

side of the story.

It is the only metabolite of estrogen devoid of uterotrophic, estrogenic, or tumorigenic activity in vivo (1, 2) and is now emerging as a potential therapeutic for the treatment of angiogenic-based diseases. Recent studies have shown 2ME₂ to be a potent nonspecific antimitotic agent in vitro and an effective oral anti-angiogenic and antitumor agent in vivo (2-5). It may be the first endogenous chemotherapeutic compound that is a physiological metabolite in humans.

2ME₂ is the product of the sequential hydroxylation and methylation of estradiol. The liver is the principle organ of hydroxylation, while the erythrocytes are perhaps the major site for methylation through the activity of a catechol-o-methyl transferase (COMT). The equilibrium of the reaction catalyzed by this enzyme favors the conversion of 2-hydroxyestradiol to 2ME₂. Accordingly, the physiological plasma levels of the latter are one to two orders of magnitude higher than for 2-hydroxyestradiol.

In vivo studies have shown that 2ME₂ inhibits the vascularization and growth rate of various tumors resulting in more than 60% inhibition of tumor size (4, 5). Consistent with these observations, we have recently found that oral administration of 2ME₂ is equally effective at inhibiting lung metastases

in the experimental B16 melanoma model. Toxic effects such as hair loss, gastrointestinal disturbance, or inhibition of leukopoiesis commonly associated with conventional chemotherapy were not observed or reported in any of the in vivo experiments (2-4).

On a final note, the association of low levels of COMT with increased breast cancer incidence may reflect not only a higher concentration of potentially carcinogenic estrogens (6) but a decrease in 2ME₂ concentration.

Yes, Virginia, there are some good estrogens after all!

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Causal Systems in Ecology

In his Research commentary "Ecological science and statistical paradigms: At the threshold" (*Science's Compass*, 23 Jan., p. 502), Brian A. Maurer states that process models are essential in advancing understanding of causal systems in ecology. He points out the difficulties in parameter inference and model comparison that accompany such models and proposes that ecologists adopt likelihood-based methods to overcome these problems (see also E. Roe, Letters, 8 May, p. 807). While I applaud his call to "ecologists to adopt more sophisticated approaches and philosophies for data analysis," I find his central focus on likelihood as a solution to the problem of model assessment too narrow.

First, many interesting ecological process models are deterministic. Without an associated error structure or stochastic component, a likelihood cannot be defined. Second, even for those process models with stochastic elements, not all likelihoods are solvable. For example, a partially observed two-compartment linear birth-death model can have a computationally infeasible likelihood (1). Third, only nested model structures can be compared by likelihood methods (2).

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More fundamentally, a likelihood does not directly assess the proposed model structure's ability to reproduce key characteristics of the phenomenon being studied. Likelihoods, and most other statistical estimators, are derived from the proposed model structure under the assumption that that model is correct. In standard statistical practice, model assessment occurs by one looking at the models performance, under the selected parameterization, with goodness-of-fit diagnostics selected to capture these key characteristics. It seems more appropriate that process models be fitted, assessed, and compared directly with respect to these goodness-of-fit criteria.

For example, the Pareto Optimal Model Assessment Cycle (POMAC) evaluates a model's ability to simultaneously satisfy multiple goodness-of-fit criteria chosen to capture key characteristics of the ecological phenomenon (3). By optimizing the model's simultaneous satisfaction of the multiple criteria, POMAC reveals model deficiencies as criteria that cannot be satisfied, or which cannot be satisfied simultaneously. This also provides a direct comparison of the tradeoffs inherent in competing model structures.

Maurer urges ecologists "to learn their statistics from the likelihood perspective" so they can compare competing process mod-

els. Ecologists should also be urged to consider methods that assess the deficiencies in and reveal the tradeoffs in, competing models.

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Corrections and Clarifications

■ In the News & Comment article "Australian partnerships: New life for research centers" by Elizabeth Finkel (24 Apr., p. 513), reference is made to a "\$138-million-a-year program." The dollars referred to are Australian, not U.S.; the U.S. equivalent is \$92 million.

■ In the report "Requirement of Ras-GTP-Raf complexes for activation of Raf-1 by protein kinase C" by R. Marais *et al.* (3 Apr., p. 109), the second sentence should have begun, "The conventional and novel PKC isozymes are activated...."

■ In Raymond R. White's letter "Does public funding corrupt?" (13 Mar., p. 1616), reference 1

[T. Kealey, *The Economic Laws of Scientific Research* (St. Martin's, New York, 1996)] was inadvertently omitted.

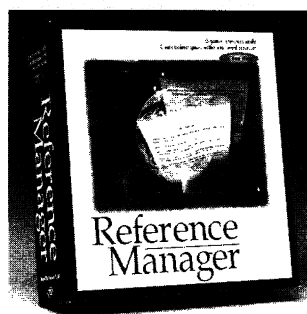
■ In Elizabeth Pennisi's article "Bioprospecting: Lawsuit targets Yellowstone bug deal" (News & Comment, 13 Mar., p. 1624), the National Environmental Policy Act was incorrectly called the National Environmental Protection Act.

■ In Michael Balter's News & Comment article "Has French AIDS research stumbled?" (16 Jan., p. 312), Willy Rozenbaum's name was misspelled.

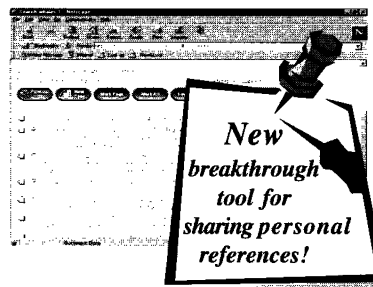
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