Letters

Hot Little Pond?

M. Mitchell Waldrop's article (Research News, 23 Nov., p. 1078) reviews the opinions of the planetary scientists who dismiss Darwin's Warm Little Pond in favor of deep-sea hot springs as the locales where life may have originated. Even if it were necessary to accept the underlying assumption of the "ocean blasters" that life actually existed on Earth before the end of the late-stage bombardment about 3.8 billion years ago, there are several problems associated with this viewpoint.

Stanley Miller has already commented on both the necessity for a protracted origin of life and the difficulties involved with the formation and stability of organic molecules under intensely hot, deep-sea conditions. But Günter Wächtershäuser's novel ideas regarding pyrite are offered by Waldrop as a model consistent with deep-sea hot springs. In this connection it is important to note that Wächtershäuser's postulates require that the environment be rich in hydrogen sulfides that are in contact with metal sulfides and pyrite. This requirement places another constraint on the use of deep-sea hot springs. This is so because the deep oceans of the early earth are said to have been saturated with the dissolved ferrous iron necessary for banded iron-formation deposition. Clearly, the insolubility of ferrous sulfides means that the *deep* sea cannot have been a place where both hydrogen sulfide and ferrous iron were present in excess. The geochemists cannot have their reduced iron and the prebiotic chemists their reduced sulfur in the deep ocean at the same time.

If hot springs were necessary, it is more likely that they were located at the surface of the earth where the "food stuffs" hydrogen, hydrogen sulfides, elemental sulfur, and sulfates can all have been available, as they are for the various thermofile bacteria today. In surface hot springs the important heating of the deep sea would still have been available, but the equally important cooling and the wetting and drying necessary for oligopeptide-nucleotide concentration and growth were also there. Of course, in this scenario life would have to have originated after the early "impact frustration" tapered off, a viewpoint that Preston Cloud (*1*) felt the very evidence for asteroid pounding itself supported. The ocean blasters need to specify why it is necessary to have life originate so early that it must have been subjected to the indignities of bombardment, how dissolved iron and sulfide could have been available at the same time in the same place, and how prebiotic nucleotide bonds grew and survived in the deep sea. Darwin may have been wrong only in his assessment of the temperatures required. Goodbye Warm Little Pond, Hello Hot Little Pond?

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Royal Shorthand

One hesitates to contradict one of the world's most celebrated philosophers, Karl R. Popper (with Günter Wächtershäuser, Letters, 23 Nov., p. 1070), but the issue is a question of fact, and Sir Karl is well known for his commitment to a criterion of falsification.

Popper and Wächtershäuser quote the famous motto of the Royal Society of London—"*Nullius in verba*"—and then, unfortunately, also give the canonical mistranslation ("there is nothing in words," in their version).

Although I am sure we all agree with their central contention that facts are more important than words, the motto of the oldest and most venerated of English scientific societies deserves its proper citation, especially since the full quote is such a lovely statement embodying such an important principle for all of us.

The motto is so often mistranslated because "*Nullius in verba*" is shorthand for a longer statement, a famous line from Horace's *Epistulae*:

> *Nullius addictus iurare in verba magistri,*
> *quo me cumque rapit tempestas, deferor hospes*
> (I am not bound to swear allegiance
> to the word of any master,
> Where the storm carries me,
> I put into port and make myself at home).

Thus, the motto advocates freedom of thought and action, not the insignificance of words. (We go astray by misreading the genitive singular "*nullius*" as the nominative "*nullus*" and by not recognizing the abbreviated citation.)

A valuable and general point does emerge from the correction. Words mean nothing in themselves, but we communicate by them and must be clear. We so often fail (not only in speaking to the general public, but even to our scientific colleagues in other subdisciplines) because we use the shorthands of our contemporary jargon and don't even recognize our elisions. Any well-educated, 17th century gentleman (a group including nearly all English scientists of the time) knew that "*Nullius in verba*" would convey a common message to all club members, just as we feel no need to explicate the terms in $E = mc^2$. We should remember that our modern shorthands can confuse others, just as we misconstrue the motto of our predecessors because numbers have superseded Latin as our imprimatur.

But enough of this. While we strive to keep words clear, we shall also remember Horace's more important advice—"*inter silvas Academi quaerere verum*" (to seek for truth in the garden of Academus).

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Carcinogenesis Models

The Perspective "Too many rodent carcinogens: Mitogenesis increases mutagenesis" by Bruce N. Ames and Lois Swirskey Gold (31 Aug., p. 970) and the article "Cell proliferation in carcinogenesis" by S. M. Cohen and L. B. Ellwein (31 Aug., p. 1001) raise significant, but often overlooked, questions about the process of carcinogenesis and the manner in which the carcinogenicity of new compounds is tested.

Mitogenesis, induced by physiological growth factors in platelets, promotes the induction of the neoplastic phenotype in carcinogen-treated cells. I have recently reported that the platelet-derived growth factor (PDGF), which is mitogenetic, is also a potent promoter of neoplastic transformation in the C3H/10T1/2 fibroblast model of carcinogenesis (*1*). I have also reported that vitamin A, an effective antipromoter in vivo and in vitro, inhibits the mitogenic response of preneoplastic cells to PDGF and EGF. (*2*).

Several noteworthy investigators have reported that wound-healing is as effective as the phorbol esters in promoting tumor formation in the mouse skin model of carcinogenesis (*3*). Apparently, this tumor promotion results from the exposure of preneoplastic cells to growth factors as a consequence of microvascular leakiness and platelet degranulation in response to 12-*O*-tetradecanoyl phorbol-13-acetate treatment. Thus, the apparent carcinogenicity of new compounds may be the result of oxidative damage and the cellular proliferation associ-

ated with the wound-healing response if the compound is highly cytotoxic.

My collegues and I have found that the apparent mouse skin-tumor promoter okadaic acid is an effective antipromoter in the C3H/10T1/2 mouse fibroblast transformation assay, a widely used cell culture system for the study of carcinogenesis in vitro and for screening the potential carcinogenicity of new compounds (*4*). These and other studies of the antiproliferative effects of okadaic acid (*5*) were conducted at noncytotoxic concentrations of okadaic acid (<10nM) that were at least 12,500 times lower than the highly cytotoxic concentrations (125μM) used to demonstrate its apparent tumor-promoting properties. (*6*).

We postulated that the tumor-promoting property of okadaic acid is the result of significant cytotoxicity to the mouse epidermis, with the resulting regenerative hyperplasia acting as the true promoter. Similar antineoplastic properties of okadaic acid at noncytotoxic concentrations have been reported in other in vitro models of carcinogenesis (7).

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Without quarreling with the qualitative conclusions of S. M. Cohen and L. B. Ellwein in their article "Cell proliferation in carcinogenesis" (31 Aug., p. 1007), I must point out that these conclusions are based on a flawed analysis of their data. Just as there are accepted standards for laboratory procedures, there are mathematical and statistical standards that modelers should adhere to. Because Cohen and Ellwein do not adhere to these standards, their approach is of little use for quantitative cancer risk assessment.

There are two problems with their analysis. Without using a formal procedure for fitting the two-event model to data, they manipulate its parameters until they obtain reasonable visual fits. A different set of parameters may describe the data better. Second, a proper analysis of time-to-tumorigenicity data requires consideration of whether or not the tumors are lethal (*1*). Cohen and Ellwein do not take such considerations into account.

Although Cohen and Ellwein refer to their model for carcinogenesis as stochastic, it is strictly deterministic, in that they investigate only the *mean* behavior of the system (*2*). A mathematical development based on the mean leads to an erroneous expression for the incidence function (*3*) and cannot model the inherent variability seen in typical carcinogenesis experiments. Cohen and Ellwein also contend that they avoid mathematical oversimplification by adopting a simulation approach. This is incorrect. Because they consider only the mean behavior and treat time as a discrete rather than a continuous variable, mathematically their development is a considerable simplification of other treatments (*3*) of the two-mutation model.

Despite my skepticism about their mathematics, I agree with Cohen and Ellwein that incorporation of cell proliferation kinetics into risk assessment procedures is long overdue.

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Response: Moolgavkar is supportive of the qualitative aspects of our work, but he states his preference for a traditional curve-fitting approach to risk assessment. The key aspects of chemical risk evaluation are of a biological nature and are best assessed by experimentation rather than with statistics. Questions dealing with genotoxicity, changes in cell proliferation rates and cell number, mechanisms of action, and no-effect thresholds cannot be resolved mathematically. The obvious example is melamine, as mentioned in our article.

Our simulation-based approach to synthesizing available information, although not a direct replacement for standard methods of statistical modeling and parameter estimation, provides a practical means for increasing our understanding of carcinogenesis and, thereby, improving the risk assessment process. We draw upon available experimental data and judgment pertaining to model inputs: mitotic rates, cell differentiation and death rates, and genetic transition probabilities. Consistency of biological assumptions dealing with model variables is maintained, not only across groups within an experiment, but also between control groups of different experiments. Incorporating experimentally induced biological discontinuities, such as bladder ulceration and partial hepatectomy, is straightforward from a modeling perspective—biological complexity and dynamism do not pose analytical difficulty. Sensitivity analysis that quantitatively explores relationships between model inputs and such outputs as the cumulative probability of a grossly visible tumor is fundamental to our efforts, leading to recognition, for example, of the contributing effect of proliferation during organ development on the resultant carcinogenesis of subsequently administered proliferative agents.

Biology—rather than mathematics-driven modeling—has convinced us that modelers all too often, perhaps unknowingly, sacrifice biological reality in their quest for mathematical tractability (for example, in carcinogenesis modeling, parameters must be treated as time-varying functions, not constants). A false security associated with exact solutions to oversimplified mathematical representations has plagued carcinogenic risk assessment. Fortunately, as mathematical representations are proposed that permit direct biological interpretation of model parameters, it will be possible to recognize modeling results that imply biological nonsense. We acknowledge that relying upon judgmental expertise, not only in model construction but also in variable estimation, can be disconcerting to the classical biostatistician charged with conducting a "scientifically objective" risk assessment.

Moolgavkar is correct that our analyses deal with cumulative tumor incidence in the absence of mortality, which was appropriate for the specific examples evaluated. Although we have not done so, mortality could be incorporated within our simulation model, thereby allowing death from causes other than the target organ tumor to reduce the risk of tumor induction. We do not retain the complete joint probability distribution of cells across the normal, initiated, and transformed cellular states, but use expected values instead in reducing computational storage and running time (*1*). We have not explored the ramifications of this shortcut. We refer to our Markov model as sto-

chastic in that the time-varying, random dynamics of the three cell populations are modeled, providing outputs that also are probabilistic. An attractive feature of discrete-time models is that the underlying mathematical expressions have a recursive form that makes for computational simplicity on digital computers. If analog computers were the norm, continuous-time simulation models would be more practical. As it is, these models require numerical integration schemes that are based on discrete-time analogs.

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Asians and UCLA Admission

The headline "Anti-Asian bias seen at UCLA" (Briefings, 12 Oct., p. 204) is more than a small stretch of the truth. During some 30 months of detailed investigation, the Office for Civil Rights of the Department of Education looked at "84 separate graduate programs with 95 separate admissions processes." The office found "a statistical disparity" in *one* case, thereby clearing the university of the charge of "anti-Asian bias" in 99% of the cases. Even the single deviant case is dubious, since the admission process in any university department involves warranted judgments on qualities not readily quantified. The overall record is clear: the University of California at Los Angeles is a national leader in Asian-American access to higher education.

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Erratum: The last sentence of David Hamilton's 21 December News & Comment article "Space program: Blueprint for ambiguity" (p. 1654) should have read, "It [the Augustine Commission] will reconvene in 6 months to assess NASA's progress."

Erratum: The first sentence of the abstract of the report "Control of yeast mating signal transduction by a mammalian β_2-adrenergic receptor and G_s α subunit" by K. King *et al.* (5 Oct., p. 121) was incorrectly printed. It should have read, "To facilitate functional and mechanistic studies of receptor–G protein interactions, the human β_2-adrenergic receptor (hβ-AR) has been expressed in *Saccharomyces cerevisiae*.

Erratum: The last name of the eleventh author of the report "Inhibition of HIV-1 replication by a nonnucleoside reverse transcriptase inhibitor" by V. J. Merluzzi *et al.* (7 Dec., p. 1411) was incorrectly printed. That author