AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE

# SCIENCE

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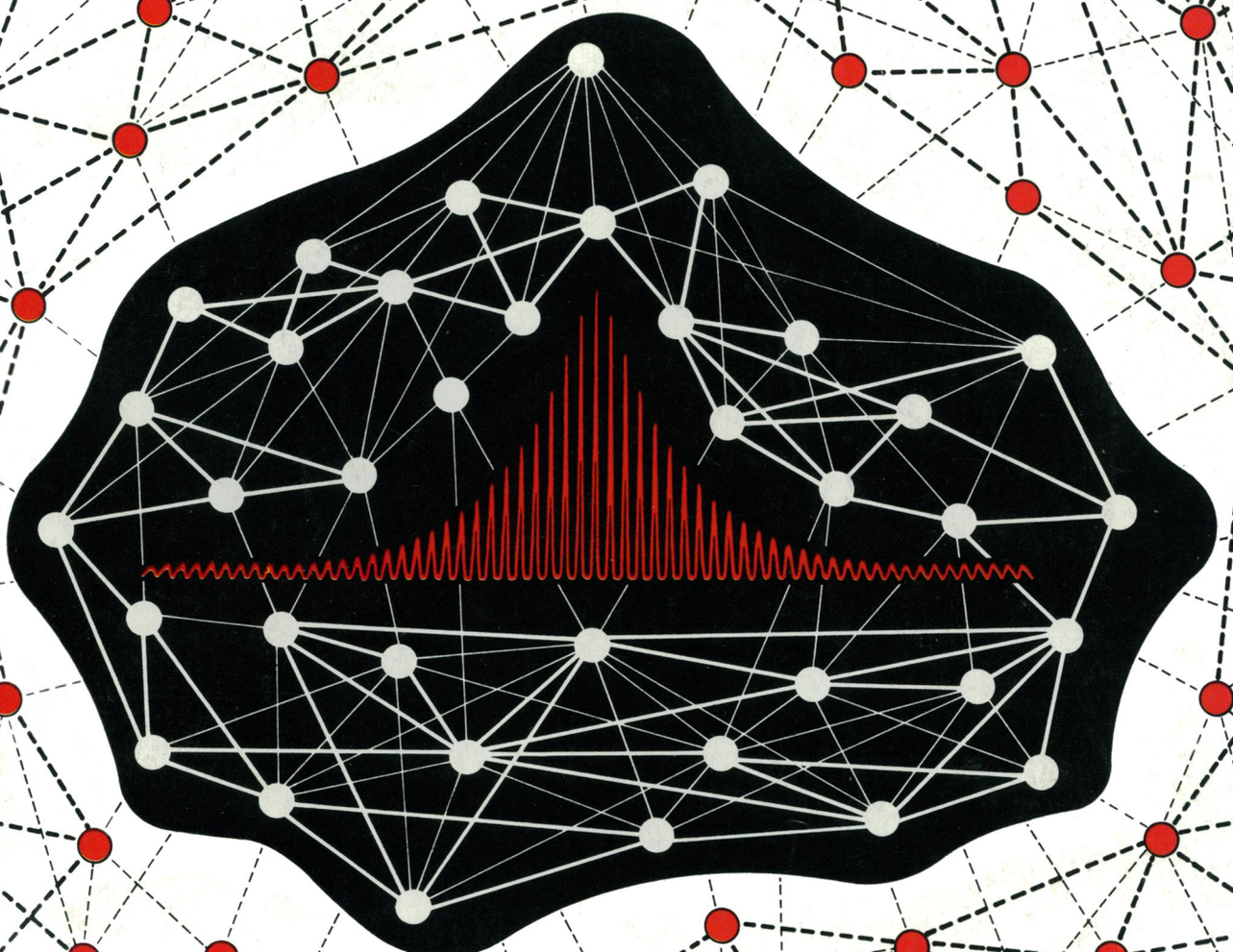

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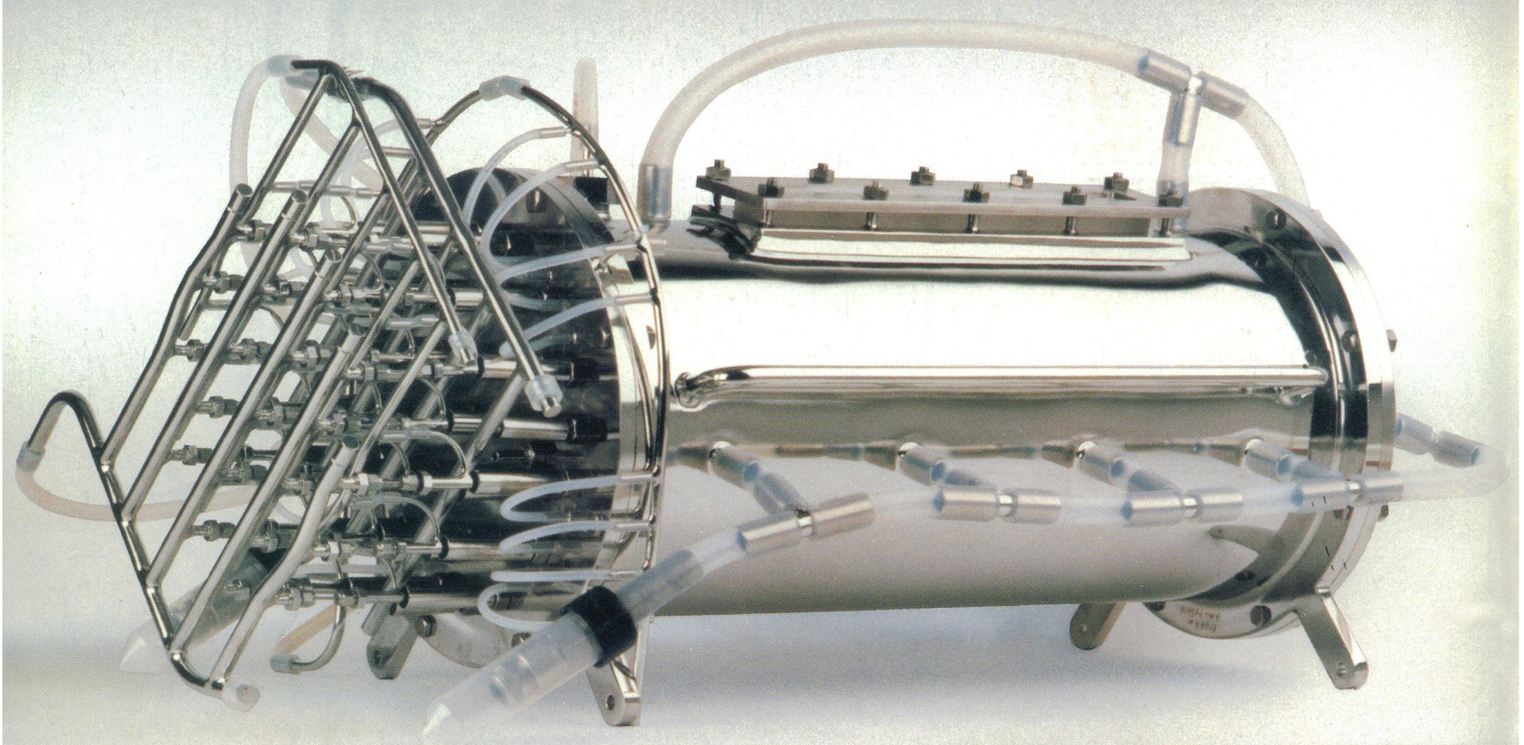

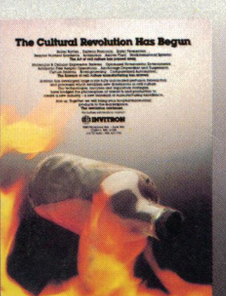


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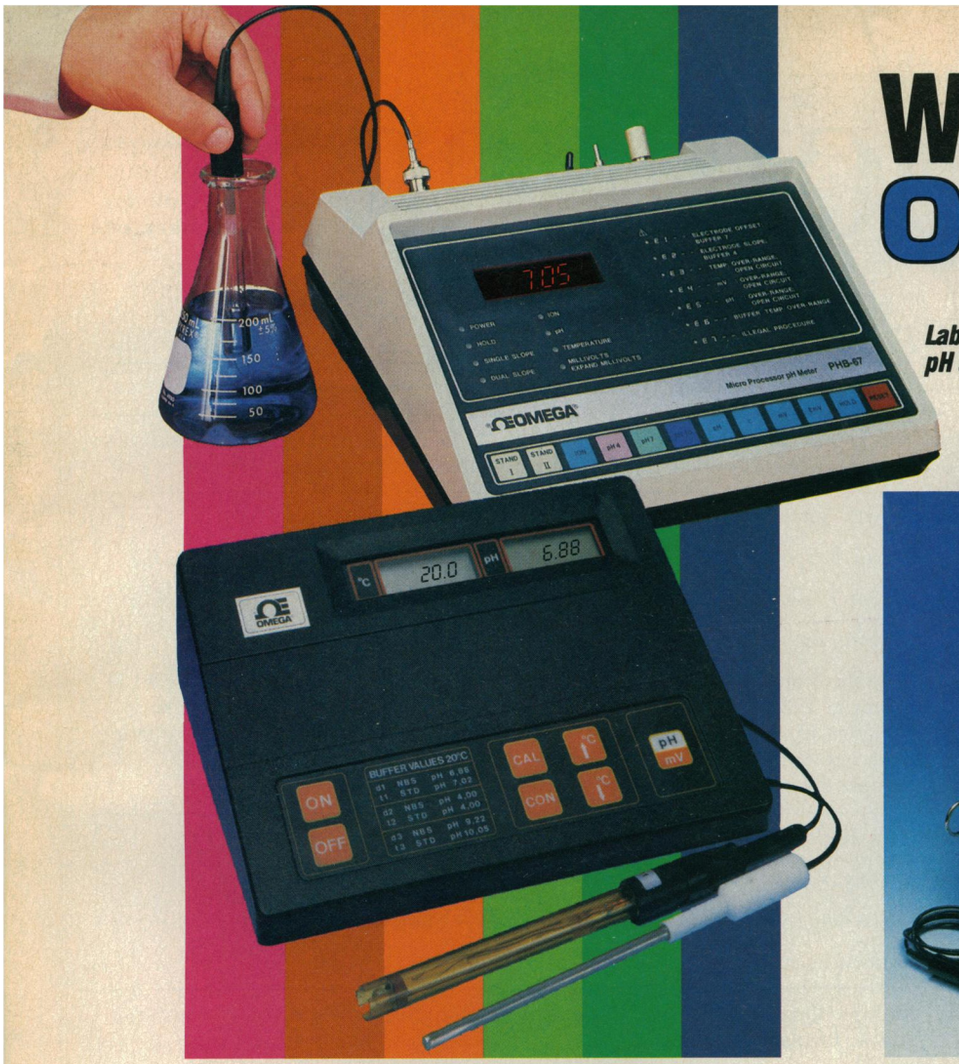


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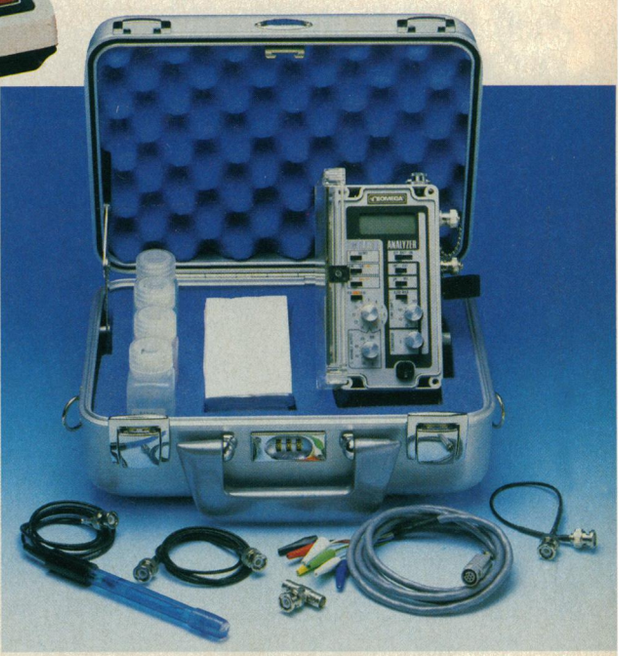


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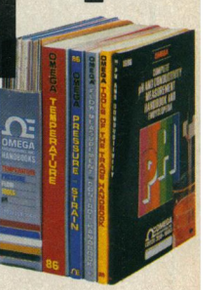


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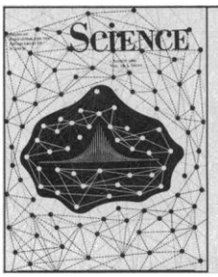


COVER Multiple-quantum NMR spectroscopy probes magnetic interactions in a network of coupled nuclei by recording the collective response of a group of coherently excited spins. The spectrum in the center, obtained from polycrystalline adamantane, shows resonances arising from the net absorption and emission of up to 60 quanta of electromagnetic radiation. See page 525. [Spectrum by J. Baum, M. Munowitz, A. N. Garroway, and A. Pines. Cover design by M. Munowitz and R. Dennis, Technical Information Division, Lawrence Berkeley Laboratory, Berkeley, CA 94720]

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## Handle on drug resistance

A new molecular model for DNA amplification in eukaryotes may provide insights into how drug resistance develops during the course of leishmaniasis, one of the major infectious diseases of the world (page 535). Garvey and Santi used the OFAGE technique (orthogonal-field-alternation gel electrophoresis) to separate DNA species—the major chromosomes and the extrachromosomal circles—from wild-type and resistant mutants of *Leishmania major*. Both stable and transitory drug-resistant mutants had extrachromosomal circles; wild-type drug-sensitive stocks did not. The circles of DNA from stable mutants may have base sequences that confer mitotic stability while those of transitory mutants would not. Studies of the structure and function of DNA circles from *Leishmania* may be relevant in drug resistance in leishmaniasis and other parasitic protozoan diseases.

## L-BSO, cataracts, and glutathione

CATARACTS develop in young mice injected at age 9 to 12 days with the drug L-buthionine sulfoximine (L-BSO); slightly older mice (14 to 17 days old) show defective spermatogenesis and hind leg paralysis or die when injected with L-BSO (page 553). Many or all of the pleiomorphic drug effects may reflect L-BSO–induced inhibition of synthesis of glutathione, a widely distributed tripeptide and the most abundant nonprotein thiol in living cells. Calvin *et al.* report that all of the experimental mice were lethargic and emaciated and had fur abnormalities; also, glutathione concentrations dropped markedly in livers, kidneys, testes, and lenses. There was no detectable glutathione in the lenses of mice treated at 9 to 12 days; their lenses were opaque when they first opened their eyes at 14 or 15 days, and, by 18 days, the pearly white opacity characteristic of cataracts was generally total. This animal model will be useful for studying details of glutathione deficiency diseases (known also in humans), for studying cataract development, and for further evaluating adverse effects of L-BSO, an agent that has been developed for altering glutathione metabolism.

## Lymphocytes in arthritic joints

LYMPHOCYTES that regularly circulate through the body to perform immune functions are found in the swollen painful joints of patients with rheumatoid arthritis; (page 556). These lymphocytes are thought to contribute to the inflammation and the pathology of the disease. They move from body fluids into joint tissue (synovium) across the high endothelial venules (HEV's). (HEV's are also conduits through which lymphocytes enter normal lymphoid organs and injured sites elsewhere in the body.) Jalkanen *et al.* studied the attachment of lymphocytes to HEV in frozen sections of synovia. The interaction had some features in common with other lymphocyte-endothelial associations but differed in the types of lymphocytes bound and in the apparent receptors on HEV to which they attached. A special recognition system thus appears to regulate transport of lymphocytes into inflamed joints, raising the possibility that a clinical approach using drugs or antibodies that interfere with the lymphocyte-synovial-endothelial interaction might be effective in treating this disease.

## Self-assembling cytotoxins

MOST drug therapy is a precarious balance between beneficial and harmful effects because drugs that can kill cancer cells or pathogens frequently also kill normal host cells (page 561). Rideout describes an approach to the development of chemotherapeutic and antibiotic drugs that involves assembly on or within cells of toxic substances from precursors that have little or no toxicity. In the prototype experiments, the assembled toxins—hydrazones forming from hydrazine derivatives and carbonyl compounds—killed bacteria and two kinds of mammalian test cells, but their precursors did not. An active self-assembled cytotoxin was identified in the lysed preparations. The success of this approach to the development of new pharmacologic agents will depend on identification and exploitation of subtle differences between normal and disease-related cells such that only the latter will preferentially bind one or more of the precursors. Harmful side effects of agents that act synergistically may be much less than those of single agents with similar inherent (possibly low) toxicity, because much smaller doses of cooperating drugs may be required.

## Channel regulation in cystic fibrosis

PATIENTS with cystic fibrosis have difficulty breathing (page 558). One factor that appears to contribute to their pulmonary dysfunction is impaired transport of chloride ions across the surfaces of epithelial cells lining the airway passages; water and electrolyte secretion then get out of balance and this may contribute to the accumulation of mucus. Frizzell *et al.* determined that epithelial cells of the airway passages have channels for chloride transport that have normal biophysical properties; however, the activity of these channels is improperly regulated. In the appropriate calcium-enriched medium, membrane patches from cells of patients with cystic fibrosis and from normal individuals showed identical channel electrical activity. But, when the β-adrenergic excitation pathway for channel activation was stimulated (with cyclic adenosine monophosphate or epinephrine), only channels of normal cells were activated. It may ultimately be possible to trace other symptoms of cystic fibrosis—sweating and pancreatic dysfunctions—to disturbed regulation of chloride channel activity in epithelial cells.

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# Treatment of Hazardous Wastes

Most observers agree that the past performance of the Environmental Protection Agency in cleaning up Superfund sites has been uninspired. In what has been called a "shell game," the net result has largely been to move hazardous waste from one spot to another or to cover the waste with a clay blanket. There has been little net destruction of the waste and hence little in the way of permanent solutions to a set of nasty problems.

Every waste dump is different in geometry, geology, and content of organic and inorganic chemicals. Organic chemicals are the most feared, most complex substances present. Technology exists to deal with part of the organic wastes (incineration), and research results are pointing the way toward dealing with much of the remainder (biodegradation). Where applicable—for example, wastes in drums—incineration can achieve essentially complete destruction. Even the most stable halogen-containing aromatic chemicals are destroyed at 1260°C. Major chemical companies have been using this procedure successfully, achieving as much as 99.9999+ percent destruction. Currently, for lack of incinerator capacity, there is a 2-year backlog of wastes to be burned. To avoid possible problems during transport to incinerators and to increase capacity, EPA should devote some of its funds to the construction of mobile incinerators to be used at Superfund sites.

Much of the organic chemical wastes have been dumped into landfills. Dilution with dirt is such that incineration is often not practical. Field experience and research indicate that biodegradation could come to have an important role. For example, benzene, toluene, xylenes, and other hazardous aromatic chemicals are found in many waste dumps and also in leakage from gasoline tanks. These chemicals and many other hydrocarbons can be oxidized in situ to $CO_2$ and $H_2O$ by microorganisms provided that they are furnished with such inorganic nutrients as phosphate and ammonium nitrogen, plus oxygen. At the site of a large gasoline spill, accompanying extraction and injection of water, nutrients were added and oxygen was provided in the form of dilute $H_2O_2$. A population of organisms ($2 \times 10^2$ per gram of soil) capable of using gasoline as a carbon and energy source increased to more than $10^6$ per gram of soil, and 65 percent of the hydrocarbons disappeared after 164 days.

Among the individual organic chemicals most prevalent at Superfund dumps are trichloroethylene, chloroform, tetrachloroethylene, and 1,1,1-trichloroethane. No organisms have been found that can grow using these substances as sole energy and carbon sources. However, the compounds can be degraded by bacteria whose growth is supported by another metabolite. As one example, methanogenic organisms (anaerobes), when supplied acetate, slowly degraded tetrachloroethylene and 1,1,1-trichloroethane, as well as chloroform and carbon tetrachloride.* A different set of organisms has destroyed halogenated hydrocarbons under aerobic conditions. This time, the energy and carbon source was methane, and 12 halogenated aliphatic hydrocarbons were degraded to some extent.† Similar treatment of $^{14}C$-labeled trichloroethylene showed fairly rapid total destruction. Products included $CO_2$ and biomass; no halogenated organic compound remained.‡

In terms of practical applications, there is a long history of use of aerobes in oxidizing many hydrocarbons such as those in oil or gasoline. However, the most troublesome components of Superfund dumps are the small halogenated hydrocarbons. Priority should be accorded to expanding laboratory investigations dealing with these substances. In addition, field experiments should be conducted using injection coupled with withdrawal of nutrient streams under both anaerobic and aerobic conditions.

The public does not welcome the establishment of waste dumps for toxic chemicals removed from somewhere else. As currently authorized sites are filled, EPA will find that it has no real alternative but to deal with the contents of most sites in situ. Prospects are good that multidisciplinary applications of science and engineering can be effective.

—PHILIP H. ABELSON

*E. J. Bouwer and P. L. McCarty, *Biotechnol. Bioeng.* **27**, 1564 (1985). †J. M. Henson, J. W. Cochran, J. T. Wilson, R. S. Kerr, in preparation. ‡M. M. Fogel, A. R. Taddeo, J. Fogel, *Appl. Environ. Microbiol.* **51**, 720 (1986).