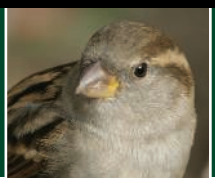

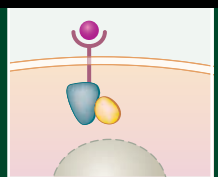

LETTERS

edited by Etta Kavanagh

Health Clues from Polar Regions

IN HIS EDITORIAL "CELEBRATING POLAR SCIENCE" ON THE FOURTH INTERNATIONAL POLAR YEAR (IPY) (16 Mar., p. 1465), Alan Leshner writes that the poles are among the scientifically richest places on Earth. Although we certainly agree, the Special Issue on Polar Science (16 Mar., pp. 1513–1540) misses the opportunity to mention another promise of circumpolar regions, namely, that they can provide options to better understand determinants of health and disease in humankind.

Indeed, one of the main health characteristics of Arctic populations, based on long-term monitoring of cancer data of some 100,000 Inuit (in Alaska, Canada, and Greenland) appears to be the pronounced deficit of breast (*1*) and prostate (*2*) cancers when compared with populations from lower latitudes. Why two of the leading malignancies worldwide should be comparatively rare in the Arctic certainly ought to be investigated. It has already been speculated that winter darkness at the extremes of latitude may offer protection against these hormone-dependent cancers (*3*, *4*). The fact that the development of frequent "winter blues" among circumpolar inhabitants is also linked to the seasonal lack of light further suggests that the Arctic could offer unique opportunities to study light-related disorders and diseases.

Empirically, the differential geographic distribution of health has provided clues to disease before: Some 63 years ago, Kennaway alerted us to the difference in liver cancer occurrence among Africans and African-Americans (*5*). Rather than being due to ethnic or genetic factors, his observation was later explained by the different geographic distribution of "extrinsic factors," namely, hepatitis B infections and the influence of aflatoxin on food products. In a similar vein, the possible effects of light (and darkness) on diseases, including cancers and seasonal affective disorders (SAD), could be studied more rigorously in populations that experience exposure to visible electromagnetic radiation that differs from that of other populations by virtue of geography. Although a considerable amount of work in these areas is already being carried out and an entire medical journal (the *International Journal of Circumpolar Health*) is devoted to health-related issues in the Arctic, more can, of course, be done. We should not have to wait for a possible 5th IPY to instigate concerted circumpolar studies of human health and disease.

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Science, Religion, and Climate Change

A MOMENT OF AGREEMENT HAS ARRIVED FOR scientists to join forces with religious groups on issues of climate change. This is signaled by the summary for policy-makers from the Intergovernmental Panel on Climate Change (IPCC)'s Fourth Assessment Report, the AAAS Board's consensus statement on climate change, and the unanimity of scientists (*1*). Lynn White Jr. proposed in these pages in 1967 that (*2*) "we shall continue to have a worsening ecologic [sic] crisis until we reject the Christian axiom that nature has no reason for existence save to serve man." In their Policy Forum "Framing science" (6 Apr., p. 56), M. C. Nisbet and C. Mooney mention the more contemporary and less divisive efforts of some evangelical leaders to frame "the problem of climate change as a matter of religious morality."

As faculty members at a Catholic university, we know the strong stance of Catholic documents on good science as the foundation for discussions of climate change. Two recent examples from the U.S. Conference of Catholic Bishops (USCCB) make IPCC findings their scientific basis. The IPCC Third Assessment Report led to the USCCB's *Global Climate Change: A Plea for Dialogue, Prudence, and the Common Good* (*3*), which states: "Global climate change is by its very nature part of the planetary commons. The earth's atmosphere encompasses all people, creatures, and habitats."

The scientific Summary for Policy Makers of the Fourth Assessment Report (*4*) was addressed by the chairman of the USCCB's international policy committee. He said in a letter to congressional leaders that the IPCC "has outlined more clearly and compellingly than ever before the case for serious and urgent action to address the potential consequences of climate change as well as highlighting the dangers and costs of inaction."

Additional reflections on climate change have come from numerous religious traditions. They are listening carefully to the science. Scientists ought to be in dialogue with them.

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Clarifying a Quote on Women in Science

THE ARTICLE "U.S. AGENCIES QUIZ UNIVERSITIES on the status of women in science" (News of the Week, 30 Mar., p. 1776) contains a quote from me that was taken out of context from a lengthy conversation and that does not represent my views on the subject.

While the specific issue I referred to in the quote (gender bias relating to which students may use what equipment) is, to my knowledge, not a problem in our department or other physics departments, the status of women is very important to us. We are committed to removing barriers to achievement and to increasing the diversity of our department. We are working hard to increase the representation of women and underrepresented minorities among our students, research associates, and faculty and to ensure that there is no discrimination nor any other barrier to achievement. We support the Title IX process as a way to help achieve these important goals.

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Notes on Modeling Light Water Reactors

AS A LONG-TIME EMPLOYEE OF THE IDAHO National Laboratory (INL), I wish to share my views on some of the characterizations made in the article "Former Marine seeks a model EMPRESS" (E. Kintisch, 9 Feb., p. 794) as they relate to modeling light water reactors. The assertions that "[e]xisting reactor computer models haven't been overhauled much since the heyday of the U.S. nuclear enterprise in the 1970s and 1980s" and that "nuclear engineers still depend on crude, 25-year-old computer programs" do not square with the facts. The RELAP5 computer code, developed at the INL for the U.S. Nuclear Regulatory Commission and the Department of Energy, has been under continuous improvement and refinement since the original release in 1978. Today's version, RELAP5-3D, is the current state of the art in modeling light water reactors and is the most widely used code of its kind in the world for safety analysis of current generation and next generation (Generation III) reactor designs.

RELAP5-3D includes a three-dimensional, two-phase flow hydrodynamic model coupled to a three-dimensional nodal neutron kinetics model. The code has been extensively validated against experimental data as documented in hundreds of peer-reviewed technical papers. The mathematical models in the code are based on first principles and literature-based empirical correlations that were defined through traditional engineering practices and procedures and are thoroughly documented (www.inl.gov/relap5/r5manuals.htm).

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The Evolution of Eukaryotes

IN THEIR REVIEW "GENOMICS AND THE IRREducible nature of eukaryote cells" (19 May 2006, p. 1011), C. G. Kurland *et al.* purport to "review recent data from proteomics and genome sequences," but delivered only biased opinions. Asserting genome sequence evidence to suggest "that eukaryotes are a unique primordial lineage," they present an introns-early (and eukaryotes-first) view of early evolution that was current in 1980 (*1*) and that was shown by conventional scientific criteria to be untenable over a decade ago (*2*). Their Fig. 1 indicates reductive evolution of prokaryotes from an ancestrally eukaryotic state; that idea was called streamlining in 1980, and its phylogenetic implications were drawn [Fig. 2 of (*1*)] in a fashion indistinguishable from its 2006 reincarnation.

The cellular structures and proteins that eukaryotes possess but that are lacking in prokaryotes are incorrectly asserted to "track the trajectory of eukaryote genomes from their origins." Uniquely derived characters lacking homologs in other taxa neither provide evidence of evolutionary relationships nor of genome trajectory, nor do they discriminate between alternative hypotheses. Were the host that acquired the mitochondrion a prokaryote, the origin of eukaryote-specific proteins and structures would follow mitochondrial origin (*3*–*5*); were the host a eukaryote (*1*, *6*), their origin would have been earlier.

The assertion that "most eukaryote proteins together with most prokaryote proteins diverge from a common ancestor" is unsubstantiated. Even at the level of protein structure, only 49 out of 1244 known protein folds (4%) are universal among 174 sequenced genomes (*7*). They claim that "[d]ifferent rates of evolution … may account for the weak, shifting affinities between the molecular machineries encoded by eukaryote, archaeal and bacterial genome sequences." However, they also claim that sequence comparisons can falsify particular models for eukaryote origins after all. Hence, they arbitrarily pick and choose among available observations relating to sequence similarity: The patterns of sequence similarity that fit their opinions are attributed to genuine evolutionary signals; the ones that counter their opinions are dismissed as rate fluctuation.

The statement that "[e]ukaryote proteins that are rooted in the bacterial or in archaeal clusters are few and far between" is inaccurate. The genomes of both yeast (*8*) and humans (fig. S1) (*9*) harbor many hundreds of proteins that have readily identifiable homologs among α-proteobacteria but not among archaebacteria, and vice versa.

They opine that "[i]t is an attractively simple idea that a primitive eukaryote took up the endosymbiont/mitochondrion by phagocytosis," yet all testable predictions of that idea have failed (*4*). By contrast, examples of prokaryotes that live within other prokaryotes show that prokaryotes can indeed host endosymbionts in the absence of phagocytosis (*10*, *11*), as predicted by competing alternative theories (*4*).

They misattribute the notion that a eukaryotic "raptor" phagocytosed the mitochondrion to Stanier and van Niel's classical paper (*12*), which does not mention mitochondrial origin, and to de Duve's 1982 exposé (*13*), which argues for the endosymbiotic origin of microbodies while mentioning "alleged symbiotic adoption" of mitochondria in passing, but without mentioning phagocytosis. Their references (*25*) and (*29*) are misattributed as examples of "fusion" hypotheses; indeed, they indiscriminately label views on eukaryote origins that differ from their own as "fusion"

Letters to the Editor

Letters (~300 words) discuss material published in *Science* in the previous 3 months or issues of general interest. They can be submitted through the Web (www.submit2science.org) or by regular mail (1200 New York Ave., NW, Washington, DC 20005, USA). Letters are not acknowledged upon receipt, nor are authors generally consulted before publication. Whether published in full or in part, letters are subject to editing for clarity and space.

hypotheses [see (*4*, *14*, *15*) for more differentiated discussion].

Finally, and most disturbing, if contemporary eukaryotic cells are truly of "irreducible nature," as Kurland *et al.*'s title declares, then no stepwise evolutionary process could have possibly brought about their origin, and processes other than evolution must be invoked. Is there a hidden message in their paper?

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Response

OUR VIEW IS THAT CELLULAR AND MOLECULAR biology, especially genomics, reveals signs of an ancient complexity of the eukaryotic cell. This new information was not available to older hypotheses for eukaryote origins; they were answering questions that were incompletely formulated.

Our primary conclusions regarding the ancestral complexity of the eukaryote cell are illustrated in fig. S1 (*1*), which depicts a microsporidian cell and the subcellular location of its eukaryote signature proteins (ESPs) (*2*, *3*). Even though Microsporidian genomes are among the most heavily reduced in eukaryotes, they still have many ESPs. An anaerobic endoparasitic life-style has reduced their mitochondria to mitosomes (*4*) and allowed the characteristic proteins of phagocytosis to be lost. Nevertheless, it is striking that characteristic ESPs are found throughout the cell; nothing in this picture suggests they are chimeric descendents of archaeal and bacterial ancestors.

We emphasize the role of molecular crowding [excluded volume effect (*5*)], which restricts the diffusion of macromolecules in cells. A dynamically efficient large cell is an impossibility, unless it is highly compartmentalized. Yes, that reasoning also applies to the smaller prokaryote cells, but the problem increases with the cube of cell radius. Molecular crowding, like gravity, is ubiquitous. We infer that it is a major physicochemical reason for the evolution of functionally specialized, membrane-bound compartments in eukaryote cells.

We also challenge the use of Blast searches to infer deep phylogeny. For primary sequences, our Markov models use only a small number of parameters and so are both tractable mathematically and "identifiable" statistically (*6*). However, they rapidly saturate from random mutations and lose all information about deep phylogeny (*7*). Even for moderately deep phylogeny, whole genome data can give different trees for the deepest animal divergences; systematic errors exceed sampling error (*8*).

Tertiary structure maintains homology longer than primary sequences, which makes them suitable for Blast searches (*9*). Nevertheless, there is no theory to relate this signal to deep phylogeny, and it can mislead (*10*). Our general understanding of the relationship between protein structure and evolutionary rates was established by the early 1970s. Kimura's neutral model leads to basic principles of molecular evolution (*11*). And in the first issue of *Journal of Molecular Evolution* in 1971, Dickerson (*12*) relates the rate of protein evolution to the numbers of unconstrained amino acid sites (and outlined how this can change) and Fitch (*13*) expanded his covarion model where individual sites, over evolutionary time, change between constrained and unconstrained states.

However, there are too many free parameters to infer phylogeny from changes in tertiary structure. Because three-dimensional (3D) interactions vary, sites where mutations are nonlethal can differ between lineages. There is thus no limit on the number of parameters required for 3D models; there is no "common mechanism" for their evolution (*14*) as there is for primary sequences. The problem occurs in both experimental data (*15*) and simulations (*16*). For example, we used RNA-shape comparison metrics (*17*) to infer that the ribozyme MRP arose from RNase P in early eukaryotes (eukaryote RNase P was more similar in structure to RNase MRP than to bacterial or archaeal RNase P). We have had to revise that conclusion (*18*) because MRP is now found more widely in eukaryotes, as is its substrate. Yes, Blastology is brilliant at picking up distant homologies but it is not, by itself, a phylogenetic method.

It is still premature to decide between introns first, early, or late (*19*). Nevertheless, our primary conclusion is that there is good progress on understanding the complexity of the ancestral eukaryote cell ("Fred"). Despite his venerable pedigree, Fred is still alive and well.

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CORRECTIONS AND CLARIFICATIONS

News of the Week: "Selfish genes could help disease-free mosquitoes spread" by M. Enserink (30 Mar., p. 1777). Kenneth Olson is not a faculty member at North Carolina State University in Raleigh, as the story said, but at Colorado State University in Fort Collins. Richard Beeman is a scientist at the Grain Marketing and Production Research Center in Manhattan, which is part of the U.S. Department of Agriculture's Agricultural Research Service, as well as an adjunct professor at Kansas State University.

News Focus: "Spinning a nuclear comeback" by D. Charles (30 Mar., p. 1782). GE Energy is located in Wilmington, North Carolina, not Wilmington, Delaware.

Special Section: Stardust: Reports: "Mineralogy and petrology of comet 81P/Wild 2 nucleus samples" by M. E. Zolensky *et al.* (15 Dec. 2006, p. 1735). An author was left out of the author list. Sirine Fakra should be listed between Stewart Fallon and Denton S. Ebel, and Fakra's affiliation should be Advanced Light Source, Lawrence Berkeley National Laboratory, 1 Cyclotron Road, Mail Stop 2-400, Berkeley, CA 94720, USA.

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