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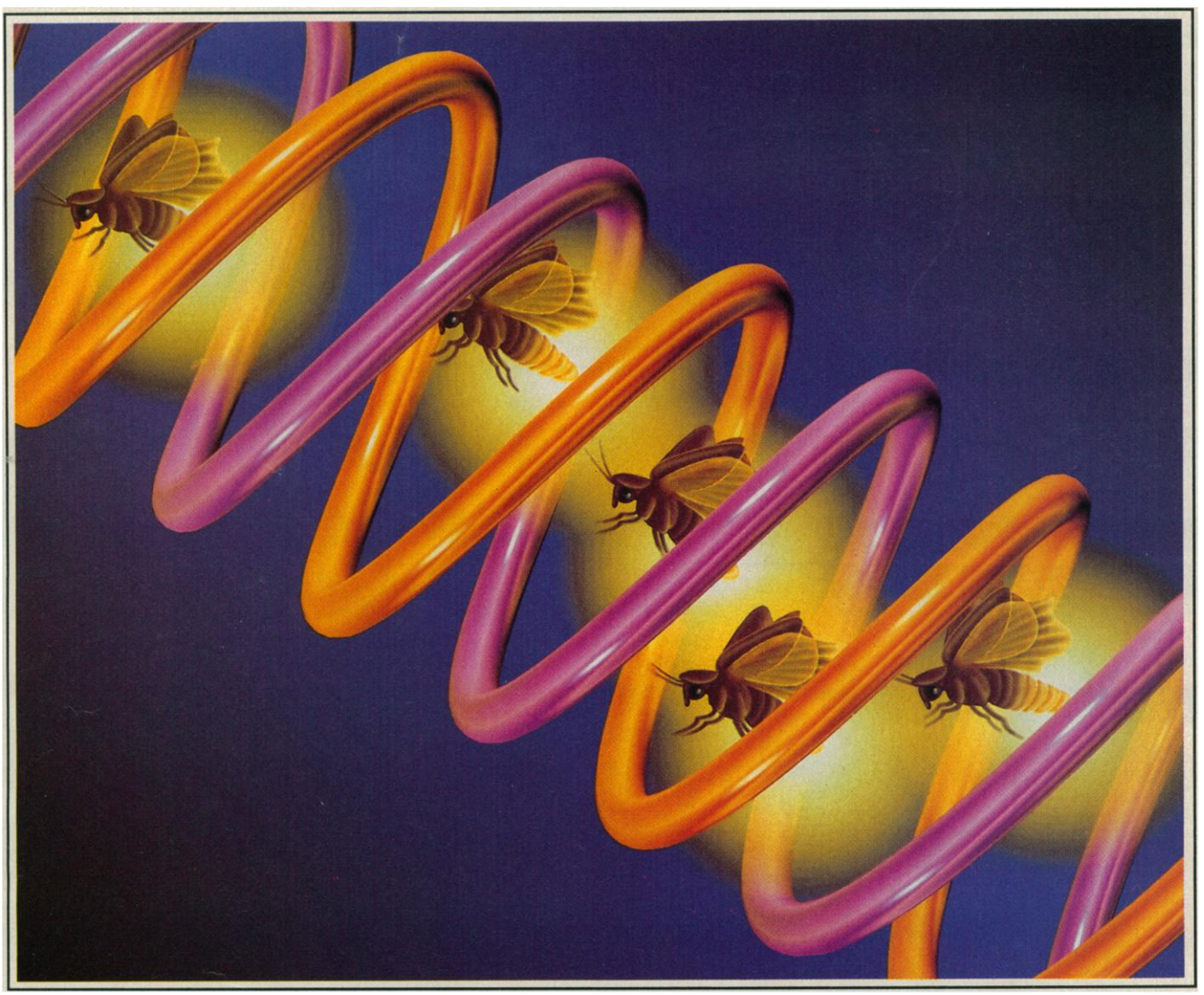

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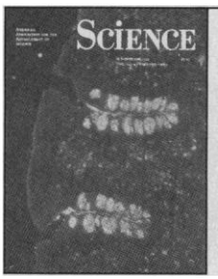


COVER Micrograph of immunolabeled taste buds from the circumvallate papilla of a rat tongue. Monoclonal antibodies have been used to isolate taste cells in order to study their properties and mechanisms of gustatory transduction. Taste cells respond to a bitter stimulus with a rise in intracellular calcium concentration that is derived from intracellular stores. See page 1047. [Photo by J. Dodd, College of Physicians and Surgeons of Columbia University, New York, NY 10032]




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## Artificial airglow: tickling the ionosphere

ATMOSPHERIC luminescence, or airglow, which is most easily observed in the night sky, can be produced and enhanced with high-power beams of electromagnetic waves (page 1022). Bernhardt *et al.* recorded, with a new charge-coupled device, the optical emissions from artificial airglow clouds generated in the ionosphere above Arecibo, Puerto Rico. The electromagnetic waves engender in the ionosphere a complex cascade of events that includes interactions of waves and particles, heating of plasma, excitation and de-excitation of atoms, and, eventually, the emission of light at visible wavelengths by neutral atoms. Airglow clouds first form in the shape of the transmitter's radiation pattern; the plasma undergoes physical changes—density is reduced and a cavity is carved out—and, as the earth's magnetic field, electric fields in the ionosphere, and heat from the transmitter exert their effects, the airglow clouds move and then snap back. Ionospheric dynamics will be increasingly understood as additional perturbations of the upper atmosphere are induced with radio waves and observed with optical imagers.

## Spliceosome assembly

MESSENGER RNA is pieced together through the splicing of regions of a precursor RNA molecule. The molecular machinery for splicing, a spliceosome, forms on the precursor and consists of small nuclear ribonucleoproteins (snRNPs) named U1, U2, U4, U5, and U6 and other proteins and transacting factors. Spliceosomes are assembled in an orderly fashion. The earliest stages in their step-by-step construction were monitored by Ruby and Abelson with an affinity purification technique (page 1028); precursor molecules were attached to a solid support, and the sequential additions of snRNPs from a yeast splicing extract were followed as some of the RNA was spliced. U1 was the first snRNP to bind; it bound only when the 5′ splice site of one precursor and the bases at the branch point near the 3′ splice site of the other were available and intact. U2 bound next if U1 had correctly associated with the 5′ and 3′ splice site regions and if molecules of ATP were available. U5 attached next, again depending on the proper assembly of the spliceosome up to that point. Similar events may characterize the assembly of spliceosomes of most species including humans, because many of the elements of splicing systems appear generally to have been conserved.

## Better proteins through chemistry

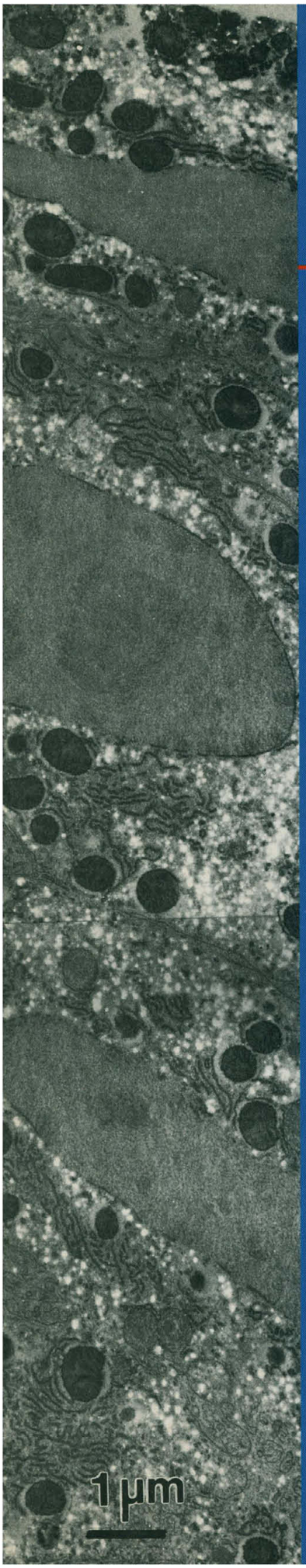
A general chemical procedure for introducing catalysts or other functional synthetic groups into the highly selective combining sites of antibody molecules is described by Pollack *et al.* (page 1038). Monoclonal immunoglobulins were exposed to a thiol-substituted affinity labeling compound (a compound that is directed to the antigen combining site and then forms covalent bonds there); covalent attachment occurred, the labeling compound was then cleaved, and only the thiol groups remained attached in the site. The thiol accelerated a chemical reaction in the site and also served as a tether to which other functional groups could be attached. These procedures and various modifications of them—other proteins, other catalytic groups, other tethers, and other tags—can confer new and potentially useful catalytic functions to antibody molecules.

## The bitter truth

CELLS in the taste buds (cover) discriminate among sweet, sour, salty, and bitter substances. Those that detect bitterness may be the most crucial for survival (while providing the least gustatory pleasure) because many poisonous substances taste bitter. Using new methods for dissociating tongue cells into small aggregates (taste buds), Akabas *et al.* studied the responses of single taste cells to denatonium chloride, one of the most bitter of substances (page 1047). Only one or a few cells in each aggregate typically responded: intracellular calcium ions rose as a result of calcium release from intracellular storage sites. Denatonium chloride cannot permeate cell membranes and thus is presumed to have bound to surface receptors on taste cells and from there to have transduced its bitterness signal through an internal second messenger; the messenger may then induce the taste cell to release a neurotransmitter that, in turn, would excite a gustatory neuron. Recognition of bitter substances seems to involve a molecular response unlike the membrane depolarization events that appear to signal the presence of sweet, sour, and salty substances.

## Rinderpest vaccines

RECOMBINANT vaccines have been prepared that protect cattle against deadly rinderpest viruses (page 1058). Rinderpest (German for cattle plague) is a highly infectious disease that presently is epidemic in Africa and Asia; its control would have major economic, ecologic, and social ramifications. Although the currently used Plowright tissue culture vaccine controls rinderpest, that vaccine is heat-labile and has not been effective in countries lacking tissue culture facilities, refrigeration, and trained laboratory personnel. Heat-stable recombinant vaccines have now been constructed by Yilma *et al.* with the vaccinia virus that was used to eradicate smallpox from the world; the virus was engineered to express rinderpest genes—hemagglutinin, fusion, or both—that typically elicit protective immunity in infected animals. Recombinant vaccines fully protected cattle from challenge doses of rinderpest viruses that killed unvaccinated animals in less than a week. These vaccines are easy to prepare, transport, and use; they should protect against all strains of the rinderpest virus and may even provide cross-protection against infections caused by related viruses, such as those responsible for canine distemper and human measles.

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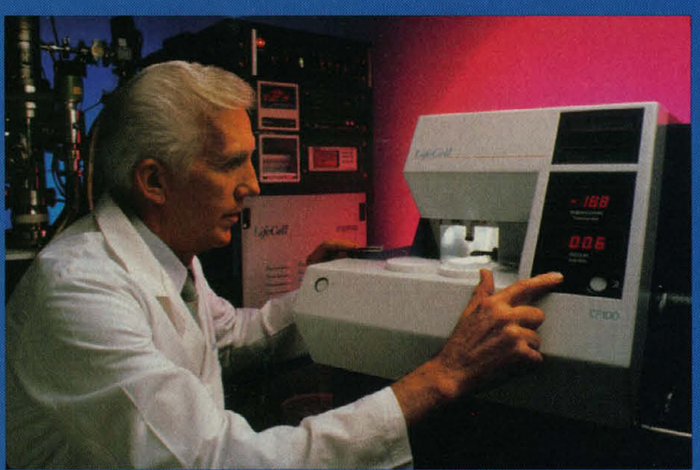

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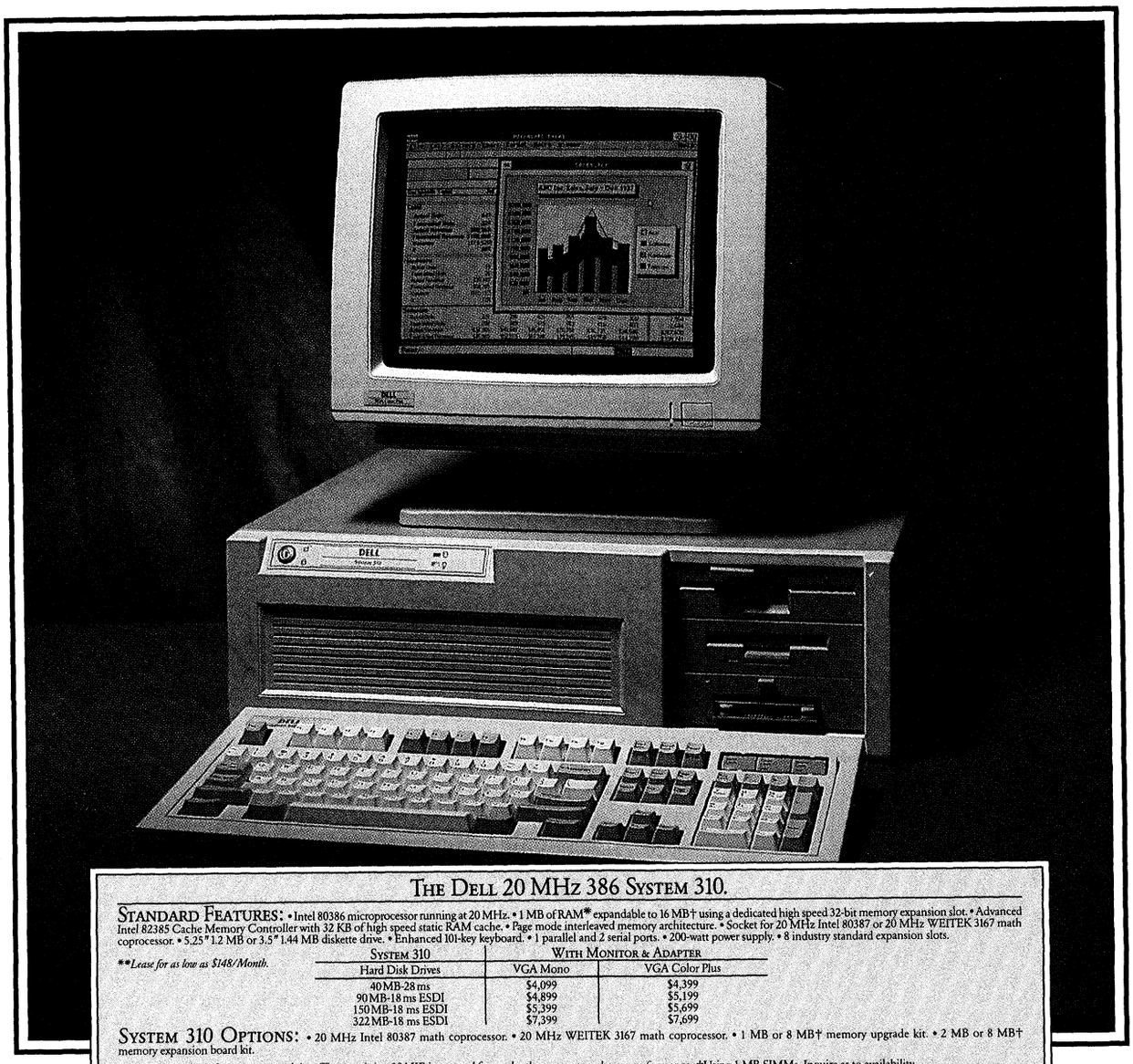

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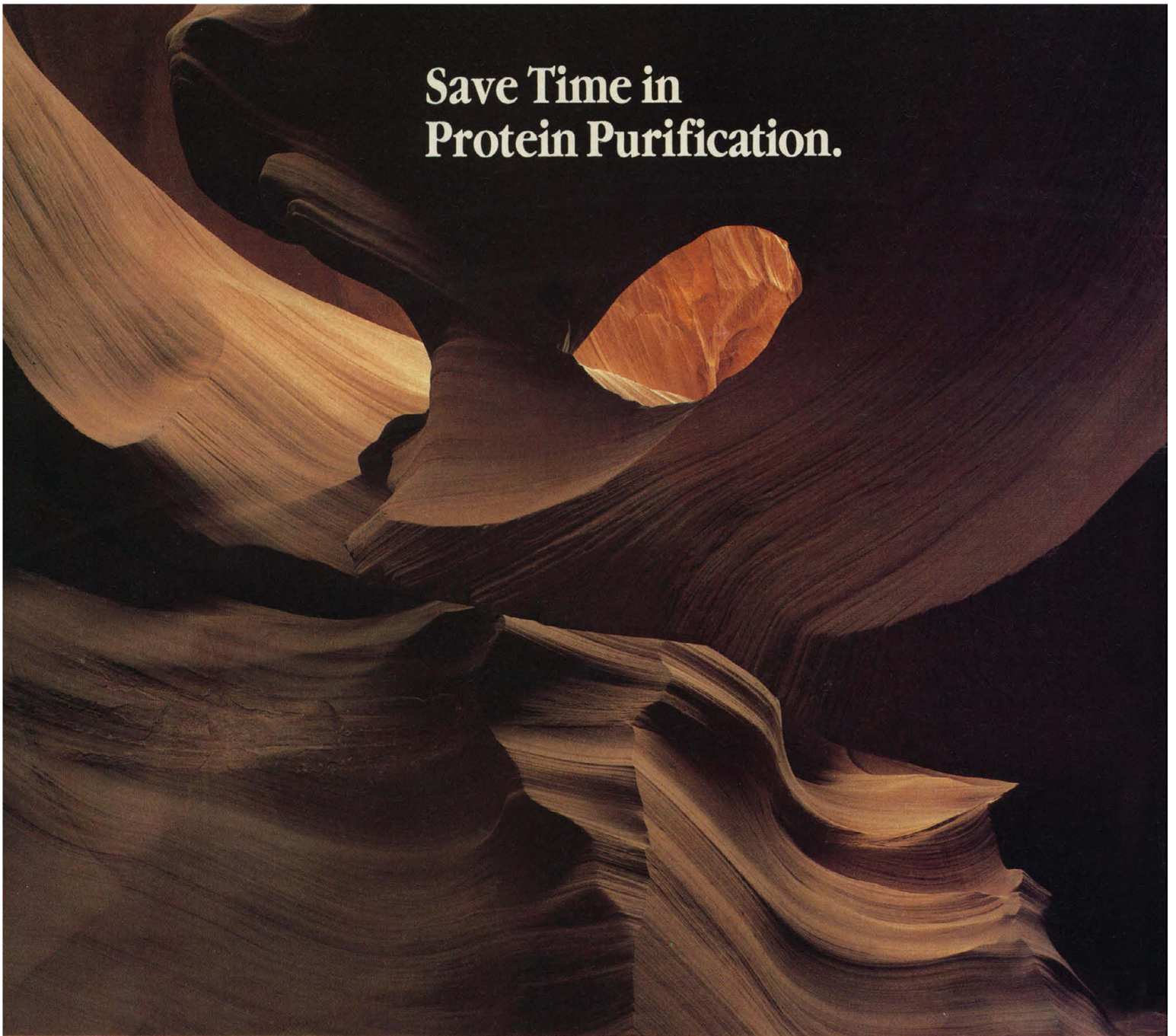


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tion "as a whole." Their conclusion that there is "no evidence of 'factors defined by lifestyle, health . . .' that might affect progression to AIDS, other than age" is not convincing unless antibody-positive heterosexual controls of the same age are included. There is also no "consensus of epidemiologists" on this claim, as two studies postulate such factors in the generation of AIDS (*3, 9*).

Similarly misleading is the suggestion of Blattner, Gallo, and Temin that the conversion to AIDS by a single antibody-positive health care worker [reported anonymously (*10*) without data on gender, latent period, or symptoms] proves that HIV causes AIDS. This one case falls into the ~5% window of all American AIDS cases that have no verifiable AIDS risks (*2*), while 95% of the 2586 health care workers with AIDS fall into the conventional risk groups (*10*). Moreover, despite much greater exposure to HIV (*10, 11*), the AIDS risk of health care workers is exactly the same as that of the general population (*2, 10*). Even the sexual distribution of AIDS cases is the same as that of the general population, namely, 92% of these cases are male, although 75% of the health care workers are female (*10*). Thus, unless the percentage of health care workers with AIDS who do not belong to the known risk groups exceeds that of the rest of the population and reflects their sexual distribution, such isolated cases are statistically irrelevant.

Trachtenberg and Winter are concerned that my "seemingly scientific" views serve as a psychological narcotic, allowing a "vulnerable population" to deny their fate. This concern is warranted only if their own, presumably more scientific, arguments that infection with HIV is necessary and sufficient to cause AIDS are correct. However, since HIV is nearly undetectable in AIDS and the pathology is not understood, the consensus of the "HIV establishment" that HIV causes AIDS appears to be "deadly" denial of biochemical alternatives. Since all other viral and microbial pathogens are biochemically very active in or on more cells than the host can spare or regenerate when they cause a fatal disease, I favor hypotheses that offer biochemically tangible bases for AIDS, namely drugs, acute infections (*5*), and malnutrition (*12*). If latent viruses or microbes were pathogenic at the level of activity of HIV, most of us would have pneumocystis (80 to 100%) (*13*), cytomegalovirus disease (50%), mononucleosis from Epstein-Barr virus (50 to 100%), and herpes (25 to 50%) (*14*) all at once, because the respective pathogens are latent, immunosuppressed passengers in the U.S. population at the percentages indicated.

In view of all of the above, it is "unfortunate" that the toxic AZT therapy of symptomatic and even asymptomatic antibody carriers designed to inhibit DNA synthesis of latent HIV (*15*) and the psychologically toxic AIDS test "have been widely disseminated to a vulnerable population."

PETER DUESBERG
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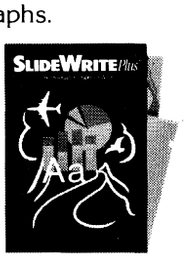


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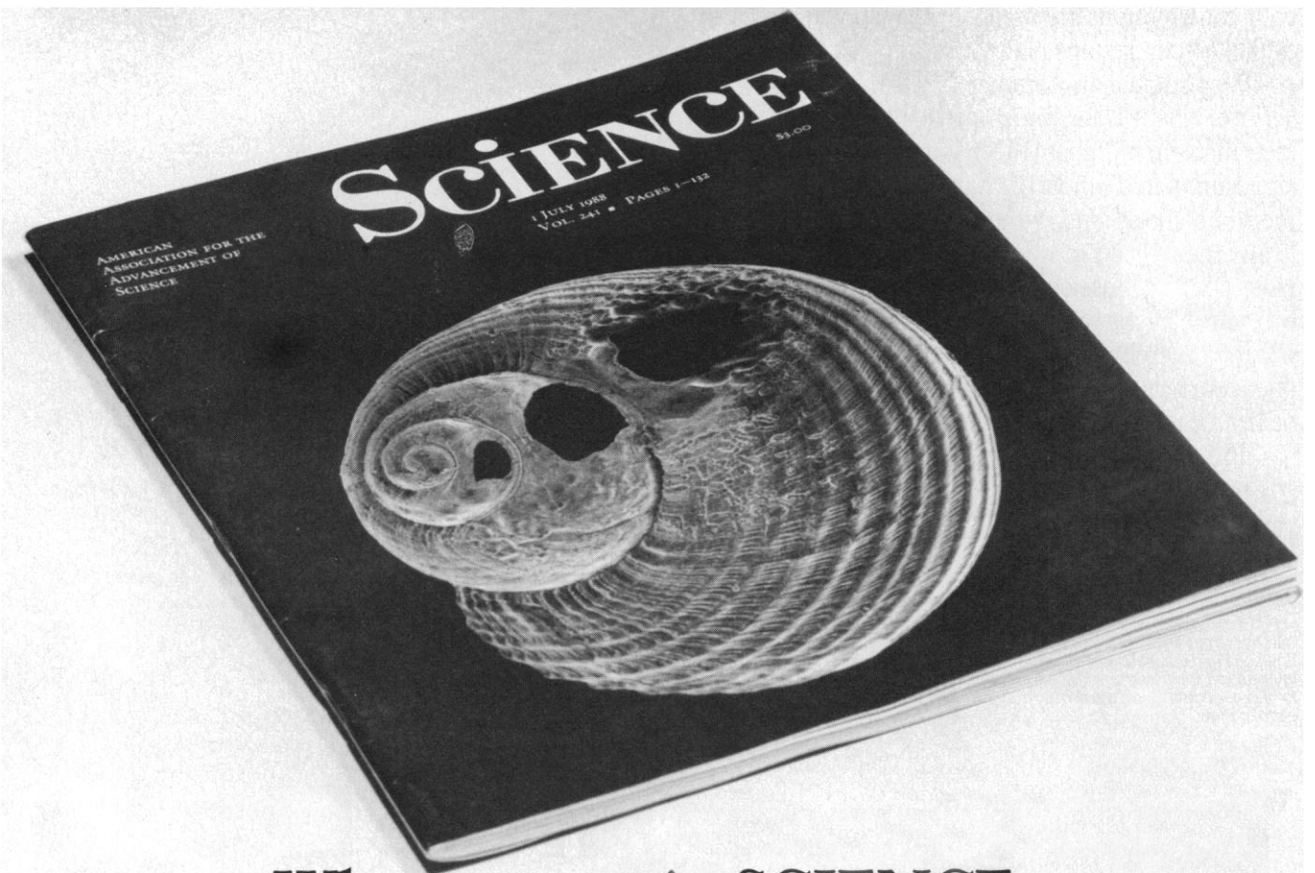


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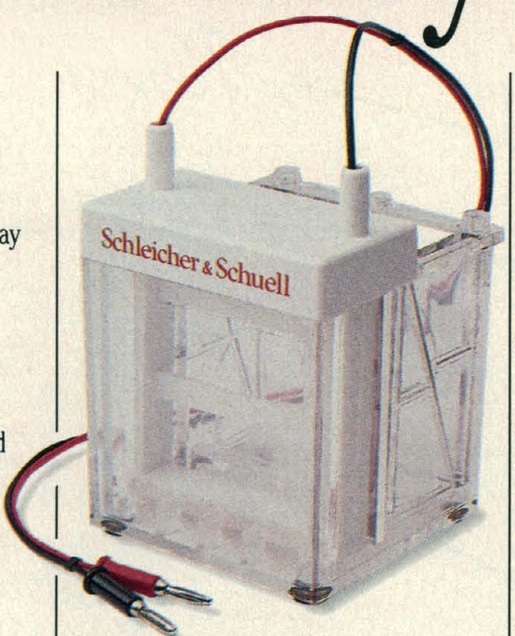


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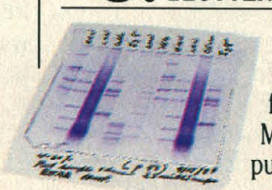

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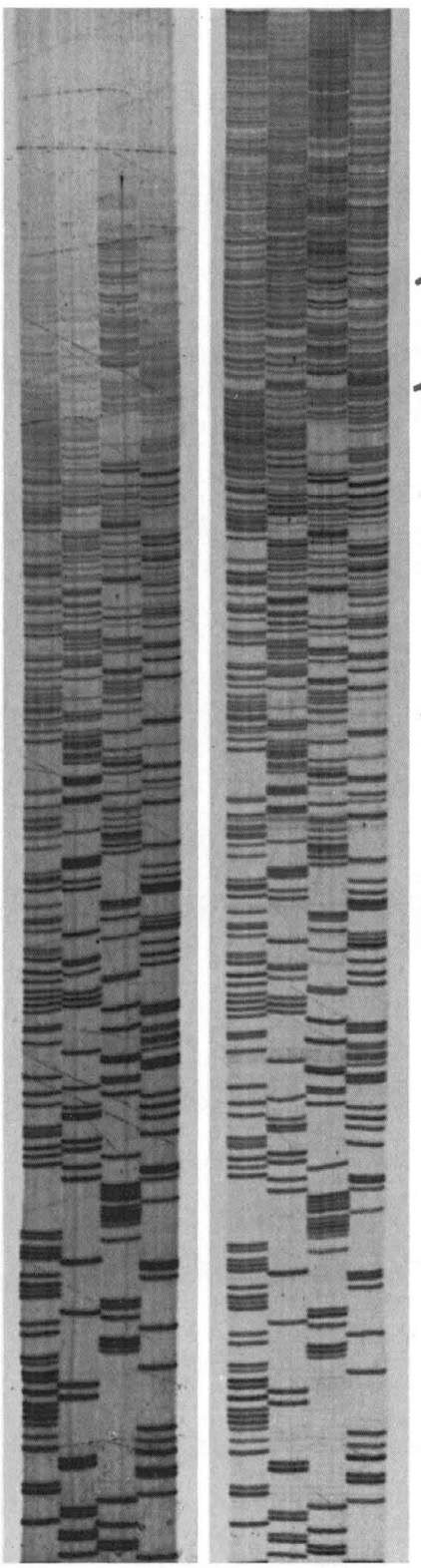


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30. Step 1. Synthetic actin pre-mRNA was transcribed in vitro by SP6 polymerase to a specific activity of $3.2 \times 10^3$ Cerenkov cpm/fmol with [$\alpha$-$^{32}$P]UTP and purified by gel electrophoresis (*47*). The actin gene templates were previously cloned (*6*) in plasmid vectors pSP65 or pSP64 and had the cryptic branch-point sequence deleted from the intron. They were linearized with the Acc I or Sty I restriction endonucleases. Step 2. Anchor RNA and pre-mRNA were hybridized in solution (70 m*M* tris-HCl, *p*H 7.6, 8 m*M* NaCl, 1.5 m*M* EDTA, 25 to 500 n*M* anchor RNA, and 25 n*M* actin pre-mRNA) by heating at 100°C for 1 minute and 65°C for 1 minute and then gradually cooling from 37°C to 15°C for 40 minutes. Step 3. Succinylated avidin (EY Laboratories) was incubated for at least 1 hour at 0°C with biotin-agarose (12-atom biotin-linker arm; Sigma) in a ratio of 2 mg of avidin to 1 ml of agarose. The coupled agarose was washed three times with five volumes of binding buffer (150 m*M* potassium phosphate buffer, *p*H 7, 1 m*M* EDTA, 15 percent glycerol, and 0.05 percent NP-40) and resuspended in binding buffer to the original volume of agarose. The RNA duplex was then incubated with the agarose (either $0.6 \times 10^4$ or $1.2 \times 10^4$ Cerenkov cpm RNA hybrid per microliter of agarose) for at least 40 minutes. A second portion of succinylated avidin (0.5 μg per microliter of agarose) was added and incubated for 30 minutes. The RNA-agarose was washed three times with binding buffer, distributed into Eppendorf tubes, and washed once with four volumes of splicing buffer [60 m*M* potassium phosphate buffer, *p*H 7, 1 m*M* sperimidine, 3 m*M* $MgCl_2$, 3 percent PEG8000, 0.5 m*M* DTT, and RNAsin at 800 U/ml) with or without 2 m*M* ATP. The splicing buffer was removed, and ATP (2 nmol per microliter of splicing extract) was added as indicated. Step 4. Typically, 60 μl of splicing extract [splicing buffer supplemented with 40 percent yeast 35P cell extract (*6*) or whole cell extract (*47*)] were incubated at 23°C for 10 minutes to deplete any endogenous ATP by adenosine triphosphatase in the extract and then added to 40 μl of RNA-agarose with or without ATP. The reactions were incubated at 23°C for the indicated times during which they were gently mixed by hand at 5-minute intervals. They were stopped by the addition of a tenfold excess of washing buffer (150 m*M* NaCl, 20 m*M* Hepes, *p*H 7.8, 3 m*M* $MgCl_2$, 0.5 m*M* DTT, 15 percent glycerol, and 0.05 percent NP-40) at 0°C and by sedimentation for 7 seconds in an Eppendorf centrifuge. The RNA-agarose was washed twice again with washing buffer at 0°C. Step 5. The RNA, and the factors bound to it, were eluted twice from the agarose at 0°C for 5 minutes with five times the volume of elution buffer (40 m*M* tris-HCl, *p*H 9, 150 m*M* NaCl, 3 m*M* $MgCl_2$, and 150 m*M* DTT) (*30*). RNA in the combined eluents was extracted as described (*47*).
31. Avidin rather than streptavidin must be used for the disulfide bond in the 12-atom linker arm to be reduced [T. M. Herman, E. Lefever, M. Shimikus, *Anal. Biochem.* **156**, 48 (1986)]. Although splicing reactions contain 0.5 m*M* DTT, this concentration is not high enough to elute the anchor RNA with multiple biotin residues during the incubation periods used here.
32. Less than 10 percent of a truncated pre-mRNA lacking the region complementary to the anchor RNA attached to the matrix either with or without anchor RNA.
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34. Unless otherwise stated, the extract we used is a fraction (35P) prepared from a 35 percent ammonium sulfate precipitate of whole cell splicing extract (*6*). This fraction is active for splicing but has less nuclease activity than whole cell extract.
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37. To calculate the amount of an snRNA bound in each reaction, we first subtracted the background (the amount of the snRNA binding to anchor RNA) to get a net value. This value was then divided by the amount of pre-mRNA on the blot in the lane for that reaction. The value is usually expressed as the percentage of the amount of snRNA bound to the wild-type pre-mRNA in the presence of ATP as determined in each experiment.
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46. The biotin ester used in the second step reacts preferentially with the allylamines in the anchor RNA. Most of the ester is removed during ethanol precipitation. Any residual ester is removed during the binding of the hybrid RNA to the support.
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49. After electrophoresis in 4 percent denaturing polyacrylamide gels, RNA was transferred to GeneScreen membrane (NEN) by electroblotting at 4°C in 2 m*M* tris borate (*p*H 8), and 0.5 m*M* EDTA at 120 V as described by G. M. Church and W. Gilbert [*ibid.* **81**, 1991 (1984)]. RNA was cross-linked with ultraviolet light from three GE G1578 bulbs at a distance of 35 cm for 10 minutes. Hybridization was as described (*26*). For probes, DNA fragments containing the yeast snR6 (*21*), snR7 (*19*), snR14 (*20*), snR19 (*17*), and the 5′ two-thirds of the snR20 (*16*) genes were $^{32}$P-labeled by random oligodeoxynucleotide-primed extension [A. P. Feinberg and B. Vogelstein, *Anal. Biochem.* **132**, 6 (1983)].
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51. We thank Z. Hostomsky for an early version of a solid-phase splicing assay; M. Ares (snR20), B. Patterson and C. Guthrie (snR7), P. G. Silciano and C. Guthrie (snR14 and snR19), P. Fabrizio (snR6), U. Vijayraghavan (mutant actins), and J. Szostak (rDNA) for cloned genes; O. Uhlenbeck for helpful advice on in vitro synthesis of small RNA's; S. Horvath for synthesizing oligodeoxynucleotides; R. Luhrmann for providing antibody to $m_3G$ cap; M. Aebi, T. Amatruda, G. McFarland, and U. Vijayraghavan for commenting on the manuscript; and D. Brow, C. Guthrie, A. Igel, M. Ares, E. Shuster, P. Legrain, B. Seraphin, and M. Rosbash for communicating results prior to publication. Supported by NIH grant GM32637 (J.A.) and by American Cancer Society Fellowship PF2647 (S.W.R.).

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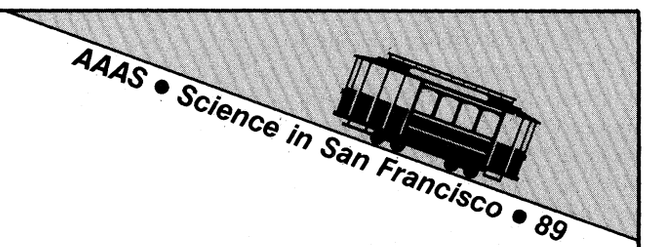


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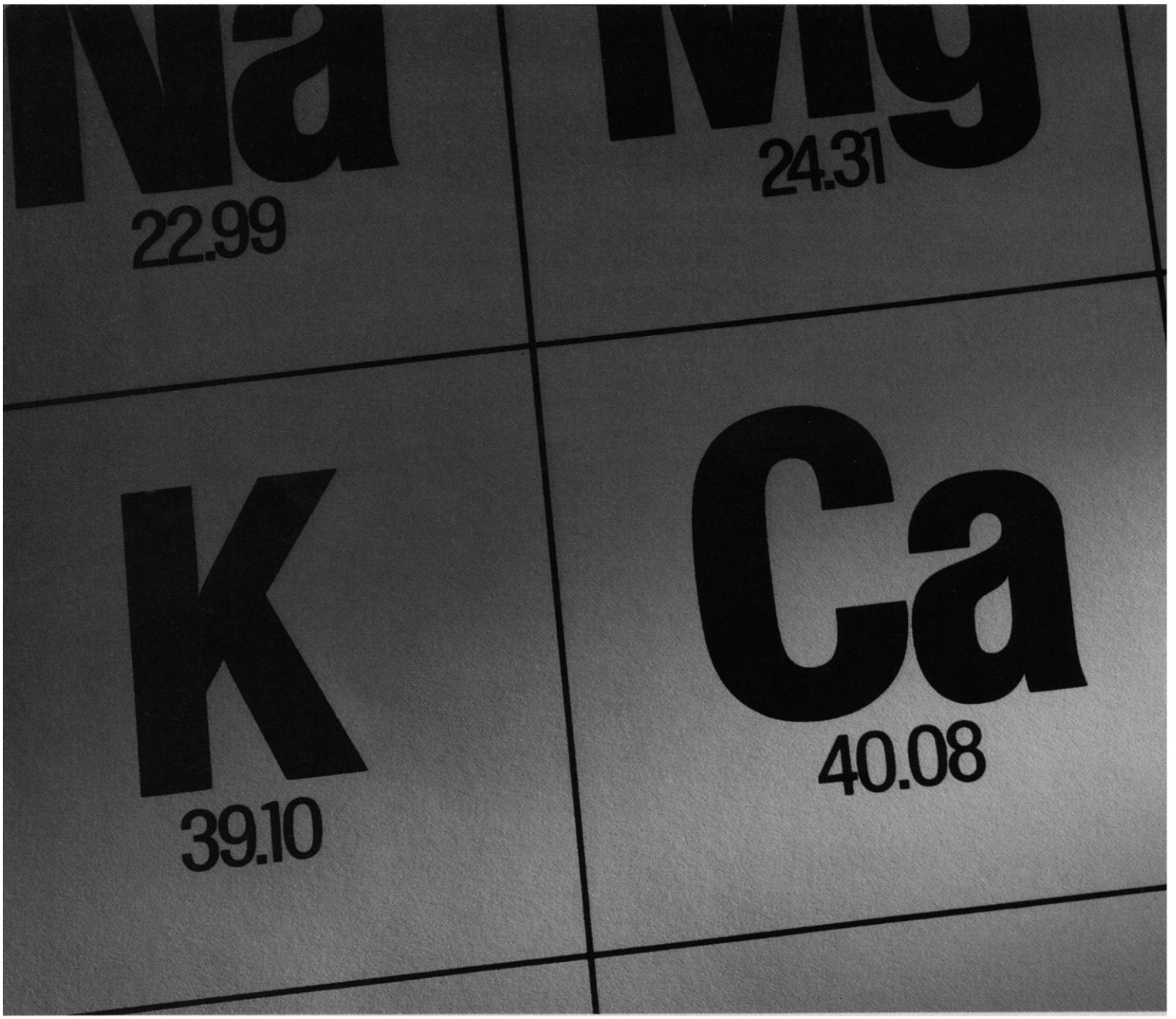


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