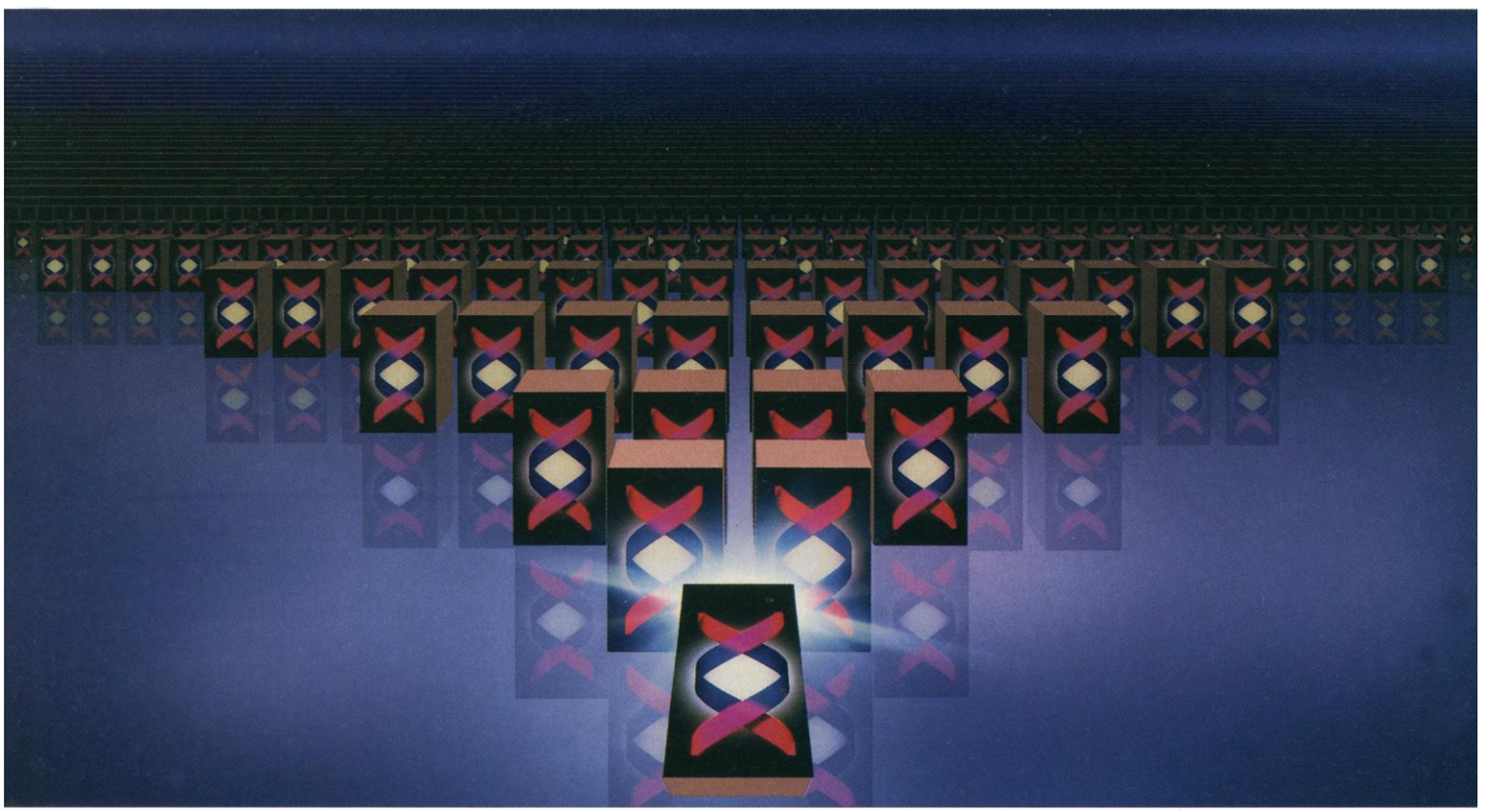

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ed for treatment and rehabilitation. The legalization policy also produced a greater societal tolerance of opium use.

The lessons from Iran's experience with "controlled legalization" offer a telling counterexample to the advocates of decriminalization. Undoubtedly there are strong legal and economic arguments in favor of some version of a policy of contraband drug legalization. But such arguments by themselves cannot support the epidemiological claim that legalization would stem the rising tide of drug abuse. There is, however, an analogy, taken from economics, that seems more fitting to drug abuse than to material production. According to Say's Law, "supply creates its own demand." Analysts would be well advised to keep this dictum in mind as they contemplate alternative drug policies.

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Koshland writes that one should observe with "scientific detachment" the present war on drugs. Other scientific spokesmen have stated that the scientist's main contribution to this "war" should be in "developing medications in order to treat addiction" (*1*).

Koshland also states that the Administration's program should "evaluate the problems of poverty, minorities, and civil rights in relation to drug use"; these are important areas, but very difficult to analyze scientifically. Koshland states that the program "should not be compromised by ancillary requirements relating to the general ambience of society." There are, however, other major problems related to the waxing and waning of the drug epidemic that might be subjected to scientific scrutiny and to quantification: the epidemic spread of dependence-producing drugs in all layers of society, especially among adolescents; the impact of drugs on fetal development, brain maturation, school performance, and the dropout rate; the effect of drugs on industrial productivity, absenteeism, public health (such as the spread of AIDS) and health care delivery; and, finally, their effect on inter-American and international policies.

Koshland says that "the country is faced today with a situation similar to prohibition" and that "[t]hose who read history know well how ineffective the law was in that case." This historical episode is not the only one that can be invoked to predict the effectiveness of drug prohibition. After enactment of the Harrison Act in 1914, there was an 80% reduction in cocaine and opiate addiction, observed years later, between 1930 and 1960 (*2*). Restrictive legislations controlled availability and consumption of these drugs in Western and Eastern Europe during the same period. The major epidemics of opium smoking in China 100 years ago, which affected nearly a third of its population, were curtailed by national and international interdiction measures (*3*) and so was the Japanese epidemic of intravenous amphetamines in the 1950s (*4*). More recent examples of effective restrictive legislation against heroin and amphetamine consumption have been reported from Sweden to

U.S. experiment with alcohol prohibition is provided by the British experience with alcohol control during a similar period. Whereas in the United States the death rate from cirrhosis of the liver dropped from 13 to 15 per 100,000 populaiton in 1910 through 1914 to 7 during the prohibition years and then climbed back to pre-1914 levels by the 1960s, in Britain the death rate from cirrhosis of the liver dropped from 10 in 1914 to 5 in 1920 and then gradually declined to a low of 2 in the 1940s before rising to a rate of 3 by 1963 (*8*). Other indicators of alcohol abuse dropped by similar magnitudes (*9*). "This remarkable achievement occurred," Milton Terris has written, "despite the fact that there was no prohibition in the United Kingdom." Britain's "wartime measures included a sharp curtailment in the amount of alcohol available for consumption, drastic restriction of the hours of sale, and marked increases in taxes on alcoholic beverages. With the end of the war, the limitations on the available quantity of alcohol were removed, but the hours of sale were extended to only half the pre-war time of opening, while taxation was increased even further."

Britain not only reduced the negative consequences of alcohol consumption more effectively than did the United States, but it did so in a manner that raised substantial government revenues; by contract, the U.S. government spent substantial revenues attempting to enforce its prohibition laws and sacrificed far greater revenues into the hands of criminal enterprises. The British experience strongly indicates that the national prohibition of alcohol in the United States was, on balance, not successful. It also suggests that more effective control measures after the repeal of prohibition might have prevented the return to high levels of alcohol abuse.

The conclusions of Siassi and Fozouni regarding the lessons of Iran's experience with an opium maintenance program are of questionable relevance to my analysis. As they noted, Iran's program was neither well conceived nor well maintained. Once it was curtailed, "other illicit sources of supply . . . at once replaced the sale from the 'legal' sources" (*10*). Moreover, other countries that did not experiment with such maintenance plans also experienced dramatic increases in opiate use; indeed the enactment of anti-opium laws in many Asian countries in which opium use was traditional—including Hong Kong, Thailand, Laos, and Iran—is believed to have played a strong role in stimulating the creation of domestic heroin "industries" and substantial increases in heroin use (*11*). Finally, a central criterion by which any maintenance program should be measured is its impact on drug users who would otherwise rely entirely on the black market; this issue is not addressed by Siassi and Fozouni.

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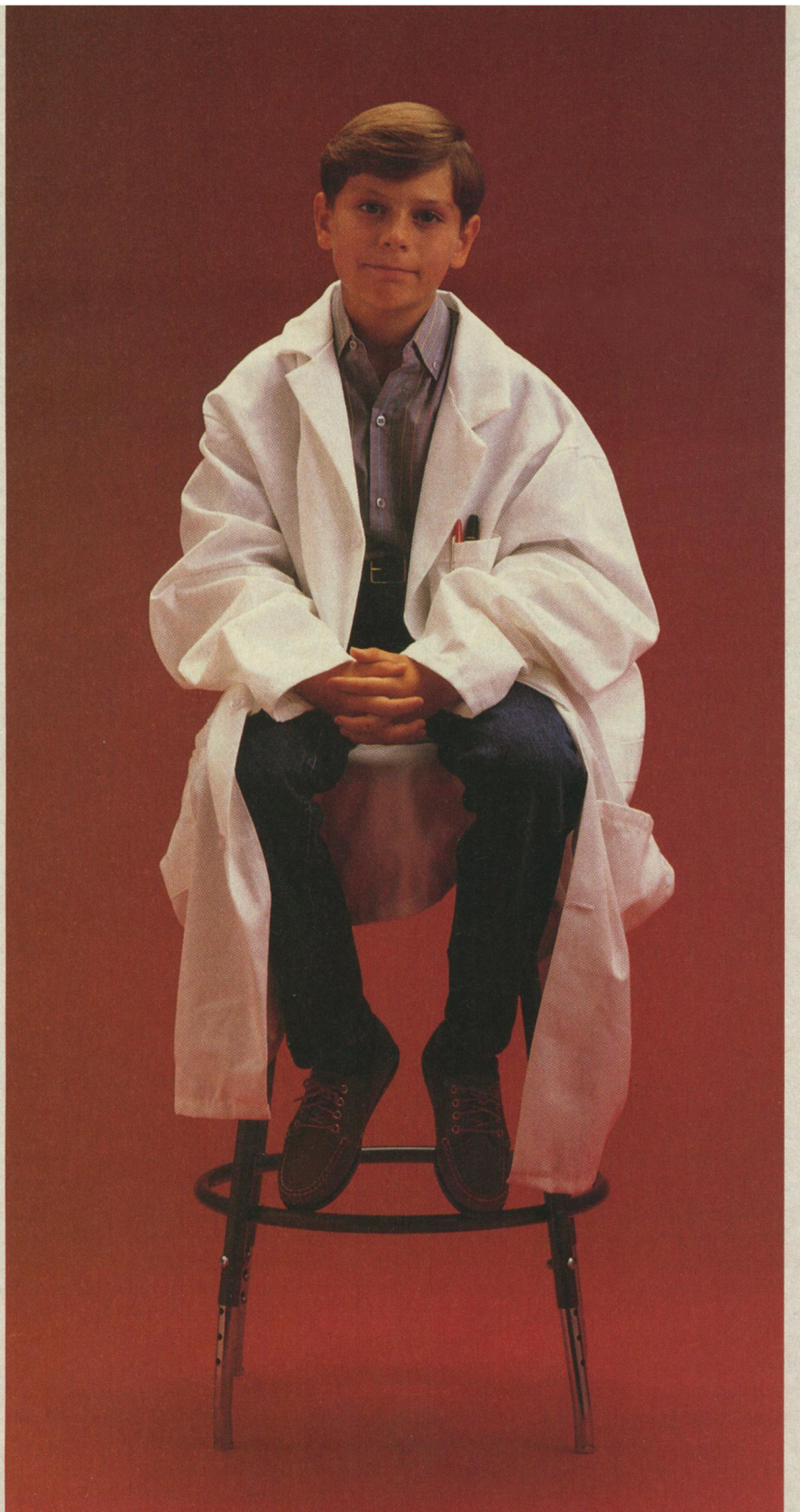

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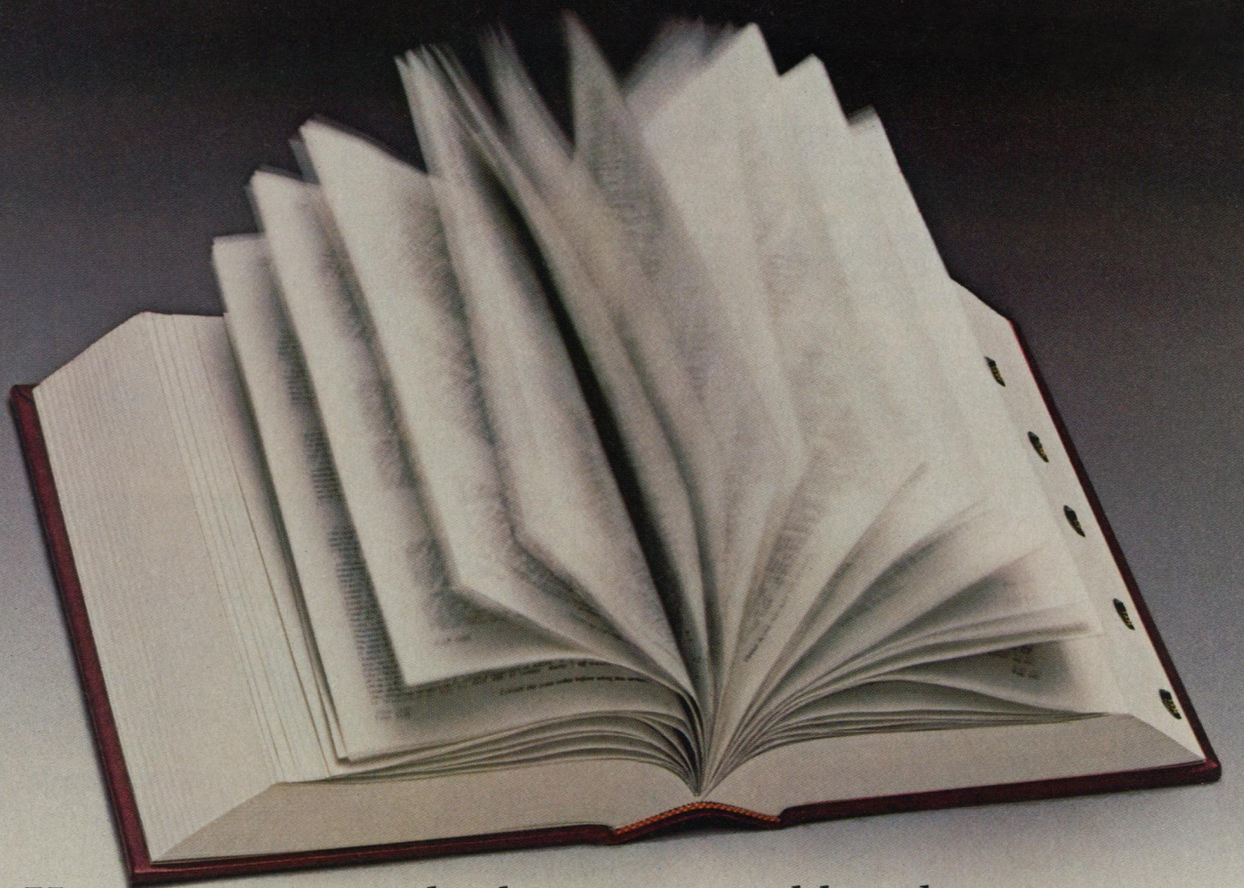

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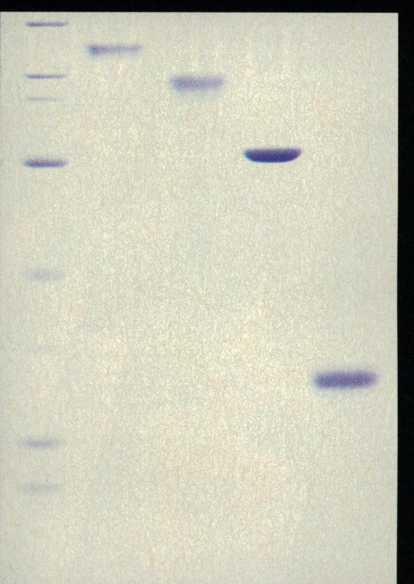

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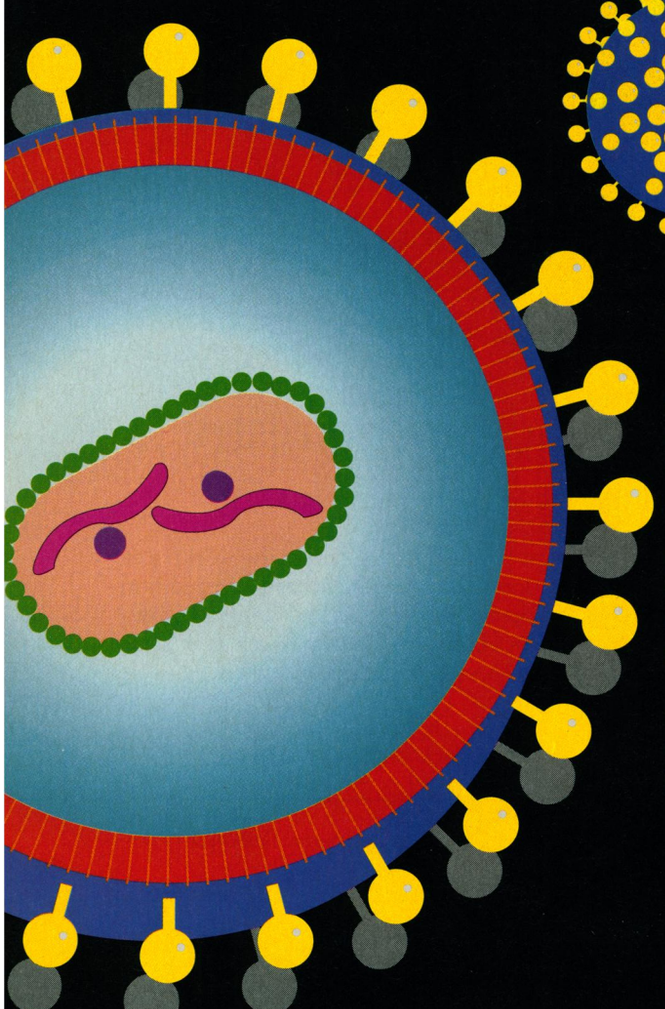

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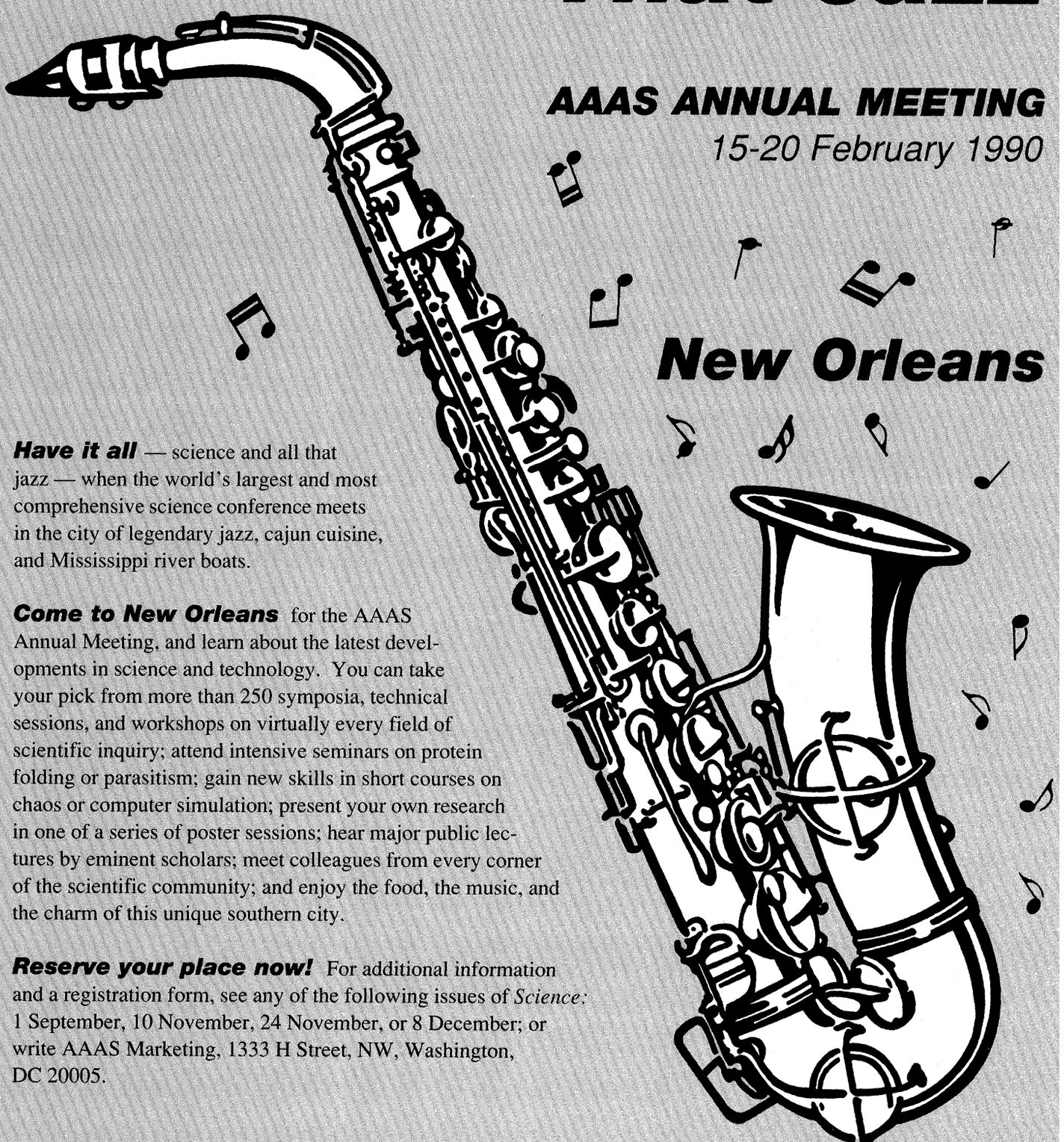

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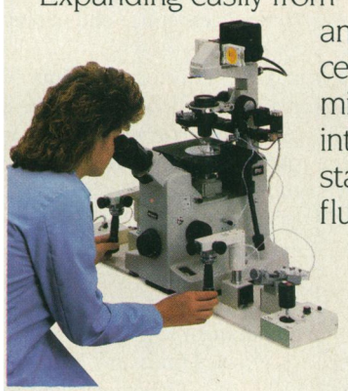

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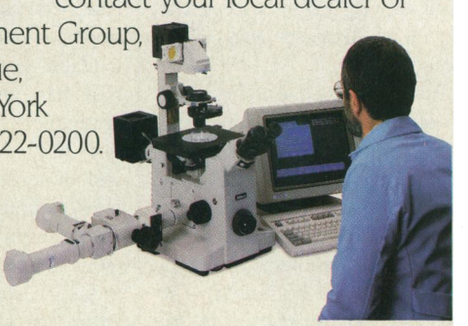

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