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Tree rings and fire scars (dark areas) of a giant sequoia from the Sierra Nevada, California. Episodic fires that burned around the base of sequoias caused scars that were subsequently healed over by tree-ring growth. Composite records (spanning 2000 years) from many fire-scarred trees in five sequoia groves document long-term changes in fire frequency and size associated with precipitation and temperature fluctuations. See page 885. [Photo: A. C. Caprio]
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East Asian Trade with the United States

A negative balance of U.S. trade with Japan is being supplemented by a rapidly increasing imbalance with the People’s Republic of China. Taiwan, South Korea, Hong Kong, and Singapore also contribute to the U.S. trade deficit.* If the present dynamic patterns of growth continue, the future economic giant of the world will be located in the Western Pacific.

The trade balance with Japan is numerically important ($50 billion deficit in 1992) but not very interesting otherwise. It arises mainly from U.S. imports of motor vehicles, their parts, and other manufactured items. Japanese net imports from the United States include aircraft and chemicals. However, effective impediments hold imports to a low level. Much of their value is in the form of food, live animals, and nonedible raw materials.

Taiwan has had the greatest commercial success of the other East Asian countries. Its annual balance of trade with the United States during the past 7 years has averaged more than $11 billion. Taiwan has built up the world’s largest monetary reserve ($90 billion).† While the country was experiencing this success, its gross national product (GNP) per capita was increasing. In 1990, that number was $5860. In comparison, the GNP per capita of China was $370 and that of South Korea was $5400.‡

The Taiwan-U.S. data indicate changes in the economy of Taiwan. In 1988, the main type of exports to the United States was items of clothing. Of all the exports, footwear had the highest value. In 1992, exports of footwear had diminished to one-third of that in 1988. A group of high-technology products had become dominant in 1992, and the top-value item was “automatic data processing machines and units thereof.”

In July 1993, Allan Bromley, who was President Bush’s Science Adviser, visited Taiwan as a guest of the government there. He was impressed with what he saw. The government is very supportive of efforts in high technology. It has funded technology parks liberally and when new enterprises arise has assisted them to become self-sustaining.

The success of the Taiwanese is not astonishing. They have performed very well as graduate students and post-docs in U.S. research universities. Many of the leaders of science and technology of Taiwan had training in the United States. But with a population of only about 21 million and an area of 36,000 square kilometers, ultimate prospects for Taiwan are limited except in combination with a larger, more populous power. That country might be China.

At times China has been badly misgoverned. After Mao triumphed in 1948, progress in education and research was substantial, but universities were closed during the initiation of the “Cultural Revolution” (1966 to 1976). Classes were resumed only on a limited basis in 1975. At that time, a poorly qualified group of students chosen on ideological considerations was admitted. When a AAAS delegation visited China in 1978, damage caused by the cultural revolution was highly evident.

During the 1980s, there was a gradual loosening of detailed centralized control of the economy. Some private enterprise was allowed to function. The GNP of China began to increase by amounts of about 15 percent per annum. To importance of this increase has been a changed relationship between China and Taiwan. After the escape of Chiang Kai-shek to Taiwan, a long period of sharp hostility ensued, but in the last decade attitudes have changed. China sought a warmer relationship, and Taiwanese exports to China enjoyed a privileged status. At first, Taiwan forbade interactions of its citizens with China. However, economic considerations and family ties have led to increasing relationships and to investments in South China. The cost of unskilled labor there is much less than that in Taiwan.

It may be only coincidence, but a substantial decrease in labor-intensive items exported from Taiwan was accompanied by a big increase in Chinese exports of such items to the United States. China today is the largest source of imported footwear for the United States. The Chinese balance of trade with the United States has risen from $3.5 billion in 1988 to a projected $21 billion for all of 1993. High-technology items, though small in value, are showing large percentage increases. A striking example is automatic data processing machines and units thereof, which in 1988 were valued at $8.38 million and in 1992 at $227 million.

Philip H. Abelson

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LETTERS

Guam ALS-PDC: Possible Causes

Mention of our work in Richard Stone’s Research News article (23 July, p. 424) about the possible causes of western Pacific amyotrophic lateral sclerosis–parkinsonism dementia complex (ALS-PDC) bears clarification. We and others seek to understand which agents in the neurotoxic cycad plant induce neuromuscular disease in animals and whether the neurotoxic mechanisms relate to the etiology and pathogenesis of western Pacific ALS.

Our studies began with minor Cyclic neurotoxin β-N-methylamino-L-alanine (BMAA) and progressed to cycasin (a larger component) and its aglycone methylazoxymethanol (MAM) (a genotoxin) because (i) both cycasin and BMAA are present in cycad flour consumed by the Chamorro population of Guam (1), (ii) both have neurotoxic properties (2), and (iii) cycasin and BMAA induce multineuronal neurons in developing rodent cerebellum (3) similar to those reported in adults with Guam ALS (4). It is a common experimental toxicologic strategy to select a dosage of a chemical agent (BMAA) that will elicit an effect within a reasonable period of time (weeks). We also used very large doses of BMAA because previous studies with the grass pea excitoxin β-N-oxahyamino-L-alanine showed that well-nourished macaques require much larger amounts than malnourished humans (the likely wartime situation in Guam) to elicit even beginning motor-system dysfunction (5). As stated before (6), the primate response to BMAA is far from a complete model of Guam ALS, and the neurotoxic properties of cycasin are of current interest.

The excitotoxic properties of BMAA are potentiated by bicarbonate and attenuated by glutamate-receptor antagonists, notably those active at non-N-methyl-D-aspartate (NMDA) receptors (7). Our macaques treated daily by gavage with more than 200 milligrams per kilogram of synthetic BMAA for 7 weeks did not display convulsions, and morphological changes in Betz cells of the motor cortex were more akin to those in chronic neuronal disease than to those in an excitotoxic neuropathy (8). These observations raised the possibility that low extracellular concentrations of excitotoxins perturb neurons without inducing seizures. Others have shown since that elevated glutamate (from transporter blockade) induces non-NMDA-mediated chronic motor neuron degeneration in mouse cord explants (9) and that cerebrospinal fluid from patients with sporadic ALS causes non-NMDA-mediated degeneration of rodent primary neuronal cultures (10). Thus, as we proposed in 1987 (8), the primate BMAA motor-system response may be broadly relevant to related non-Guam diseases, notably sporadic ALS.

While cycad or its components have the capacity to induce locomotor disorders in a variety of species (cow, goat, guinea pig, rat), these conditions are little understood. Experience with primates fed cycad flour has led to mixed results: Dastur and his colleagues (11) reported the induction of motor neuron degeneration and limb weakness in rhesus monkeys, but Gurraro et al. (12) did not produce any clinical signs of neurological disease in two cymolous monkeys given aluminum and manganese plus cycad flour with unknown concentrations of cycasin and BMAA.

We and others are at an early stage investigating the neurotoxic potential of cycad chemicals and their possible relationship to western Pacific ALS-PDC. There are compelling reasons to continue this systematic study.

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References

There has been a long-standing but unsuccessful search for an environmental cause of ALS-PDC not only on Guam but also in two other places with a high incidence of ALS-PDC, the Hobara and Kozagawa regions of the Kii Peninsula on Honshu Island in Japan and the Ayu and Jakai villages of West Irian in New Guinea. ALS-PDC appeared in these culturally different and relatively isolated regions at about the same time as it did in Guam, and its incidence then steadily declined. The pathology of ALS-PDC shows that it is distinctly different from classical ALS and Alzheimer's disease. Neurofibrillary tangles are not present in ALS, and while they are present in Alzheimer's disease, their distribution is different from that in ALS-PDC (1). Senile plaques, sparing of the globus pallidus, and clinical differences (2) also distinguish Alzheimer's disease from ALS-PDC. However, the clinical features and pathology of ALS-PDC strongly resemble postencephalitic parkinsonism–ALS, a sequel of encephalitis lethargica first described by Constantin von Economo in 1917 (3). Encephalitis lethargica accompanied the swine influenza pandemic in the 1920s, peaking in 1920 and 1924, and disappeared at the end of the decade. Because of their coincidence they were believed to be related, but this remained unproved. However, postencephalitic parkinsonism–ALS continued to appear over the next three decades. Guamanian ALS-PDC was first recognized in 1947 and was initially thought to be a late sequel of encephalitis lethargica, but attention soon focused on environmental toxins. It is probable that small epidemics of encephalitis lethargica have recurred for centuries, each having been referred to with different names, such as “febrilis comatosa” and “La Nona” (4). We may now be observing the decline of a postinfective illness that has finally run its course on Guam, West Irian, and the Kii Peninsula. The genetic isolation of island, valley, and tribal peoples may have produced a marked susceptibility to disease that has far more genetic importance than we realize.

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References

Stone's article on Guam disease concentrates on the search for a toxic agent or agents as a cause for ALS-PDC, but there is suggestive evidence—epidemiological, pathological, and clinical—that Guam disease may be due to a transmissible agent, probably a virus. There are many affinities between Guam disease and postencephalitic syndromes. Encephalitis lethargica, after raging for some years, also vanished and apparently died out completely around 1927. It too could produce neurological syndromes for many years or decades after the original infection—the longest such interval in my experience was 45 years. And these syndromes could be extremely variable—some patients presented ALS-like syndromes, some amnesia, and a great many parkinsonism, all of which are common in Guam disease. Moreover, as I saw myself during a recent visit to Guam, ALS-PDC can also present as catatonia, tics, or arousal syndromes intensively sensitive to the “awakening” effects of L-dopa, precisely as in postencephalitic patients.

It is difficult to imagine a toxin having effects so varied, so unpredictable, so delayed; it is much more plausible to conceive of an infectious agent, with perhaps an animal reservoir or vector that was destroyed or altered around the time of World War II.

It is crucially important, as Stone points out, that this unique disease be cracked before it disappears, for even if its etiology is different, it could cast a flood of light on every sort of neurodegenerative disease and process. And it is especially important that the current research on Guam itself be properly funded and encouraged, for this is where we will find the answer.

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Quantum Mechanics: Not Mysterious

I write to disagree fundamentally with the 12 March article by David H. Freedman (Research News, p. 1542). Leaving aside the discomfort I feel with language like “mysterious,” “queerness,” and “somehow [collaps-
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excluding glycine, and 0.64 if glycine is included (I). Thus, the suggested correlation between buried surface area and helix propensity extends well beyond the data presented in our report (3).

With respect to the consistency between the site 131 and site 44 substitutions, as we noted in our report (3), the respective ΔΔG values are in excellent agreement (correlation of 0.97, excluding Asp131 and Glu131, which appear to form a salt bridge). The site 131 variants for which crystal structures are available is limited and, as noted by Shortle and Clarke, in several cases their surface areas and ΔΔG values cluster together. Nevertheless, the site 131 data, insofar as they are available, are in good agreement with those at site 44.

Shortle and Clarke suggest that we discarded data for Phe44 and Trp44 because the trans conformations (x1 ~ 180°) observed for these side chains may be an artifact of different crystal environments. To the contrary, as we have confirmed from a survey of 100 well-determined structures in the Brookhaven Protein Data Bank (I), the conformations adopted by Phe44 and Trp44 in the mutant lysozymes correspond to the most commonly observed conformations for Phe and Trp within α-helices in general. Because Trp44 and Phe44 adopt the trans conformation, they make contacts with the side chains of Glu49 and Lys48. These contacts are tenuous [note 22 in (3)], and we therefore showed the result of both including and deleting them from the surface area calculations (3).

We emphasized in our report that calculations of surface area are very sensitive to a number of uncertainties. We also noted that the expected changes in solvent-accessible surface area and attendant hydrophobic stabilization are small (less than 1 kcal/mol). The major uncertainty in the surface area calculations probably does not come from errors in the crystallographic coordinates, as suggested by Shortle and Clarke, but from other factors. In surface area calculations (2, 8), a static model is assumed, whereas proteins are well known to be mobile. A static model may suggest that a pair of mobile side chains on the surface of a protein are in contact and therefore are partly inaccessible to solvent. This contact may, however, be transient, in which case the calculated inaccessibility to solvent would not represent the average behavior of the side chains (compare with the discussion above regarding Trp44 and Phe44). Another major uncertainty relates to the appropriate estimation of solvent-exposed area in the unfolded protein (3).

The generally good agreement between "helical propensity" scales obtained by a variety of different methods suggests that there is an underlying physical basis for these values. In our report (3), the lack of an ideal site at which to perform the analysis, the inherently narrow range of thermodynamic values, and the assumptions made with regard to the nature of the folded and unfolded states are rightly expected to cause perturbations from ideality. The critical test of any conclusion, therefore, relies upon consistent observation within a larger body of data. The available data (I) indicate that for many amino acids the hydrophobic effect is a primary contributor to observed helix propensity values. Other factors, including side chain entropy, appear to be less important for the majority of residues.

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REFERENCES

26 July 1993; accepted 14 September 1993

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The AAAS–Newcomb Cleveland Prize is awarded to the author of an outstanding paper published in Science. The value of the prize is $5000; the winner also receives a bronze medal. The current competition period began with the 4 June 1993 issue and ends with the issue of 27 May 1994.

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1994 CALENDAR OF EVENTS

Endocrinology

Endocrinology Under 35
Scientific Organization: A. De Bellis (I) • E. Schipani (USA)
Rome, Italy • May 25-27

Paracrine and Autocrine Signals in the Hypothalamic Pituitary Complex
Scientific Organization: L. Martin (I) • D. de Wied (NL) • S. M. McCann (USA)
Stresa, Italy • September 9-10

Endothelins in Endocrinology
Scientific Organization: I. T. Cameron (UK) • M. J. Dunn (USA) • M. Serio (I)
Florence, Italy • October 6-8

Immunology

Differentiation Therapy
Scientific Organization: A. Kimchi (IL) • G.B. Rossi (I) • S. Waxman (USA)
Herzlia, Israel • March 7-10

Cytokines: Basic Principles and Practical Applications
Scientific Organization: A. K. Abbas (USA) • S. Romagnani (I)
Florence, Italy • March 28-30

Primary Immunodeficiency Diseases
Scientific Organization: F. Arai (I) • M. D. Cooper (USA) • F. S. Rosen (USA)
Orvieto, Italy • June 18-21

New Horizons in Gynaecological Malignancies
Scientific Organization: D. Ayalon (IL)
Herzlia, Israel • November 16-18

Reproduction

Puberty: Basic and Clinical Aspects
Scientific Organization: C. Bergada (ARG)
Buenos Aires, Argentina • April 6-8

Male Factor in Human Infertility
Scientific Organization: J. Tesarik (F)
Paris, France • April 21-22

Immunocastruception
Scientific Organization: O. Nilsson (S)
Uppsala, Sweden • June 30 - July 1

Recent Advances In:

Nutritional Aspects of Osteoporosis
Scientific Organization: P. Burckhardt (CH) • R. P. Heaney (USA)
Lausanne, Switzerland • May 5-7

Where Phenotype Does Not Match Genotype
Scientific Organization: M.I. New (USA)
Volterra, Italy • October 13-14

Gordon Research Conferences
co-sponsored by Ares-Serono Symposia for Europe

Fractals
May 1 - 6 • San Miniato (I)

Extrachromosomal Elements: Mitochondria and Chloroplasts
May 1 - 6 • Volterra (I)

Phase Transitions in Non-Metallic Solids
May 8 - 13 • Volterra (I)

Bioelectrochemistry
September 18 - 23 • Irsee (FRG)

New Visualization Technologies for Science Education
September 25 - 30 • Irsee (FRG)

Modern Developments in Thermodynamics
October 2 - 7 • Irsee (FRG)

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present not just in infants and young children but throughout development. Many would agree with his statement that “under the constant pressure of culture, magical and other anomalous beliefs are . . . banished to the domains of fairy tales, dreams, and fantasies.” Especially in Western culture, magical and superstitious beliefs are expected to be relegated to the world of fiction. Yet Subbotsky claims that as the child develops, these beliefs “keep their potency and importance. . . . The unusual structures give way, but they do not disappear.” The boundary between the two spheres of consciousness becomes more and more stable, but it never becomes impermeable. Hence, given the proper conditions, magical or superstitious beliefs can always be reactivated, even in adults.

Subbotsky’s experimental findings also inspire him to attack another deep-seated assumption in psychology—that what we see reflects what we think. The fact that in his studies children would often initially deny possessing any magical beliefs but then go on to exhibit such beliefs through their behavior leads him to propose a dissociation between the “verbal level of behavior” and actual behavior. He argues that scientifically based concepts of causality, object permanence, space, and time appear first in verbal judgments and only later begin to dominate practical action. Psychologists who study cognitive development often conduct their research by asking children questions; their answers are taken to reflect their understanding. But according to Subbotsky, the information we can gain from verbal responses represents only half the story; simply questioning children “does not permit an assessment of whether the fundamental oppositional structures (nonpermanent object, magical causality, permeable solid object, reversible time) are able to control children’s behavior in a practical situation.”

This book may be met with skepticism by many readers. Certainly the ideas proposed are unorthodox. But it may be time to reexamine long-standing assumptions in developmental psychology and begin to give serious consideration to the “unusual realities” of fantasy, imagination, and myth. Interestingly, in arguing for granting these unusual realities a legitimate place in our consciousness, Subbotsky grants research on these topics a more legitimate status. Despite some weaknesses in his theory (in particular, in his discussion of infancy), on the whole the book is provocative and stimulating, and the evidence from preschool and school-age children is most compelling. As Subbotsky points out, “Independent of age and level of cognitive development, all individuals in everyday practice have to answer certain questions: What is true and what is false? What exists in reality and what appears only to us?” How children and adults formulate answers to these fundamental questions is what Subbotsky bravely seeks to address in this book. I imagine there are very few of us who study the human animal who, whether or not we agree with his answers, would not benefit from attending closely to his discussion of these issues.

JACQUELINE D. WOOLLEY
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