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* Patented Process; Cetus Corporation
This Week in Science

Editorial

661 Engineering Research Centers

Letters


ScienceScope

671 AXAF's indirect costs soar higher; budget woes ground NIH scientists; etc.

News & Comment

672 Science Budget: Selective Growth ■ Science and the Domestic Spending Squeeze ■ Civilian R&D: The Big Four Federal Spenders
676 Where Have All Japan's Scientists Gone?
677 Sequencing Venture Sparks Alarm
678 Third World: S(ave) O(ur) S(leep))!
679 Stepping Up the Pressure On Indirect Costs
680 Briefings: Zagury in the Clear ■ Debut for 425-Million-Year-Old Fossil ■ Sarin Indicted ■ Neuro Nerves Calmed ■ More Turmoil Over Orphan Drugs ■ Picture-Perfect Plankton

Research News

682 Pollutant Haze Cools the Greenhouse ■ Hot Nights in the Greenhouse
684 Molecular Design Gets Into a Hole
685 Yellowstone Ecosystem: "Win-Win" Solution
686 “African Eve” Backers Beat a Retreat ■ Choosing a Human Family Tree
688 Boring in on β-Amyloid's Role in Alzheimer's

Articles

690 When Do Anomalies Begin?: A. LIGHTMAN AND O. GINGERICH

Reports

COVER  Granophyre from the roof zone of the Muskox intrusion, Northwest Territories, Canada, with a skeletal quartz crystal (violet, ~0.17 millimeter long) surrounded by optically continuous vermicular quartz intergrown with alkali feldspar (blue). The intergrowths reflect the final crystallization of a magma rich in silica and alkalis that coexisted with an underlying silica-poor magma. See page 708. [Photograph by Brian W. Stewart, California Institute of Technology, with cross-polarized light and a 575-nanometer retardation plate]

705  Modeling 100,000-Year Climate Fluctuations in Pre-Pleistocene Time Series: T. J. CROWLEY, K.-Y. KIM, J. G. MENGEL, D. A. NORTON

708  Diffusive Isotopic Contamination of Mafic Magma by Coexisting Silicic Liquid in the Muskox Intrusion: B. W. STEWART and D. J. DEPAOLO

711  Reaction Planning: Computer-Aided Discovery of a Novel Elution Reaction: R. HERGES and C. HOOCK


717  On the Probability of Matching DNA Fingerprints: N. J. RISCH and B. DEVLIN


723  Reversal of Integration and DNA Splicing Mediated by Integrase of Human Immunodeficiency Virus: S. A. CHOW, K. A. VINCENT, V. ELLISON, P. O. BROWN


728  Processing of the Amyloid Protein Precursor to Potentially Amyloidogenic Derivatives: T. E. GOLDE, S. ESTUS, L. H. YOUNKIN, D. J. SELKOE, S. G. YOUNKIN

730  The Influence of Prior Synaptic Activity on the Induction of Long-Term Potentiation: Y.-Y. HUANG, A. COLINO, D. K. SELIG, R. C. MALENKA

733  Chondroitin Sulfate as a Regulator of Neuronal Patterning in the Retina: P. A. BRITIS, D. R. CANNING, J. SILVER

Technical Comment


Book Reviews

740  The Detection of Gravitational Waves, reviewed by P. R. SAULSON  Neuronal Networks of the Hippocampus, C. KOCH  Electrogenic Ion Pumps, B. HILLE

Vignettes: The Market for Books  Books Received

Products & Materials

744  Cell Lysis Reagent Simplifies DNA Release  Particle Size Analyzer  DNA Insertion Marker  Light Box  Nanoliter Injector  Centrifugal Ultrafiltration Devices  Photon-Counting Spectrofluorometer  Premixed Electrophoresis Buffers  Literature
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Engineering Research Centers

An innovative program sponsored by the National Science Foundation (NSF) is having important consequences at a number of universities. The fostering of 18 Engineering Research Centers (ERCs) has led to better instruction of engineering students, enhanced interdisciplinary research leading toward practical applications, and beneficial interactions with and financial support by industry.

In 1985, concerns began to arise about declining U.S. industrial competitiveness. The ERC program was created to respond to this and to the fact that many opportunities in engineering research required an interdisciplinary approach. A 1990 NSF publication described goals of the ERCs: "A primary objective of the program is to bring engineering and scientific disciplines together to address fundamental research issues crucial to the next generation of technological advances.... An equally important aim is to educate a new generation of engineering students in a cross-disciplinary team approach to problem-solving, increasing their ability to contribute productively to industry.... A major goal of the ERC Program is to facilitate the more efficient transition of advances in fundamental research in universities into high-quality, competitive products and processes in industry."

Each of the 18 ERCs occupies a niche within six technological fields: manufacturing and design; materials processing for manufacturing; optoelectronics, microelectronics, and communications; bioprocessing and biomedical engineering; resource recovery and utilization; and infrastructure and environment. Major technologies that influence the nation’s quality of life and economic strength are included in the ERC efforts.

The ERCs derive their funding support from diverse sources. The total contribution from NSF during 1991 of $45.6 million constituted 33% of the total. Industry supplied 30%, other federal agencies 20%, universities 11%, and states 6%. In addition to money, industry contributes equipment and often stations company personnel at the universities. The monetary support takes the form of membership fees. There are as many as three levels of membership entailing differing fees and privileges. The fees also vary among the ERCs. Some have top annual fees as high as $200,000. For others, the maximum is $100,000 or less. The lowest level ranges from $5,000 to $25,000 for small companies.

At present there are a total of 697 participating memberships held by 483 companies. Some of the major U.S. companies have multiple memberships. For examples, IBM participates and pays fees in ten centers. Eastman Kodak, GE, and AT&T are each members of nine centers. The total memberships continue to increase.

Industry engineers on campus teach classes in conjunction with faculty. They participate in research with faculty and students. They advise students on career choices as well as on research directions. They act to ensure effective transfer of information between the ERC and their company and vice versa.

One of the advantages enjoyed by participants in ERCs is their research support infrastructure. They enjoy unusually good research and computer equipment. Technicians and maintenance funds ensure the readiness of equipment to produce reliable measurements.

One of the latest ERCs to be activated involves the Universities of Minnesota and Wisconsin with the center located at Madison. Its special niche is plasma-aided manufacturing. In a partial vacuum, high electric fields give rise to an ionized plasma whose characteristics depend on pressure and gaseous content. The phenomena are complex. It is a goal of the center to gain a complete understanding of everything that takes place, from the initiation of an electric field in the plasma to an actual industrial application. Research at the center includes plasma etching or deposition, plasma synthesis of high-technology refractory materials, and plasma modification of materials. Already the hardiness of many irregularly shaped metallic objects has been usefully improved by nitrogen bombardment. The total present and potential markets for applications of plasma-aided manufacturing have been estimated to be more than $100 billion.

The other ERCs have programs that also are relevant to industrial competitiveness. Progress that is being made by each of the ERCs is described in an NSF report that will be released soon. An examination of the report shows that the $45.6 million devoted annually to the centers is being leveraged to produce highly significant effects.—PHILIP H. ABELSON

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Access to Genetic Sequence Data

In Leslie Roberts’ News & Comment article “MRC denies blocking access to genome data” (13 Dec., p. 1583), the head of the British Medical Research Council (MRC) Human Genome Mapping Resource Center, Tony Vickers, is reported as saying he does not know why researchers might want to scan through and download genetic sequence data freely. He says that the MRC possesses analytic software that small labs could not easily have access to otherwise.

This attitude is wrong and disappointing. One of the main aims of the Human Genome Project should be to develop innovative new software for analyzing sequence data and collating it with other biological data. My colleagues and I are now working on artificial intelligence techniques that we intend to apply to learning to recognize structure in sequence data. This work has funding from the National Institutes of Health, and teams at a number of other universities are doing similar research. Free access to primary data will be essential for testing the methods that are developed.

Computer science and artificial intelligence promise to make available tools for performing sequence analyses far deeper than simple recognitions of homology. It would be a grave mistake if the MRC, or any other database custodian, adopted as a standard any particular existing analytic software.

CHARLES ELKAN
Department of Computer Science and Engineering,
University of California, San Diego,
La Jolla, CA 92033-0114

Chronic Fatigue Syndrome

I would like to address Joseph Palca’s Research News article “On the track of an elusive disease” (20 Dec., p. 1726). I have used the polymerase chain reaction, under conditions of reduced stringency, to seek out viral sequences related to either herpes viruses or retroviruses in patients with the chronic fatigue syndrome (CFS). This work led to the culturing of a virus that appeared to contain sequences of both herpes virus and retrovirus. I notified the Centers for Disease Control (CDC) early in 1991 that an atypical virus had been repeatedly cultured from a CFS patient. The cytopathic effect (CPE) seen in culture was characterized by foamy cell changes. A virus inducing a similar CPE was isolated from a patient with an unexplained severe encephalopathy. Many additional patients have also tested positive by culture. CDC officials were invited to visit my laboratory and review the culture findings, but declined to do so.

A meeting sponsored by the California Department of Health in San Francisco and a National CFS Advisory Council Meeting held at CDC in September 1991 provided additional opportunities to present ongoing research and to show photomicrographs of the CPE and electron micrographs of the viral particles. At each meeting, I emphasized the importance of obtaining additional sequence data to characterize the type of virus involved. Contrary to Palca’s account, I did not consider the audience at either San Francisco or at CDC to be “hostile.”

A brief report describing the culture and electron microscopic findings in the initial CFS patient was submitted for publication and was rejected. I consider a reviewer’s comment to Palca that most of the data were “negative or uninterpretable” to be a breach of the confidentiality of peer review that may reflect the type of personal bias that has continually led to questioning of even the existence of CFS. The best response to this type of skepticism is to continue to perform careful science and to obtain conclusive sequence data on the viruses we have isolated. My laboratory is actively engaged in this research.

I trust that the publicity associated with our work will encourage the efforts of others to investigate CFS patients for evidence of viral infection.

W. JOHN MARTIN
Department of Pathology,
University of Southern California School of Medicine,
Los Angeles, CA 90033

Response: Martin’s concern that the confidentiality of the peer review was breached by my report is understandable but unfounded. In the course of interviews for this story, one expert in the field criticized Martin’s work and explained that he knew its details because he had been asked to peer review a paper Martin had submitted for publication. The scientist did not share his review or the paper with me, nor even say to which journal it had been submitted. I mentioned his role as a reviewer simply to give the reader some indication of his credibility as a critic, and to protect his confidentiality, I did not name him.—JOSEPH PALCA
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**Alar: The Aftermath**

Eliot Marshall's News & Comment article about Alar and its hydrolysis product UDMH (unsymmetrical dimethyl hydrazine) (4 Oct., p. 20) offered a balanced account of the economic fallout 2 years after Alar was taken off the market, but muddied the waters by putting a somewhat bizarre spin on the results of new rodent bioassay of UDMH. A subsequent editorial by Daniel E. Koshland, Jr. (1 Nov., p. 629) reinforced and compounded Marshall's misinterpretation. Even a cursory look at the actual data in the 1991 and 1973 bioassays shows clearly that "the basic toxicology on Alar" has not "taken a surprising turn." In fact, given the vitriolic criticism of the earlier study, the new industry-sponsored results are only surprising for how much crow the critics may have to eat. In the 1973 study (1), 42 out of 50 male mice given 23.3 milligrams of UDMH per kilogram of body weight per day (mg/kg/day) developed blood-vessel tumors. Eighteen years later, 31 out of 67 male mice (46%) given 7.3 mg/kg/day developed these malignancies, along with 63% of those given 13 mg/kg/day (2). How can these new data be viewed as anything other than a confirmation and amplification of the earlier study, at even lower doses than previously analyzed (3)?

Marshall's article and a subsequent response by Victor J. Kimm at the Environmental Protection Agency (Letters, 29 Nov., p. 1276) emphasize small changes in the official point estimate of UDMH's potency. At most, such changes represent a tiny "signal" compared with the "noise" inherent in potency estimates (which itself is only a fraction of the total uncertainty in risk) (News & Comment, 9 Mar. 1990, p. 1173). In the case of UDMH, even the factor of 20 Marshall discusses is largely an artifact of different methods EPA has used to adjust for peculiarities in the bioassay data (4). Without all the arcane of potency calculation, one can easily show that Alar posed a potentially serious hazard. Using national survey data on apple juice consumption and the manufacturer's own data on UDMH residue levels, one can show that a plausible dose estimate for many young children was about 0.0005 mg/kg/day, or about 1/2000 of the equivalent dose that causes tumors in roughly half of all mice (5). Therefore, unless the dose-response function is sharply nonlinear or has a threshold, the excess risk to many children was roughly 1 in 4000, or 250 times the 1 in 1 million standard generally regarded as de minimis.

So, it seems that the risk assessments Koshland disparages as "clearly dubious" were more prophetic than were the dire
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the neuroepithelial end feet, which in turn would signal neuronal precursor cells to polarize and differentiate in the wrong place or time. The attachment of both vitreal and ventricular end feet and the correct timing of their detachment are believed to be critical to retinal ganglion cell differentiation, resulting in the localization of the cell body at the vitreal surface (2, 26). Thus, chondroitin sulfate, perhaps along with other glycosaminoglycans, may be a key regulatory factor in these phenomena.

Our results suggest that the graded front of chondroitin sulfate that recedes centrifugally across the retina, perhaps in combination with bound tropic and trophic factors (27), allows retinal ganglion cells to differentiate sequentially and polarize their cell bodies and axons in their proper orientation.

REFERENCES AND NOTES

15. MAB TUJ1 is directed to a neuron-specific type III b-tubulin isofrom. [M. K. Lee, J. B. Turtle, L. I. Rehahn, D. W. Cleveland, A. Frankfurter, Cell Motility and the Cytoskeleton 17, 118 (1990)]. Because this isofrom is detectable in neurons as early as terminal mitosis, the antibody allowed for the detection of RGC bodies and their axons during the earliest stages of their differentiation.
16. MAB CS-56 is specific for the GAG portion of native chondroitin sulfate proteoglycan and binds to both the 4- and 6-sulfated moieties.
17. Embryonic eyes were dissected and extracellular tissues removed. Retinas were mounted vitreal side up on sartorius filters, fixed with 4% NBF, permeabilized with 0.3% Triton X-100 and incubated with CS-56 or TUJ1 overnight at 4°C. For double labeling, primary and secondary antibodies were added sequentially. Whole mounts were incubated in goat antibody to immunoglobulin M and G (gamma chain-specific).
19. Chondroitin ABC lyase purified from Protein vulgaris catalyzes the eliminative cleavage of N-acetylb-hexosaminide linkages in chondroitin 4- and 6-sulfate, yields mainly disaccharides with A4-hexurionate at 85 Hexa-sulfate, heparin and heparan sulfate, and leaves the core protein intact.
20. Control retinas were grown in media with no chondroitinase (n = 30). In addition, retinas were cultured in the presence of keratan sulfate, heparin and heparan sulfate, and leaves the core protein intact.
21. Rat eyes were taken at E12.5 and E13.5. Retinas along with intact lens and vitreous were cultured in DMEF-12 supplemented with 10% FCS in 24-well dishes at 37°C in a humidified environment with 5% CO2 for 24 or 48 hours. The media used for enzyme perturbations included chondroitin ABC lyase (ICN, 1 U/ml). In some perturbation experiments a broad spectrum protease inhibitor was added (2-Makroglobulin, ICN, 1 mg/ml). Under these conditions, retinas remained healthy: no differences in numbers of pyconic nuclei visualized in serial 1-μm plastic sections were observed between control and treated retinas. In preparations that were cultured for 48 hours with chondroitin ABC lyase, chondroitin sulfate could not be detected with CS-56 immunostaining.
22. In the enzyme treated retinas, the radial nature of the non-neuronal cells (TUJ1-negative), as identified with antibodies to nestin, remained intact.
28. We thank A. Frankfurter for the TUJ1 antibody, C. Doller and K. Sofranko for technical assistance, U. Rutishauser for the anti-NCAM antibodies and the endonemuraminidase, R. McKay for antibodies to nestin, and R. H. Miller, M. P. Myers, and R. J. McKean for comments on the manuscript. Supported by the National Institutes of Health, the Daniel Heumann Fund, and the Brumagin Memorial Fund.

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"Frankly, I'd rather be mythical than extinct."
Pumping Ions


All cellular life forms establish ionic concentration gradients across their cell membranes by active transport of ions. Apparently proteins that couple ion transport to a source of free energy have arisen several times in evolution. Escherichia coli uses an ATP-dependent ion pump that is homologous to the well-known Na\(^+\)-K\(^+\), Ca\(^2+\), and H\(^+\)-K\(^+\) pumps of animals. Halobacteria evolved light-driven pumps for H\(^+\) and Cl\(^-\), and almost all bacteria and eukaryotes have cytochrome oxidase that pumps protons as part of electron transport and coupling proteins (F_0F_1 ATPase) that synthesize ATP at the expense of the proton gradient.

The Na\(^+\)-K\(^+\) pump has been studied for half a century. The concept of energy-requiring vectorial transport was introduced more than 50 years ago, and by 30 years ago the energy source (ATP) had been identified, the concept of a strictly stoichiometric coupled transport cycle had been established, and an appropriate ATPase activity had been discovered in broken cell membranes. Subsequently the transport protein was solubilized, purified, and sequenced, and a large number of intermediate steps in the overall cycle were revealed. Perhaps the most interesting intermediates are several "occluded" states in which transported ions seem to be trapped as in an airlock in their transit across the membrane.

Despite a long history of sophisticated observation, we still do not understand the molecular details. How are ions picked up on one side of the membrane and deposited on the other? Peter Läuger's posthumous book provides an admirable distillation of a complex experimental literature and a clean theoretical structure for kinetic analysis. It is exciting to be guided by such a sure hand through what would otherwise be very difficult theoretical and experimental territory. Läuger's legacy will be a paradigm for thinking in this field for many years to come. This is a biophysical masterclass. It will reward repeated study.

The book begins with a short overview of classes of ion pumps and then settles into a serious introduction to physical principles and the theoretical background of each of the methods for studying pumps. We learn about the thermodynamics of state diagrams, energy levels and efficiency, steady-state and transient kinetics, the contribution of pumps to electrical properties of membranes, and the theory of membrane fragments coupled to planar bilayers. This part would make an excellent graduate reading seminar in biophysics, a skillful case study exercising a wide range of physical thinking in a biological context. It will be equally interesting to researchers studying bioenergetics and molecular motors who face the same problems of kinetics and energetics of cyclic state diagrams. The presentation here cuts deftly to the core and is a strong model of a self-consistent kinetic framework achieved through notational simplicity and deep physical insight.

The second half of the book reviews progress made on each of the pumps. This part will be especially useful to those who teach about primary active transport and bioenergetics in classes in cell physiology. The style is refreshingly direct. Sharp conclusions are drawn without waffling over fuzzy data. The greatest amount of space is devoted to the Na\(^+\)-K\(^+\) ATPase. The classical Post-Albers cycle is reviewed in detail, together with newer extensions. Results of rapid mixing, filtration, current-voltage, voltage- and ATP-jump, and charge-transient experiments are brought in to establish microscopic rate constants and rate-limiting steps. All is summarized in a reaction diagram with 14 states and 20 reaction steps. Values for 29 rate constants are estimated. At this level tremendous progress has been made in the last 15 years.

As the title implies, active transport of ions moves electric charge as well as making a concentration gradient. In Läuger's earlier field of ion channels, the ability to measure charge movements and voltage sensitivity of elementary steps has been central to rapid progress in understanding. The same powerful approaches are now being applied to ion pumps, and the formalisms developed in this book show how electrical measurements can be used to dissect elementary steps of the transport cycle.

A valuable feature of this well-produced book is the combination into a neat and readable package of both the theoretical background and the observations of a large field of transport research. Experimentalists trained in the use of Ockham's razor may be surprised at the large number of steps, coefficients, and rate constants used to describe the action of one macromolecule. Indeed, the models go well beyond existing observation. However, the book teaches us how to prepare the framework for future analysis by meticulous representation of each anticipated process. Experiment then can determine which steps are rate-limiting or kinetically important. Structural biologists may also be surprised at the relative lack of structural correlates of any of the kinetic events in pumping. This book may be the first and last monographic summary of a great era that will surely stimulate molecular discovery through genetic engineering and possibly atomic-resolution crystallography. It is a great read and a must for all in the transport and bioenergetics fields.

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Books Received


Vignettes: The Market for Books

The impressive reviews that had marked the appearance of [Loren Eiseley's] *Darwin's Century* were hardly mirrored in the volume's sales. Some 3,500 books had been shipped during the five months following publication, and Eiseley's royalty income, based on thirty-seven and one-half cents a copy, shrank to a mere $251.63 for the six-month period ending October 31, 1959. . . . *The Darwin market seems to be glutted,* . . . wrote [Eiseley's editor at Doubleday] ominously in May 1959.

—Gale E. Christianson, in *Fox at the Wood's Edge: A Biography of Loren Eiseley* (Holt)

Extended general treatises on cellular biology have largely gone out of fashion in favor of more circumscribed works dealing with particular aspects of the subject.


If a prompt translation is any measure of the country's receptivity to the theory expounded in the work translated, then in the case of the *Origin of Species* Italy ranked as the third most receptive, along with Russia and the Netherlands.

—Giuliano Pancaldi, in *Darwin in Italy* (Indiana University Press)

Dear Sir

I am much flattered by your enquiry after my book but it will not be out till March.

I shall have no copies of it in my own hand but if you wish it I will send word to the Publisher to send you a copy but I thought that before doing so I would ascertain whether you might not rather like to order it of your own bookseller.

I am Sir/Your obliged servant

—Michael Faraday writing to Edmund Robert Danielli, 15 January 1827, as transcribed in *The Correspondence of Michael Faraday*, vol. 1 (Frank A. J. Lames, Ed.; Institution of Electrical Engineers, London)


