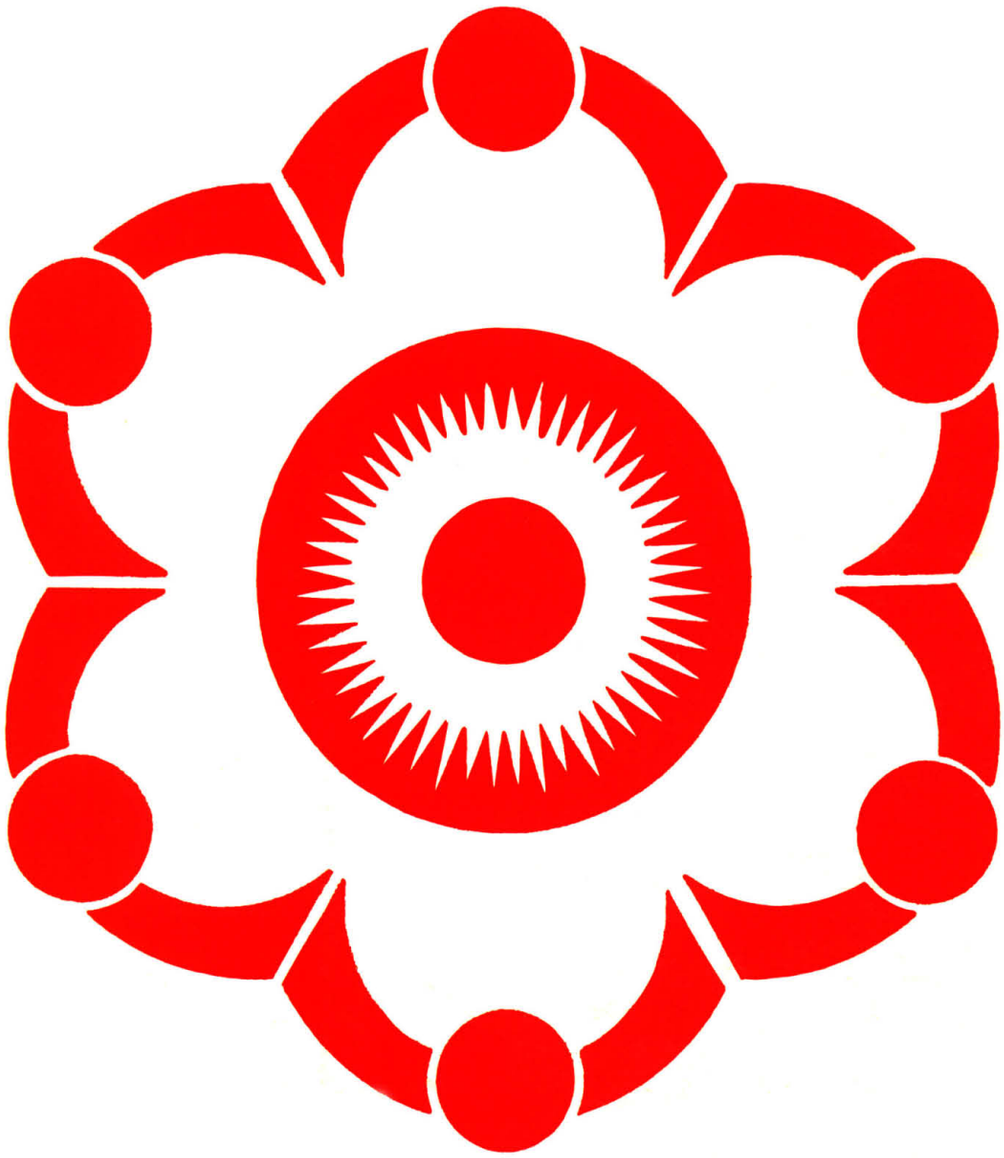
SCIENCE

18 May 1973

Vol. 180, No. 4087

AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE



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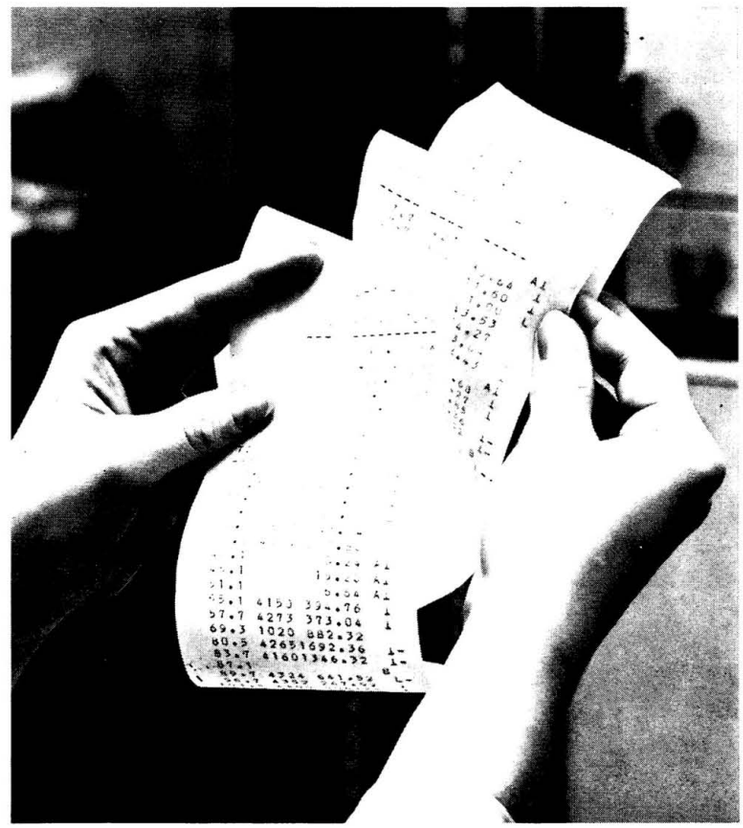

...in concentration, percent concentration, molar ratio, and 440/570 nm ratio.

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18 May 1973

Volume 180, No. 4087

SCIENCE

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COVER

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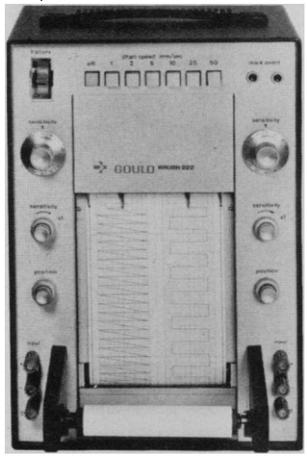

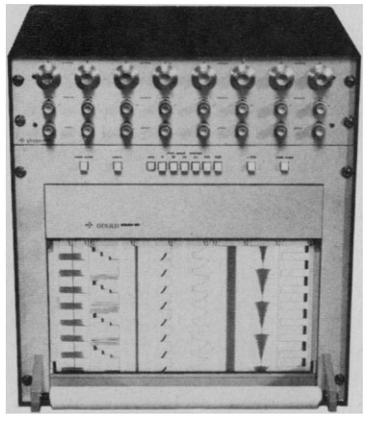

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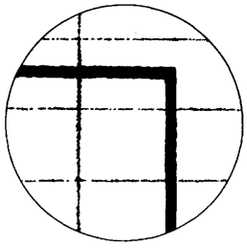
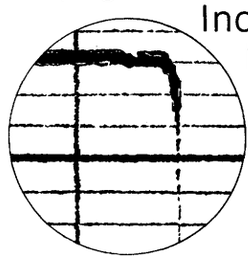


Our traces



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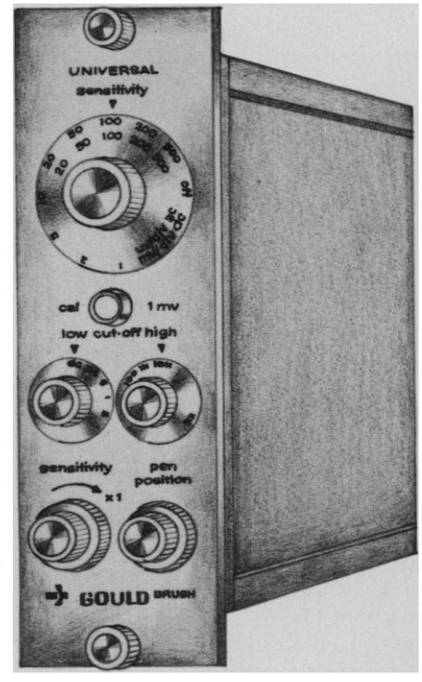

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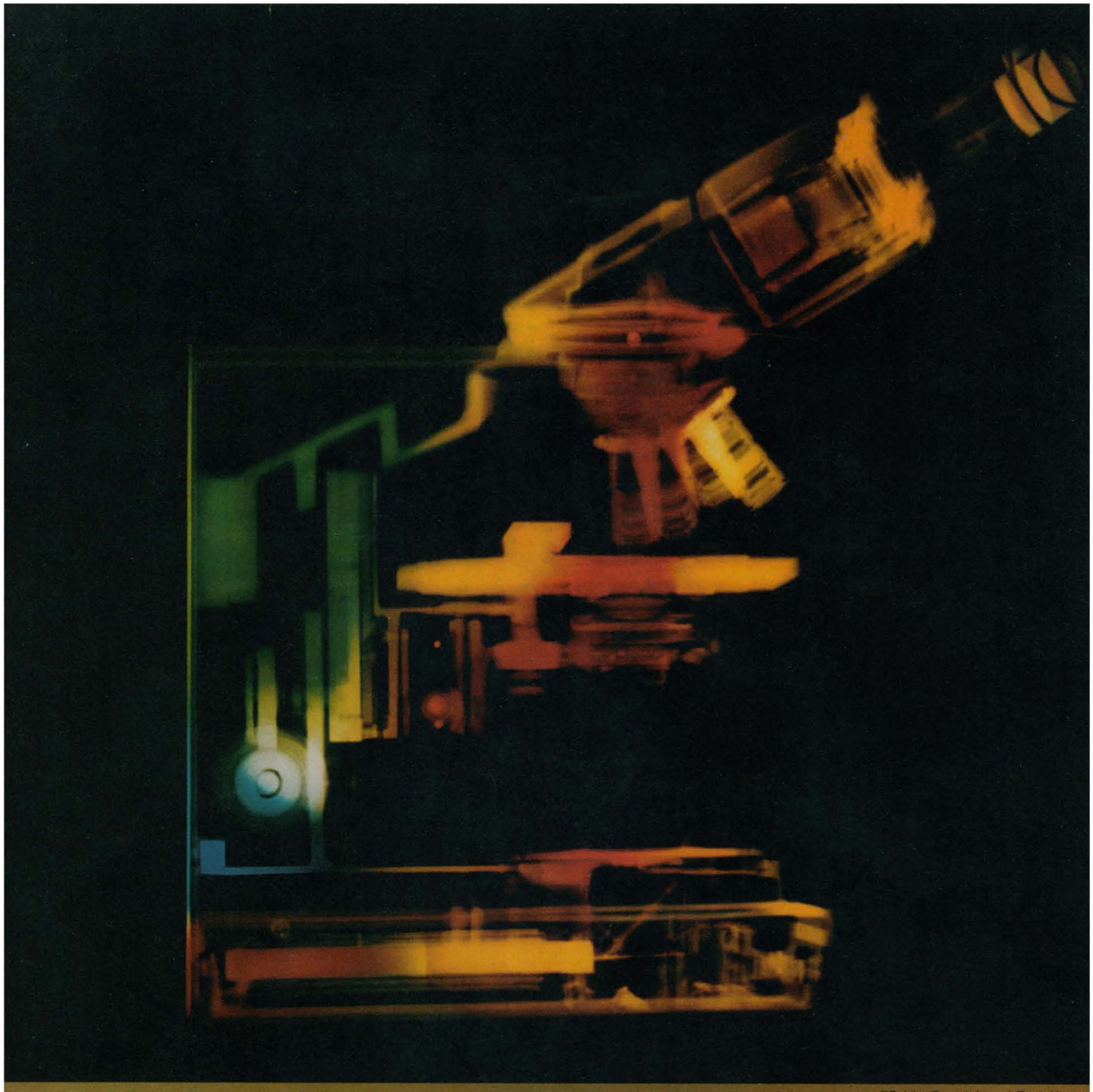

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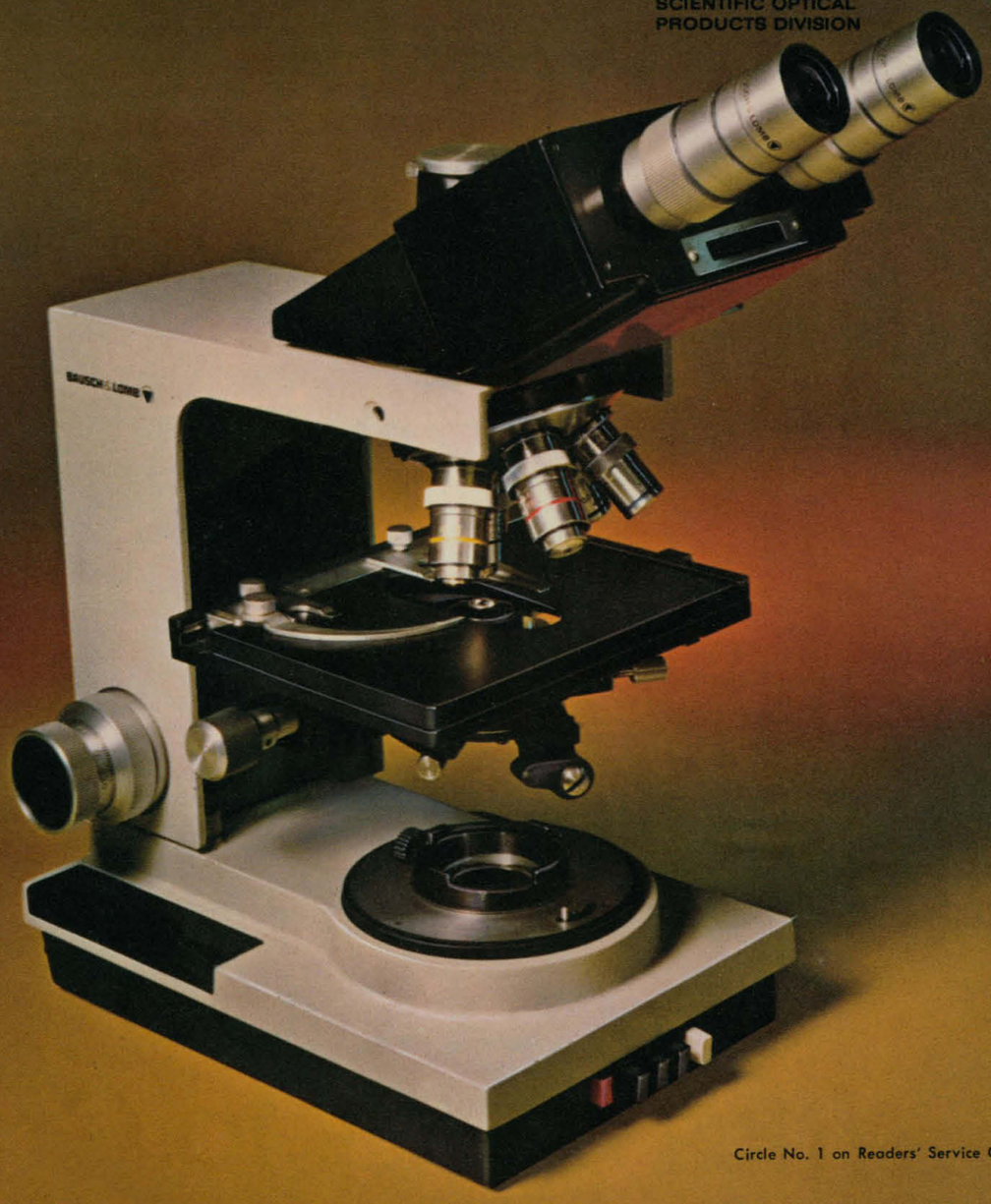

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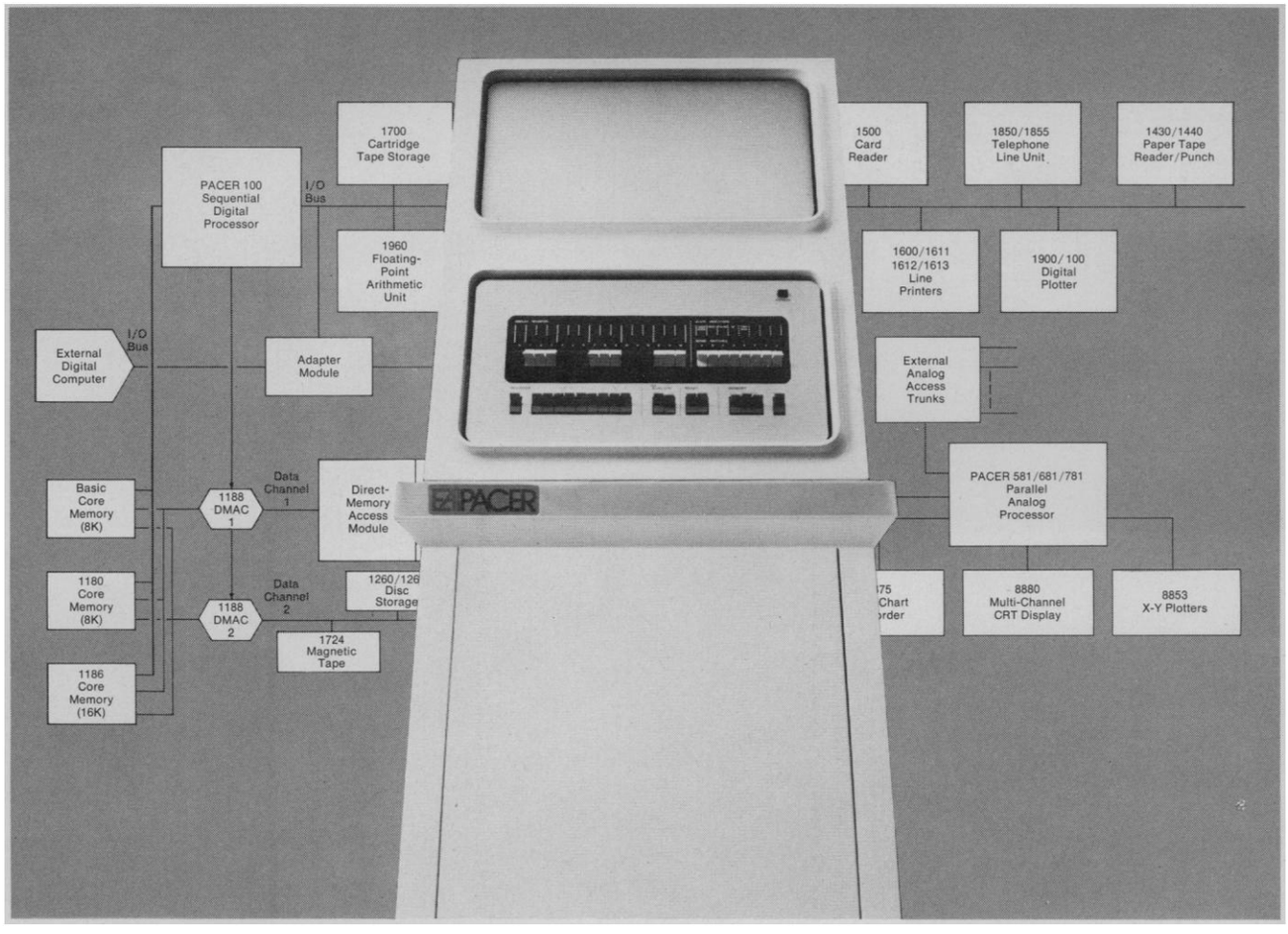

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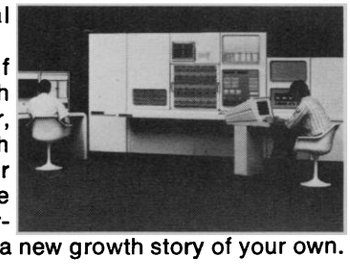

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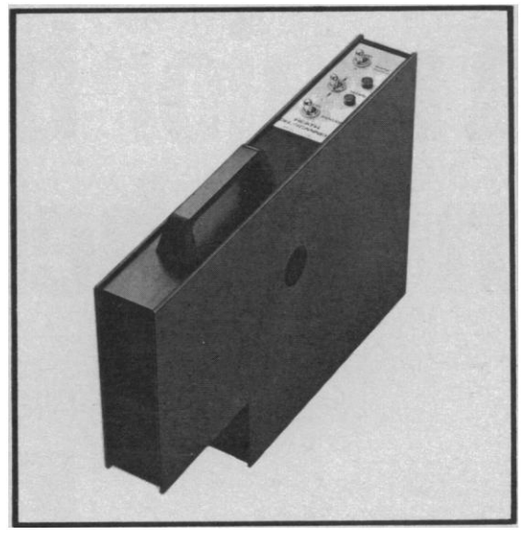

If you're looking for an easy and accurate way to quickly scan acrylamide gel columns, the new Heath/Schlumberger Gel Scanner is the answer. As an accessory for our single-beam UV-visible spectrophotometers, it offers a high performance, low-cost approach to scanning gel separations.

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The EU-705-11 accepts 5 to 10 mm gels up to 150 mm in length. Two scanning speeds of 5 mm/min and 20 mm/min are provided with a one-to-one relation established between gel scanning speed and chart recorder speed for easy correlation of absorbance with gel position. Scanning apertures of 0.2 mm and 0.05 mm provide excellent resolution. The module can be used for a UV or visible scan in both directions with an automatic shut-off at the end of each scan. Manual override of the scanning system is possible at any time during the scan for specific positioning of the carrier. Gels may be positioned dry on the teflon-coated holder provided or placed in a cuvette. An additional holder is included for scanning of thin negatives. And the price is only $750.*

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(fluorescamine)

reagent for assaying primary amines in the picomole range

a reagent of great sensitivity

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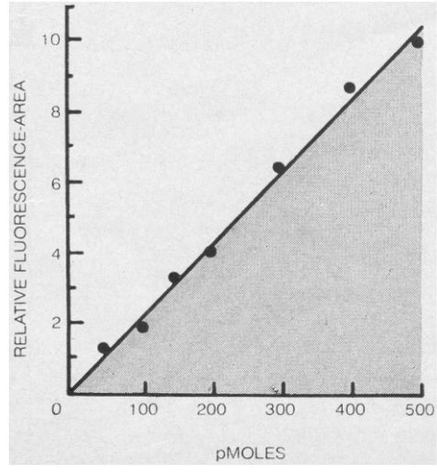
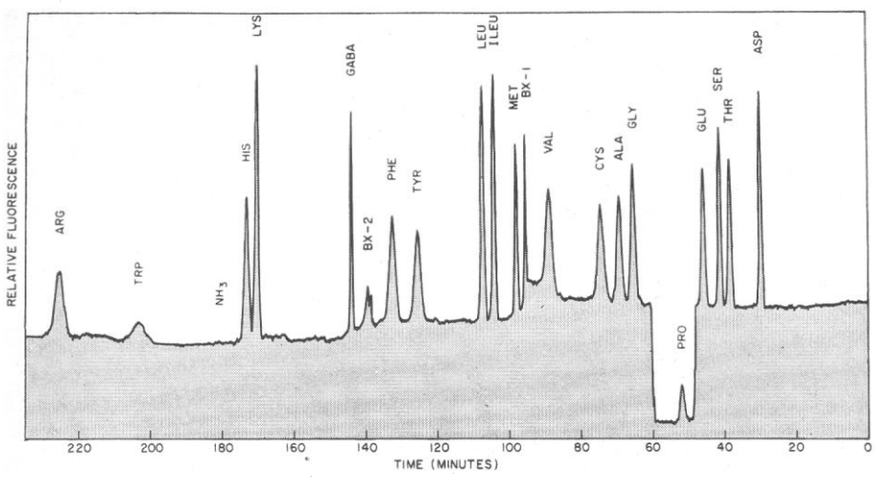
an assay of great simplicity

Primary amine solutions are buffered appropriately; FLURAM, dissolved in acetone (or other water-miscible, nonhydroxylic solvents) is added; in seconds at room temperature the reaction is complete, and excess reagent is hydrolyzed rapidly; the fluorophors formed are stable for several hours under conditions of assay; fluorescence is proportional to amine concentration.

Linearity of fluorescence with various amounts of arginine applied to the short column of the amino acid analyzer.



TOTAL FLUOROMETRIC AMINO ACID ANALYSIS (500 picomoles)



adapts readily to automation

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secondary amino acids are easily converted to detectable primary amines

Although FLURAM does not react directly with proline and other secondary amino acids, by introducing a simple intermediate step these substances can be converted to primary amines which are detectable with FLURAM.

adaptable to varied analytical procedures

FLURAM can be used in aqueous solution, in organic solvents and on solids. On thin layer chromatograms it has been used as a spray to detect amino acids and peptides.

present range of application is wide; potential unknown

Because FLURAM reacts with primary amines to yield highly fluorescent derivatives, it is uniquely suited for both manual and automated microanalysis of many biologically important compounds such as amino acids, peptides, proteins, catecholamines, amino sugars, oxytocin and vasopressin. Other applications of FLURAM currently being explored include peptide sequencing, genetic studies, assay of proteolytic activity of enzymes, monitoring for completeness of coupling reactions in peptide synthesis and labeling of proteins. The enormous range of potential applications for FLURAM should expand knowledge in the field of molecular biology and find eventual value in clinical medicine.

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	5.0	10.0	33.3	28.4
	6.0	9.0	40.0	26.7
Brand A	0.5	15.0	3.2	33.0
	5.0	15.0	25.0***	28.0

*Manufacturers' recommended volumes. Comparative information is available on request.
**PCS's counting efficiency was determined on a Nuclear-Chicago Mark II LSC; Brand A's on a Packard Tri-Carb.
***Maximum sample is 25%—40% is not recommended.

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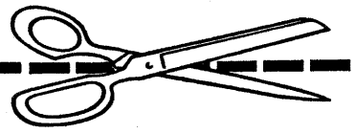

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	13077	α-NPO
	13109	BBOT
	13111	PBBO
SOLID SCINTILLATORS	13076	Anthracene
	13078	TPB
	13079	p-Quaterphenyl
	13080	*trans*-Stilbene
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	13082	DPH
SOLVENTS	13011	p-Dioxane
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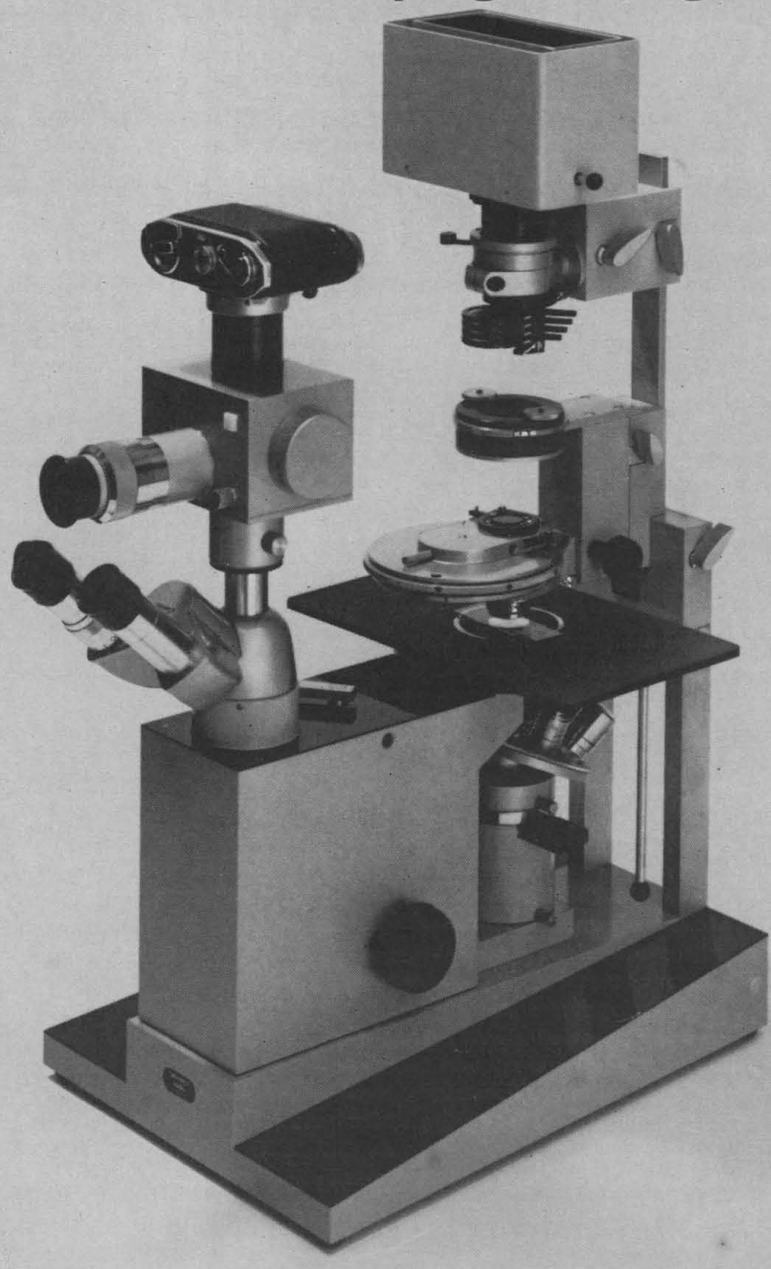

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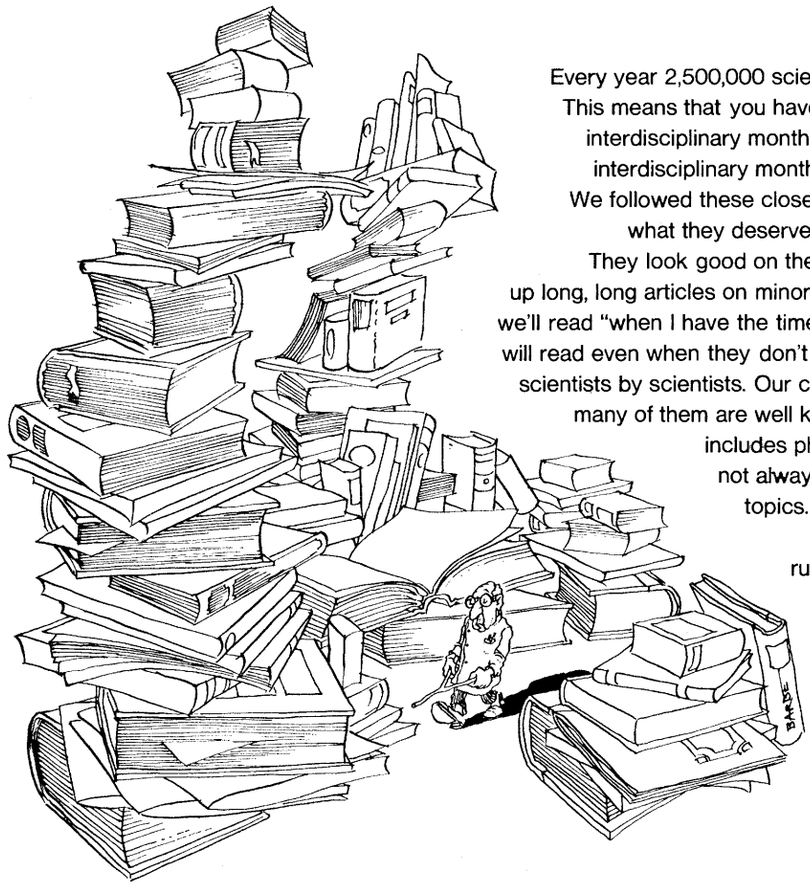

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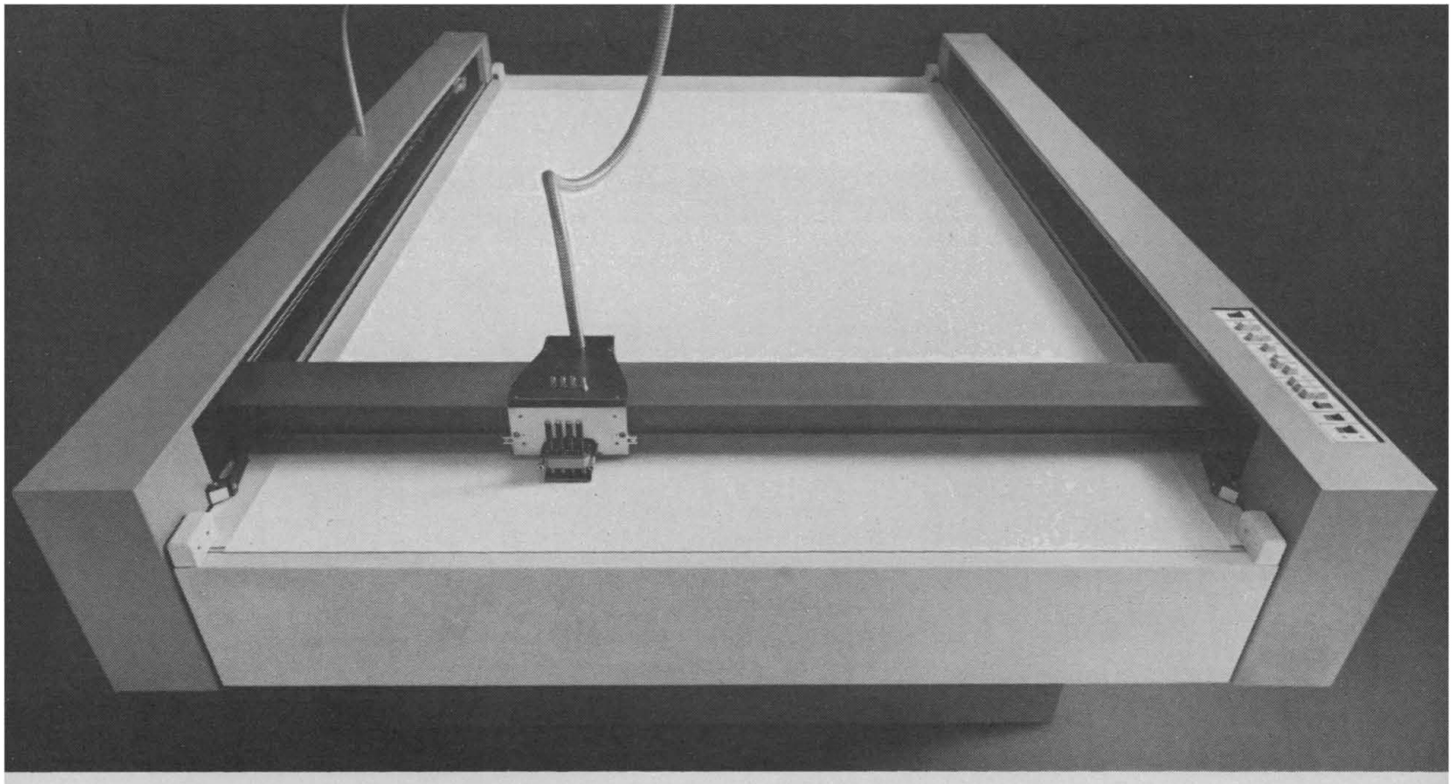

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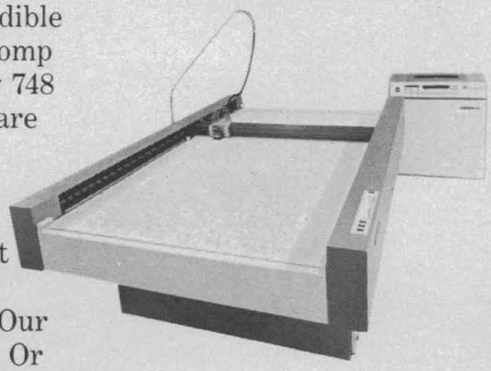

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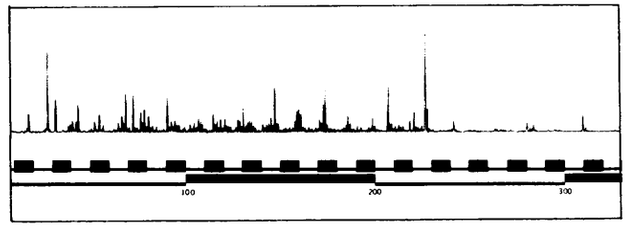

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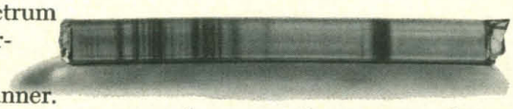

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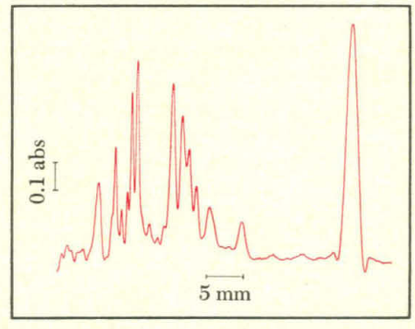
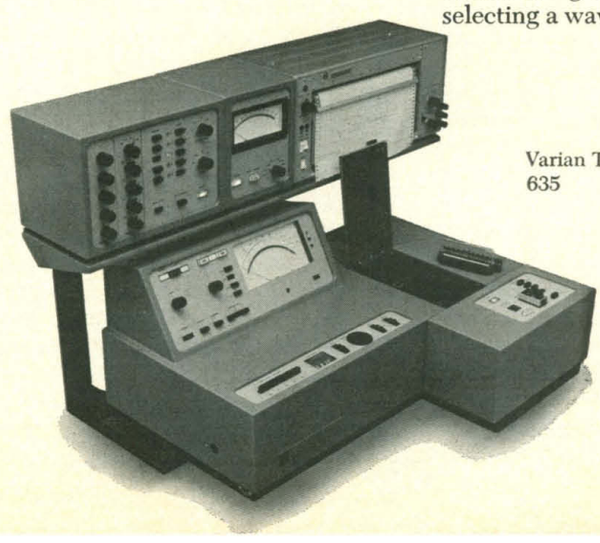


This spectrum of an SDS polyacrylamide gel separation of extracted E coli protein was recorded using the Techtron 635 spectrophotometer and new gel scanner to demonstrate the resolution to be expected with a typical gel separation. Wavelength setting: 550 nm; slit: 0.05 mm; transport speed: 5 mm/minute.



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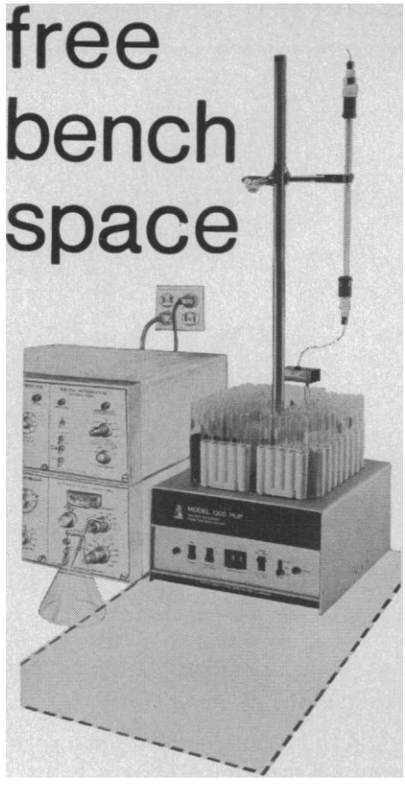

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ceived by people living in the mountains." Since the rule of thumb is that cosmic radiation increases in the order of 1 millirem per year for each additional 100 feet of altitude, even the spectacular Austrian Alps cannot have many people living at 17,000 feet.

LEONARD A. SAGAN
Department of Environmental Medicine, Palo Alto Medical Clinic, 300 Homer Avenue, Palo Alto, California 94301

Mercury Vapor Sources

I read with great interest Robert S. Foote's report on mercury vapor concentrations in buildings (11 Aug. 1972, p. 513) a few days after I installed a new fiberglass air filter, which was laced with mercury, in my furnace. I would be interested to learn if similar filters were in use in the buildings that Foote tested, and what effect they may have had on his results. The use of mercury on air filters in central heating systems would seem to be an excellent means of distributing mercury vapor throughout the home.

ARTHUR S. BROOKS
Center for Great Lakes Studies, University of Wisconsin, Milwaukee 53201

Foote found high concentrations of mercury vapor in three doctors' examination rooms. He comments that mercury thermometers had been broken there in the past.

I wonder if a more likely source of the mercury vapor might be the mercury-containing sphygmomanometer used by most physicians. In this instrument one pumps air from a rubber bulb through a flat rubber bag which has been fastened tightly around the patient's arm, and then through a rubber tube into a mercury reservoir. Air pressure forces mercury from the reservoir into a vertically positioned glass tube. At the end of the procedure a valve on the pumping bulb is opened, permitting the air in the system to rush out under pressure. In this manner, air containing mercury vapor could enter the room. Perhaps Foote would care to examine the mercury concentration in this effluvial air. If this is indeed a significant source, then thought should be given to redesigning these instruments.

SARAN JONAS
Department of Neurology, New York University Medical Center, New York 10016

Concentrations of mercury in wood-paneled or nonpainted homes, in which fiberglass filters (of unknown brands) were used in the furnaces, were very low. It appears that little mercury contamination is caused by the use of such filters.

Paint containing mercury compounds was probably the contributing factor in homes where high mercury concentrations were found.

ROBERT S. FOOTE
GeoSensors Inc., 9731 Denton Drive, Dallas, Texas 75220

A Decent, Hardworking Word

Why do you allow a pair of silt-stained brigands like Irving and Harington ("Upper Pleistocene radiocarbon-dated artefacts from the northern Yukon," 26 Jan., p. 335) to arm themselves with bone awls and flint knives, sneak up behind a decent, hardworking word like "artifact," and stab it in the "i"?

Even Webster's Third, which sanctions everything from the Precambrian to the Aquarian, prefers the "i," although it suggests that if we really are going to get our usage from layer d of fluvial and lacustrine basin-fill sediments, we could go all the way to "artefac."

FRANK SARTWELL
1801 16th Street, NW, Washington, D.C. 20009

Although I am diffident about matching my pedantic talents against Sartwell's, I draw encouragement from the knowledge that Harington and I do not stand alone in our position with respect to the proper (I do not insist that it is correct) spelling of artefact. It is the custom of members of the Society for American Archaeology to spell "artefact" with an "e," for the very good reason that this would have been the spelling in Latin had the word been current when Latin was. Thus, also, "archaeology," with an "ae" rather than the vulgar neologism spelled with an "e" alone.

It is a question of values, which those of us who labor in the traditions of antiquity perceive, perhaps, more clearly than do most of those who do not, and which in any case we steadfastly refuse to relinquish, even in these times of wholesale abandonment of values, standards, and even whole fields of scholarship (for example, etymology) for the racy, the new, and, let us hope, the short-lived fads so prevalent today.

The use of "i" is but one more example of cultural mutation, one that should be suppressed lest its deleterious effect spread to bring about, for example, "eliphant" and "Sartwill."

W. N. IRVING
Department of Anthropology, University of Toronto, Toronto 181, Canada

The Dryden Papers

Over the past 22 months, the Milton S. Eisenhower Library of the Johns Hopkins University has been collecting and collating the papers of the late Hugh L. Dryden (1898–1965), who was aerodynamicist at the National Bureau of Standards from 1919 to 1947, director of the old National Advisory Committee for Aeronautics from 1947 to 1958, and deputy director of NASA from 1958 to 1965.

His papers have been located at Johns Hopkins at the request of Mrs. Dryden because Dryden received his Ph.D. in mathematics and physics from Johns Hopkins in 1919, when he was 20 years old.

The basic collection of Dryden papers is now complete. An archival system is ready to accommodate all other letters, memoranda, notes, reports, photographs, and other forms of documentation that directly relate to Dryden's life and times.

It is hoped that those friends and associates of Dryden who presently hold correspondence (and other relevant documentation) in their private files will donate these items to the Dryden collection. In cases in which the material may have intrinsic value to the donor, Xerox copies will be equally satisfactory.

Dryden's career cut across the lives of tens of thousands of persons in hundreds of different ways. In addition to documentation, the collection will also include what rarely gets put on paper. Anecdotes live only in the minds of mortal men, and when they die the anecdotes die with them. Those persons who have Dryden anecdotes to contribute are especially invited to send them in.

Those who wish to contribute their Dryden materials to the Hugh L. Dryden Papers should send their materials to the address below.

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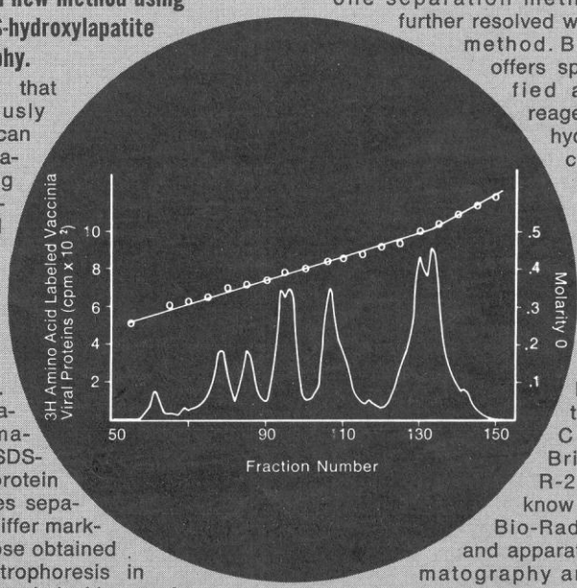

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Tenure

Academic tenure is often confused with job security. Thus it is well to start with a reminder that the basic and justifying purpose of tenure is to ensure academic freedom. Job security is an effect, an advantage, even a necessary condition, but not the purpose. However, several important changes have taken place since the twin concepts of permanent tenure and academic freedom became generally accepted: nontenured faculty members have come to enjoy about as much freedom as tenured ones; in the 1950's and 1960's many faculties grew lax in granting tenure too early, too generously, and to persons who did not need its protection; and a great increase in faculty size has perhaps brought about an absolute, although not a relative, increase in the number of tenured members who have gone to seed or have otherwise taken advantage of their job security.

These points are all discussed in the report* of the Commission on Academic Tenure in Higher Education, as are a number of recommendations for improving faculty decisions on the granting of tenure. The recommendations are thoughtful and timely: unless standards are tightened, the next two decades of slow growth in faculty size will be a deadening period with insufficient room for the entry of able new recruits and with faculties blocked by over-tenuring from adjusting their own ranks to maintain vigorous adaptation to changing needs.

If protecting academic freedom is the reason for tenure, then tenure should be granted only to those whose academic freedom is important to society, and on this point the commission has not gone far enough. Their model is the scholarly or research-oriented department in which academic freedom is subject to threat and in which tenure constitutes a necessary safeguard. It is not clear, however, that the policies appropriate in this case are equally appropriate for all types of postsecondary institutions or that there are no good alternatives to tenure within a large and complex university.

Tenure is not needed for administrators in their administrative roles; for counselors, librarians, and persons in other supporting roles; or for certain teachers. On many a campus there are some teachers whose activities have little to do with academic freedom: members of practicing professions, who, often on a part-time basis, teach their professional skills in medicine, law, art, architecture, or other fields; and instructors in the elements of language, music, mathematics, and vocational fields. Members of these groups want status, rewards, and appropriate measures of job security, but term contracts and other alternatives to permanent tenure should be considered. One obvious danger of this suggestion is that some members of the departments involved will be considered second-class citizens. Another is that any institution that departs from current customs will limit its own recruiting opportunities. However, classes and gradations already exist, and universities are now in a buyer's market.

The commission argues that the way to preserve the tenure system is to select more carefully those individuals whose probationary performance indicates that they merit its privileges and will honor its responsibilities. A further protection would be to narrow eligibility to those groups that truly need tenure in order to be free to make their most critical and objective contributions to students, to scholarship, and to society.—DAEL WOLFLE, *Graduate School of Public Affairs, University of Washington, Seattle 98105*

**Faculty Tenure, A Report and Recommendations by the Commission on Academic Tenure in Higher Education*, William R. Keast, Chairman, and John W. Macy, Jr., Cochairman, (Jossey-Bass, San Francisco, 1973).

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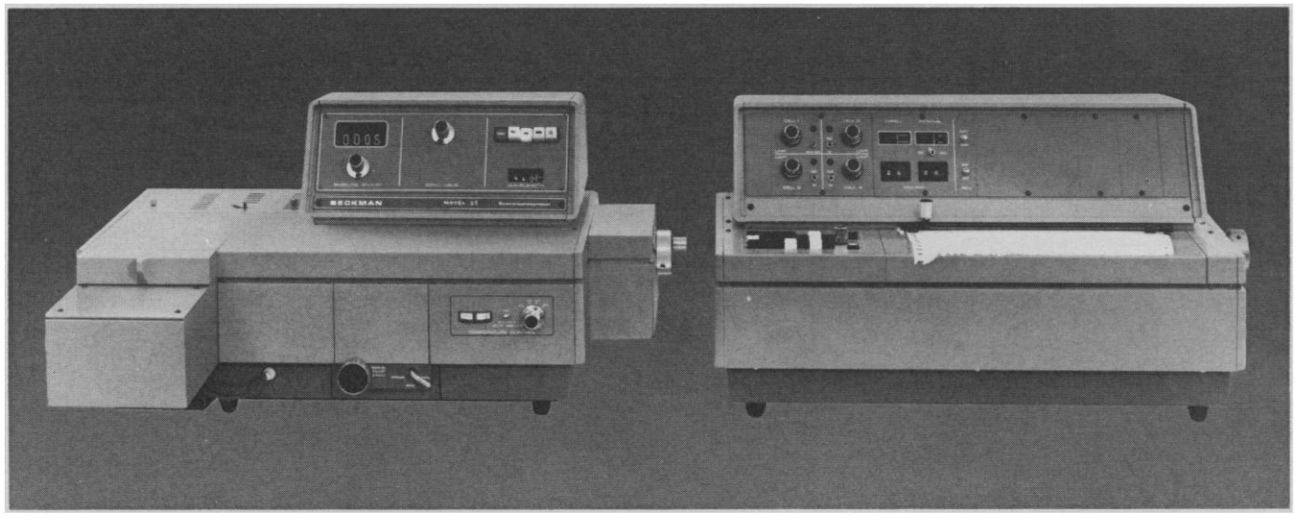

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Some examples might be: ecology of the Pacific coastal zone, modern urban transportation in the light of BART, astronomy and astrophysics in western America, possible energy budgets of the United States by 1990, looking toward world systems management in the 1990's, and the large space telescope.

The proposal should consist of the symposium title, name and address of the arranger, a 300-word synopsis of the purpose and content of the symposium, a list of potential participants, and a brief description of the audience expected. It should be sent to **Dr. Howard D. Greyber, AAAS Director of Meetings, 1515 Massachusetts Avenue, NW, Washington, D.C. 20005.**

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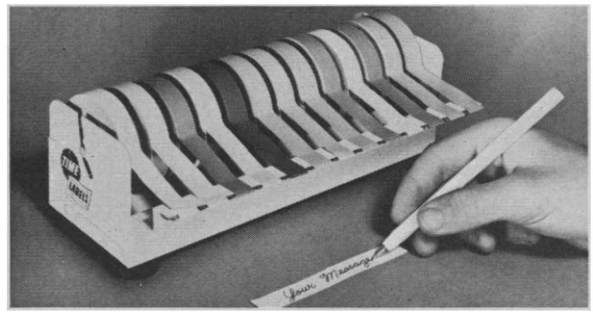

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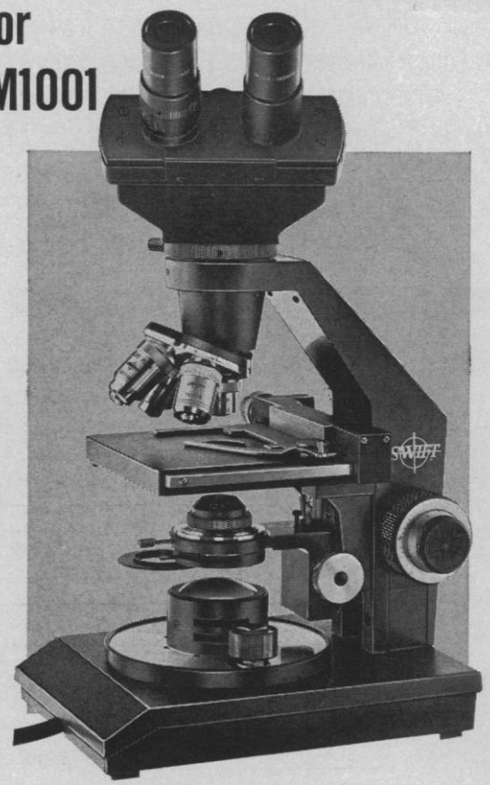

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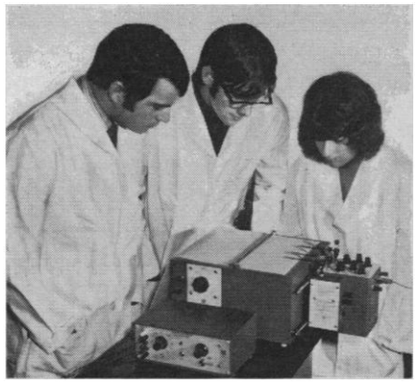

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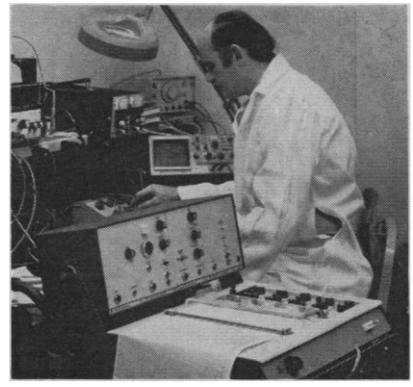

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tive for the presence of reverse transcriptase and DNA product bound to 70*S* or 35*S* RNA.

M. Apple (University of California, San Francisco) described a technique for aspirating fluids from nonlactating human breasts. Apple reported his studies in which synthetic templates were used to detect DNA polymerase in the fluids from nonlactating breasts. A specified level of enzyme activity was found in 41 of 116 women without family history of breast cancer, 8 of 9 women who themselves had undergone mastectomy, and 13 of 17 women with family history of breast cancer.

P. Roy-Burman (University of Southern California) has been testing for reverse transcriptase activity in milk samples from wild mice trapped from three areas. Electron microscopy of breast biopsies, breast tumors, and the banded milk particles of these mice showed both type C and type B particles. Both types of milk particles contained reverse transcriptase activity, and antibodies against reverse transcriptase from murine leukemia virus (MuLV) inhibited the enzyme of the type C virions from these milks. Roy-Burman also reported that reverse transcriptase activity of added RD-114 virus (a candidate human oncornavirus) disappeared completely, as determined by the simultaneous detection technique, in 11 of 17 human milk samples. In his laboratory, 8 of 43 randomly selected selected human milk samples were found to contain reverse transcriptase and 70*S* or 35*S* RNA.

D. Gillespie (NCI) reported that 70*S* RNA containing homogeneous poly(A) sequences about 200 nucleotides long was found in human leukemia cells. Gillespie also reported that DNA synthesized with RNA templates from four different strains of MuLV failed to cross-hybridize against the RNA's isolated from these strains of viruses.

The outcome of the meeting can be summarized as follows:

1) Reverse transcriptase and 60*S* to 70*S* RNA are being found in human milk particles having a buoyant density of 1.16 to 1.19 g/ml by all groups making such studies.

2) The particles isolated from some human milks were found to contain poly(A) sequences in their RNA molecules.

3) Some human milks mixed with MuMTV caused severe loss of infectivity and morphological destruction of the virions. There was also a decrease in reverse transcriptase activities of

MuMTV, AMV, and MuLV when these viruses were mixed with human milks. This decrease could be correlated with the amount of ribonuclease found in the milk.

4) Unclassified viruslike particles as well as C-type and occasionally B-type particles are found in human milk samples, which also contain a virulytic factor or factors in varying amounts. Correlation between family history of breast cancer and the presence of viruslike particles or reverse transcriptase in human milk samples is poor. Methods of preserving and separating the various types of particles are rapidly improving.

5) The elution profile of a poly(dT) synthetase from human milk particles on phosphocellulose columns was found to be strikingly different from that of known oncornaviruses.

AKHIL VAIDYA
Institute for Medical Research, Camden, New Jersey 08103

Interferon

The interferon system has been recognized as a major defensive response of the host, whether cell or animal, to infection by viruses and possibly by other agents. Apart from its theoretical aspects, interferon is potentially important in human chemotherapy, both in virus and tumor treatment. The current status of interferon research was summarized in a recent international workshop which was held in Williamsburg, Virginia, under the auspices of the Antiviral Substances Program of the National Institute of Allergy and Infectious Diseases.

The first session was devoted to control mechanisms in interferon induction. Studies with metabolic inhibitors have suggested that interferon production by the cell may be controlled in the following way. Messenger RNA (mRNA) for the interferon molecule (a protein) is not expressed in unstimulated cells because of the presence of a repressor protein that binds to the interferon mRNA. When a cell is "induced" to make interferon, the repressor is inactivated, or perhaps its production is stopped, so that the interferon mRNA can be translated. Under some conditions the amount of interferon produced is actually increased in the presence of metabolic inhibitors; one proposed explanation is that the interferon mRNA continues to be produced and translated while the repressor protein is not. Some investigators think that other control mechanisms are likely to operate during transcription.

The event in virus replication that triggers the production of interferon remains only partially defined. Double-stranded forms of RNA are in general better inducers of interferon than are single-stranded forms, and this has been interpreted by some to indicate that the double-stranded nucleic acids formed during virus replication are the triggering entities. However, the fact that under some conditions with Chikungunya virus one can get more than normal amounts of interferon in the absence of any detectable viral RNA synthesis, either single- or double-stranded, would suggest that some activity of the input virion may be the initiating process. Other data suggest that function of virion-bound polymerase may be important in induction by Newcastle disease virus, while with reovirus viral assembly may be responsible.

From studies with derivatives of the synthetic inducer polyinosinic acid · polycytidylic acid [poly(I) · poly(C)] it was concluded that: (i) an unblocked 2′-hydroxy group is needed for activity, and (ii) modifying the structure so as to alter toxicity and activity did not alter the therapeutic index. The possible importance of the cell membrane in interferon induction by poly(I) · poly(C) is becoming increasingly apparent. In regard to stimuli of microbial origin, two materials were discussed: it has been determined that the essential moiety of the lipopolysaccharide interferon stimulator from endotoxin is the lipid A fraction; a soluble protein from *Escherichia coli* was also described as a potent inducer of interferon.

Included in the second session was a discussion on the molecular mechanism of the antiviral action of interferon. Most investigators agreed that cells initially treated with interferon show a selective defect in the translation of a viral genome. This selection defect has been demonstrated both in whole cells and with cell-free systems. The translation of viral RNA may be inhibited to a much greater extent if the cells that furnish the cell fractions are first treated with interferon and then infected with virus as compared to interferon treatment alone. The factors responsible for the decreased translation are in the cell sap and on the ribosomes. Data were presented indi-

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cating that in the normally infected cell there are proteins that bind to mRNA's of both viral and cellular type, but that in cells exposed to interferon the binding of viral RNA to cell protein is greatly decreased. It is thus possible that inhibition of translation is attributable to the modification of the protein factors that bind to mRNA prior to translation. When fractions from cells are exposed to very large amounts of interferon, translation of hemoglobin 9*S* mRNA is also inhibited, but translation of endogenous and synthetic mRNA is only slightly affected. However, the above-mentioned investigations are being conducted with interferons of varying degrees of purity, and hence preparation of pure interferon for biochemical and biological studies is necessary.

A possible second mechanism of the antiviral action of interferon involves an inhibition of transcription of viral genome by virion-bound polymerase. Studies with intact cells have shown that indeed there is less radioactivity in new early mRNA in interferon-treated cells than in those that were not treated with interferon, under conditions where the radioactive mRNA is probably the product of the action of the virion polymerase. However, several possible explanations other than an inhibition of the polymerase were advanced to explain the decrease, and the question was not resolved.

Interferon preparations exert an antitumor effect in experimental animals either infected with oncogenic viruses, or inoculated with transplantable tumors, or treated with chemical carcinogens. Interferon preparations enhance the activity of sensitized lymphocytes and unsensitized macrophages, and sometimes increase the antibody response to certain antigens. These preparations inhibit the growth of some tumor cells and even of some normal cells in tissue culture. Whether interferon inhibits the multiplication of tumors directly or by enhancing the host's ability to reject the tumor remains to be determined.

A session on methodology dealt with the production, purification, and assay of interferons, and with reference reagents. Considerable efforts have been made to improve methods for producing human interferon, intended either for therapy or as a source from which pure interferon might be made for structural studies. As was mentioned earlier, yields of interferon have been increased by utilizing

metabolic inhibitors during production. Prior treatment of cells with small amounts of interferon also increases the yield of new interferon when these cells are subsequently stimulated. With the use of human diploid cells, one laboratory has been able to produce material having a titer of 10^5 units.

Mouse interferon has been purified to the point of yielding a product with 10^8 reference units per milligram of protein. No comparable degree of purification has been obtained with human interferon. Two factors that contribute to purification difficulties are (i) the low isoelectric point of human interferon, which precludes the use of certain chromatographic procedures that have been useful with other interferons, and (ii) the apparently greater instability of human interferon.

The various forms of interferon from any one animal species vary considerably in size and charge. Some data have been interpreted to suggest that some, though not necessarily all, of the size heterogeneity comes from the view that native interferons are oligomers containing 2, 4, or 8 identical subunits that can be dissociated at low salt concentrations.

Interferon assays still depend on inhibition of virus replication. In one new method the amounts of specific neuraminidase resulting from influenza virus infection are measured, and this forms the basis for another precise and sensitive interferon assay.

Reference standards of interferon are available for chick, mouse, rabbit, and man; there is also a poly(I) · poly(C) reference standard for interferon inducers. These standards may not be totally satisfactory, but they do provide some means of comparison from one laboratory to another.

With respect to the possible role of interferon in the control of disease, evidence presented from experimental animal models indicates that both exogenous interferon and endogenously induced interferon [poly(I) · poly(C) being the inducer most frequently utilized] have been successful in the prophylaxis and early therapy of lytic as well as oncogenic virus infections.

Criteria utilized for selecting model systems for therapy studies include (i) the host must be at risk from further virus replication, (ii) the virus infection must be sensitive to the quantity of interferon applied, (iii) the host must be responsive to the interferon inducer (even though the prior viral infection may have induced a

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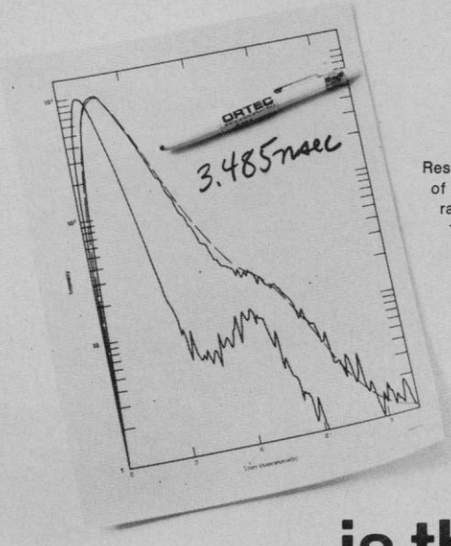

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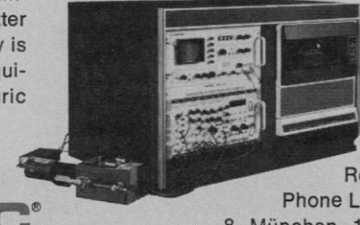

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state of hyporeactivity to further production of interferon) and to interferon, and (iv) interferon, or inducer, must reach the site of infection. Some investigators have found that exogenous interferon is more effective than endogenous; others have found them equally effective. There were also reports of growth inhibitory action against certain protozoa and intracellular shigella. Potentiation by interferon of the toxicity of some double-stranded nucleic acids was also reported.

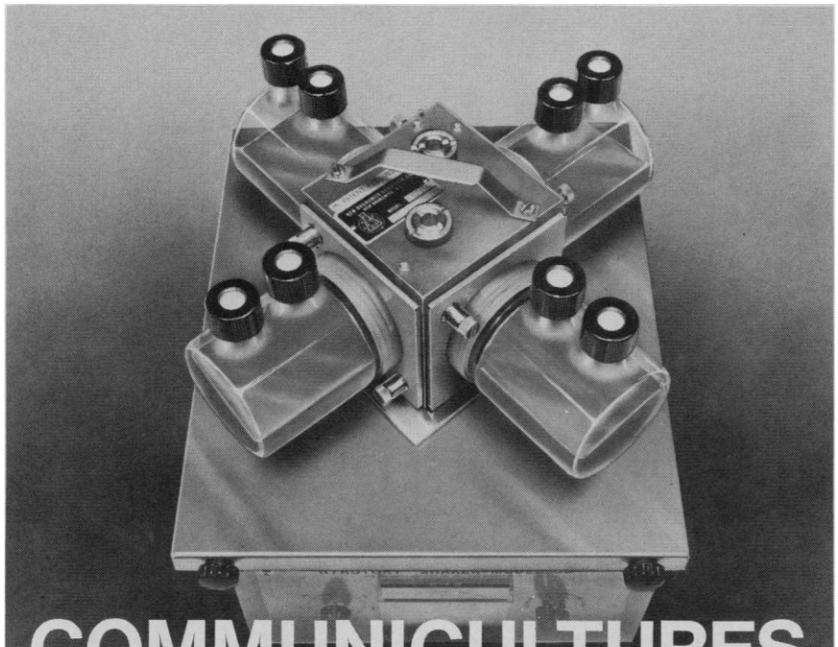
Problems identified with the potential utilization of exogenous interferon include: the short half-life of exogenously administered interferon in vivo, the low dosages available for therapeutic trials, the difficulty of injection at site of infection in most clinical circumstances, the diffusion gradients between blood and site of infection (such as the blood-brain barrier). Problems associated with inducers [primarily based on data from studies with poly (I) · poly(C)] include: toxicity, possible immunologic alterations, hyporeactivity, and decreased capacity of the infected host to produce interferon. These problems must be considered in planning clinical trials.

The reticuloendothelial system may be the source of the interferon appearing in response to certain inducers. Studies with the low-molecular-weight inducers, such as Tilorone and perhaps endotoxin, have demonstrated that a glass-adherent cell (presumably a macrophage) obtainable only from lymph nodes or spleen, respond with interferon production in vitro. Studies of interferon stimulation by nonspecific mitogens and Newcastle disease virus, as well as with viral and nonviral antigens reacting with immunologically sensitized cells, have demonstrated that interferon (as well as lymphokines) can be produced by stimulated lymphocytes. The immune-specific interferon response is increased by addition of macrophages to lymphocyte cultures. Gradient separation of lymphocytes suggests that the blastic response occurs in cells other than those producing interferon. Studies with antiserums to the theta factor have implicated thymus-derived lymphocytes in interferon response of mouse lymphocytes to concanavallin A, phytohemagglutinin, and pokeweed mitogen.

The administration of old tuberculin causes the production of circulating interferon by mice infected with BCG (Bacille Calmette-Guérin). This interferon, but not other types of interferon, seems to be closely associated with migration inhibitory factor.

Studies of the effect of interferon on lymphocyte function indicate that relatively high titers of interferon diminish the blastogenic response of lymphocytes stimulated by nonspecific mitogens, and that under certain conditions interferon preparations may potentiate antibody production in mice, while under other conditions no enhancement was noted.

When the use of human interferon in patients was discussed, one investigator reported that daily parenteral administration of up to 3×10^6 units of interferon over periods of up to 1 year produced only some fever and no permanent effects. Diffusion of interferon is known to be retarded by effective blood-brain, blood-eye, and blood-respiratory tract barriers. Poly(I) · poly (C) has also been given to many patients with cancer and neurological disease with no significant metabolic or hematological adverse effects. Rather low levels of circulating interferon were produced by patients receiving poly (I) · poly(C). In one patient (report



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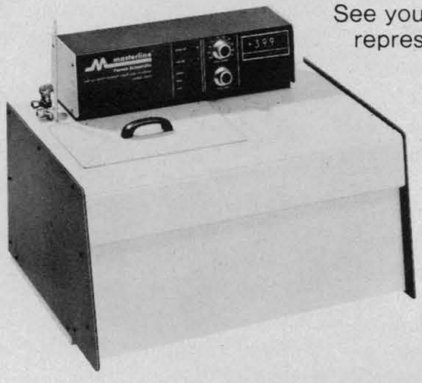

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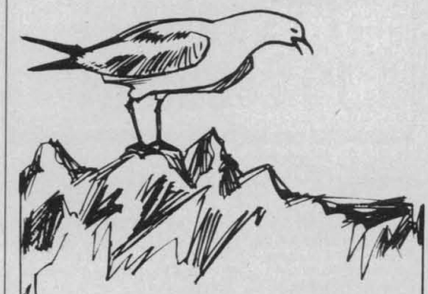

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