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COVER Bell tower of First United Methodist Church in Chatham, Cape Cod, Massachusetts, at dawn (6:26 a.m. on 23 June 1986; solar elevation: 12°35.4′ above horizon; natural illuminance levels: 12,200 lux ambient and 6,300 lux in the line of gaze). Exposure to artificial light of comparable intensity can rapidly reset the human circadian pacemaker by about 6 hours. See page 667. [Charles A. Czeisler, Neuroendocrinology Laboratory, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115]

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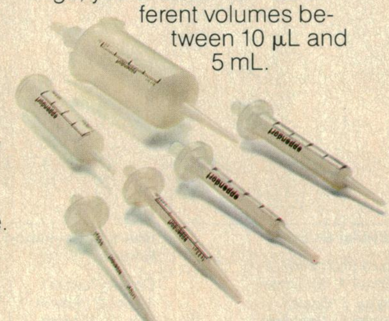

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This Week in SCIENCE

Frozen assets

THE Arctic is one of the earth's remaining frontiers and is of potential importance for purposes as different as the tapping of natural resources (for energy, minerals, and food) and the promotion of international cooperation (page 633). The Arctic includes territories of Canada, Greenland, Scandinavian countries, the Soviet Union, and the United States. Much of the region is inhospitable: the ocean is covered in large part with a thick layer of ice; sea navigation occurs predominantly along the coasts, although submarines can traverse and icebreakers can plow through the central waters; the arid, cold climate leaves many regions barren but others rich in tundra vegetation; glaciers are common on highlands; mountain peaks are capped with ice. Despite these conditions, arctic research is expanding: global weather and marine life are affected by melting and freezing of the Arctic Ocean; ice cores contain records of past climates on the earth; particulates in the snow and ice can be used to measure pollution in the Northern Hemisphere; studies of the native populations and the geography of the region suggest paths of the earliest movements of people to the Americas. Washburn and Weller discuss these and other topics as they relate to the U.S. Arctic Research and Policy Act which attempts to coordinate arctic research with a respect for the culture, needs, and priorities of indigenous peoples.

Immune-endocrine links

REGULATION of the immune and endocrine systems is interrelated (page 652). Interleukin-1 (IL-1) induces glucocorticoid hormones, and the hormones are powerful inhibitors of IL-1 and other mediators of inflammation and immunosuppression. Thus a feedback circuit is in operation. Besedovsky *et al.* found that blood corticosterone and adrenocorticotropic hormone increased in response to elevations of IL-1; when purified IL-1 was injected into mice and rats, the glucocorticoids rose in a dose-dependent fashion. IL-1, which is the only mediator of several tested that produced these effects, appears to act directly on the pituitary-adrenal axis and not through a secondary mediator. It is likely that when IL-1 reaches a certain level in the circulation during infection, inflammation, or other immune responses, this axis is activated, blood glucocorticoids increase, and down-regulation of the immune response occurs, usually with beneficial but sometimes pathologic consequences.

Cell killing by the AIDS virus

SEQUENCES of the *env* gene of the AIDS virus may control the virus's ability to kill helper inducer T cells; death of such cells in patients is a factor in immune suppression (page 655). Fisher *et al.* studied variants derived from a cloned AIDS virus. One variant that had deletions in portions of both the *env* and *orf* genes remained infective and could multiply within T cells in culture yet did not kill the cells. Variants with only *orf* gene deletions retained not only their infective and replicative capabilities but also their cytopathic properties. *Env* and other viral genes—*gag, pol, tat*, and perhaps *art*—have previously been shown to be critical for viral replication, a process that now does not appear to be obligately coupled to killing. Since the *env*-deletion variant has a markedly reduced ability to kill, it may be useful as a starter virus from which to develop a safe AIDS vaccine.

Enzyme improvements available on cassettes

A sophisticated protein engineering technique has been applied to the issue of how changing a single amino acid in the active site of an enzyme alters enzyme-substrate interactions (page 659). Estell *et al.* used the cassette mutagenesis method to replace glycine with other amino acids at position 166 in the substrate-binding site of subtilisin. This position is favorably situated for interactions between substrates and side chains of amino acids that replace glycine (which has no side chains). The cassette, a synthetic DNA duplex, is inserted where a similarly sized piece of DNA had been spliced out of the enzyme. The activity of subtilisin changed depending on what substitution was made and what substrate was tested; factors contributing to subtilisin's changed catalytic efficiency were hydrophobicity and steric repulsion. Cassette technology has many future applications in experimental protein and synthetic chemistry and in the production of more efficient enzymes for industrial use.

Setting the human biological clock

EACH day the biological clock that controls physiologic, behavioral, and cognitive rhythms in humans must be reset to a 24-hour period because the clock's natural period is longer than 24 hours; the direct action of light as a primary synchronizer of this clock has now been demonstrated (page 667). Czeisler *et al.* found that bright light (cover) rapidly reset the circadian pacemaker of a 66-year-old woman; her exposure before her regular bedtime to light for 4 hours each evening for 1 week isolated light effects from those related to her sleep-wake cycle. Dramatic and rapid changes in the rhythmic profiles of body temperature and cortisol secretion—markers of the circadian pacemaker—were detected, and a 6-hour phase shift occurred. The sensitivity of the human circadian clock to light thus makes it like clocks of other species. Bright light—phototherapy—has been used in treating depression and other affective illnesses (in which a direct effect of light on the internal clock has been hypothesized but not established); phototherapy may prove effective also in easing problems associated with jet lag, shift work, and other sleep-wake disorders.

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To Lift the Lamp Beside the Research Door

Give me your tired, your poor,
Your little scientist yearning for a grant,
The wretched refuse of the Budget Battle,
Send them, competition-tossed, to me:
I lift the lamp beside the Treasury door.
(with apologies to Emma Lazarus)

Those would be appropriate words for a new statue entitled "Miss Enlightened Self-Interest." This high-wage nation is entering the era of the global economy with a science policy that would have any well-trained accountant dying of shame. We analyze, by merciless peer review, the grants of low-income science (in the $\$10^5$ range); condemn those who go outside the peer review process for middle-income science ($\$10^7$ range); and allow the top brackets of "big science" ($\$10^9$ range) to be evaluated by nonscientists. An analogy would be a meticulously itemized office budget: Pencils ($17.50), Typewriter ($327.96), and Miscellaneous ($10,000).

What is the outcome of such a process? At a time when foreign competition in the computer business is at a peak, low energy physics is being cut back in total funds and in dollars per grant. At a time when the infant biotechnology industry needs encouragement and personnel, training grants and postdoctoral fellowships are being reduced and eliminated. At a time when we must create methods to adjust to major demographic shifts both internally and in a changing global economy, social scientists are competing for dwindling funds. At a time when materials science research and new chemical products are needed more than ever, the National Science Foundation, their main source of funding, announces the possibility that summer salaries may be eliminated and that program directors must negotiate downward. At the same time, massive projects with only remote relevance to the national welfare are enjoying favor. "Little science" is being told that it is in a zero-sum game; big science is being told that it is in an infinite-sum game of "add-ons."

Does this mean that we should eliminate big science because of the budget squeeze? Certainly not. Does it mean that relevance must be a sine qua non of basic research? Certainly not. Does it mean that we should reexamine our procedures for scientific priorities? Certainly, yes.

The first step in reevaluation is remembering that little science can be intellectually adventurous and has produced the big breakthroughs—the lasers, the transistors, the recombinant DNA's—which spark totally new directions in research and industrial applications. Thus it is vital in this new era of balanced budgets to establish a priority that ensures healthy support of little science. But we need big projects too, even big irrelevant projects. They are like our national parks, our Statue of Liberty, our voyage to the moon. We must think big, and supercolliders, sequencing the human genome, the space shuttle, and space telescope are goals that challenge our imaginations and organizational abilities. Almost all big science projects are worthy. The problem is that they cost so very much money.

If even one big project were deferred, there would be all the incremental funding needed for little science. Therefore it seems time for truly big science to enter an era of competition with programs of similar size rather than with the much smaller projects of little science. One item that should be compared with the big science projects is the sum of all the incremental cuts in little science.

We scientists will find it difficult to list the diverse projects in a priority order. The least we can do is have peers outside the immediate discipline evaluate the scientific claims of the advocates of big projects so that Congress can place the programs in proper relation to others of similar size.

The time has come to evaluate big projects against each other and against the restoration of cuts in little science in the same way that we evaluate small projects. The republic, through its elected representatives, will and must have the final word. The scientific community, however, should help make that final word an informed decision. In this way, enlightened self-interest can lift the lamp beside the research door.

—DANIEL E. KOSHLAND, JR.

fervently critical of them. I appreciate the former and will make brief comments relative to the latter.

At the present time, the United States has several billion dollars worth of unmanned, high-priority spacecraft in its launching queue, and the queue grows longer month by month. The list includes a comprehensive mix of spacecraft for commercial, applicational, scientific, and military purposes.

The true national urgency is to reestablish a diverse and resilient launching capability as quickly as possible. Because of massive and complex safety considerations (of which the well-known O-ring problem is only the tip of the iceberg) in requalifying the shuttle for the flight of human crews, we can best do this by returning to primary dependence on combinations of expendable launch vehicles.

There is no comparable urgency to resuming manned shuttle flights, and there is even less urgency to developing a large space station. One may recall that no U.S. manned flights were conducted for nearly 6 years—July 1975 to April 1981—yet this period was one of the most fruitful in the history of space exploration and exploitation.

For the more distant future, we can derive guidance from the recent report of the National Commission on Space (*2*) and its many kindred antecedents (*3*) and from the forthcoming report of the National Academy of Sciences (*4*).

But I find it extremely difficult, if not impossible, to foresee any substantial real growth in the federal budget for civilian space purposes during the next decade of prospective fiscal restraint.

Meanwhile, our dedication must be to use the best means at our disposal, limited though they will be, to ensure that our national space effort produces the maximum possible yield of truly significant results.

That is my point.

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REFERENCES AND NOTES

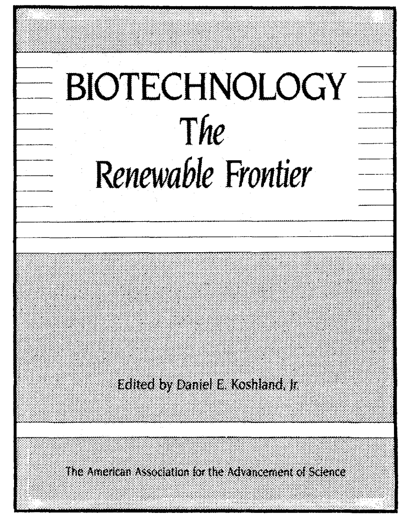
1. My Perspective was essentially a condensation of a lecture that I gave at a Coe College convocation on 1 November 1982 and later elsewhere. I invite the reader's attention to my article, "Space science, space technology and the space station" [*Sci. Am.* **254**, 32 (January 1986)], which was written in the autumn of 1985 and contains a fuller development of my views.
2. *Pioneering the Space Frontier, The Report of the National Commission on Space* (Bantam, New York, 1986).
3. W. Ley and C. Bonestell, *The Conquest of Space* (Viking, New York, 1951); W. von Braun, *The Mars Project* (Univ. of Illinois Press, Urbana, IL, 1953) (Translation of *Das Marsprojekt*, 1951); *Colliers* **129**, 22 (22 March 1952); W. von Braun, *ibid.*, p. 24; W. Ley, *ibid.*, p. 30; F. L. Whipple, *ibid.*, p. 32; J. Kaplan, *ibid.*, p. 34; H. Haber, *ibid.*, p. 35; O. Schacter, *ibid.*, p. 36; F. L. Whipple and W. von Braun, *ibid.* **130**, 38 (25 October 1952); W. Ley, *ibid.*, p. 46; F. L. Whipple, *ibid.* **133**, 21 (30 April 1954); W. von Braun and C. Ryan, *ibid.*, p. 22; S. B. Kramer and R. A. Byers, *Proposal for the Assembly of a Multi-Manned Satellite* (LMSD-48347, Lockheed Missile Systems Division, Sunnyvale, CA, 18 December 1958); *The Challenges of Space*, H. Odishaw, Ed. (Univ. of Chicago Press, Chicago, IL, 1962); *The Post-Apollo Space Program: Directions for the Future, Space Task Group Report to the President* (Government Printing Office, Washington, DC, 1969).
4. Space Science Board, *Major Directions for the Space Sciences: 1995–2015* (National Academy Press, Washington, DC, in press).

Erratum: A number was inadvertently omitted from the News and Comment article "Pentagon plans new antisatellite tests" by R. Jeffrey Smith (25 July, p. 409). In a discussion on page 410 about potential Soviet evasion tactics (second column, second paragraph), the numeral 2 was omitted from the following sentence: "The problem stems in large measure from the fact that target coordinates for the weapons must be supplied more than 2 hours before an attack."

Erratum: The Voyager 2 spacecraft is powered by radioisotope thermoelectric generators. A decrease in output by this power source, not solar batteries (This Week in Science, 4 July, p. 7), may at some future time bring an end to the effective operation of the Voyager 2 spacecraft.

The new frontiers in biology today are the frontiers of biotechnology tomorrow . . . .

BIOTECHNOLOGY: The Renewable Frontier



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