pharmaceutical companies developing rhGH products, Met-rhGH and natural sequence rhGH, were required to conduct the same studies independently before these products received approval. Although the rbGH products may be biologically indistinguishable from each other, they are being evaluated as separate products.

It is generally accepted that bGH is biologically inactive in humans when administered parenterally, and the lack of effects has been documented. We share Kronfeld's concern regarding the extra-label abuse of any animal drug by young athletes. With regard to this potential for abuse, if rbGH is approved, the label will contain information stating that the product is for use in animals only. Although there is no warning label for any over-the-counter veterinary drug that can ensure that human use will not occur, the warning label serves as a deterrent for such illegal use. We believe that the extra-label abuse of rbGH is unlikely because of its lack of activity in humans.

The extensive review of the multilactational target animal safety studies has not been completed by the FDA, so we cannot comment on whether or not an increase in mastitis or infertility will occur. These conditions are being monitored in all animal safety and effectiveness studies and will influence the agency's final decision concerning rbGH. Moreover, the use of antibiotics in lactating dairy cattle is regulated by having specific milk discard periods follow the use of approved antibiotics. State and federal regulatory systems monitor milk for drug residues and remove adulterated sources from commercial sale. As with all unapproved animal drugs, the use of unapproved antibiotics in lactating dairy cattle is illegal unless the drug is given under strict supervision by a veterinarian or authorization has been provided for such use under an investigational new animal drug or new animal drug application by the FDA. This authorization includes an appropriate milk discard period to ensure that the use of such products will not present an increased risk to consumers of milk products from treated dairy cattle.

We appreciate comments from the scientific community concerning our review of the human food safety of rbGH. We have always believed that all products regulated by the FDA should be evaluated strictly on the basis of their scientific merit and that FDA scientists should maintain a high level of objectivity in reviewing studies submitted by pharmaceutical companies.

JUDITH C. JUSKEVICH
C. GREG GUYER
Food and Drug Administration, Rockville, MD 20857

Interpreting Cancer Tests

Jean Marx's 9 November News & Comment article (p. 743) about the controversy engendered by Bruce Ames' criticism of the maximum tolerated dose (MTD) bioassay points out the broad range of agreement that now exists concerning testing for carcinogenicity and how the results of these tests should be interpreted. Ames criticizes an obsolete status quo, and his critics defend an abandoned practice. Thus they obscure the significant changes that have occurred in the science of carcinogenicity and the lessons learned from those 1000-plus bioassays.

As Samuel Cohen observes, the practices under attack were based on a previous generation's theories of carcinogenesis. Those led to two precepts now found wanting: (i) exposure to any "animal carcinogen" in any amount will increase cancer risk in humans; and (ii) the dose-response curve for carcinogens is best represented by a straight line from the highest response to zero. From these came, in the 1970s, the regulatory procedures Ames criticizes, procedures now beginning to change in the wake of scientific advances. Several examples of compounds are now recognized where a "threshold" dose response appears to exist (all of these either mimic or alter the physiology of endogenous hormones). Morever, there are now several well-studied examples where an animal cancer model is considered not to predict human response: Marx's article refers to two of these, D-limonene and saccharin. As William Farland observed during the recent National Academy of Sciences workshop on "two-stage models," substances can be "situational carcinogens," causing cancer under some circumstances of exposure but not under others. Science is outstripping the legal framework in which it is applied: neither the Environmental Protection Agency's (EPA's) Guidelines for Carcinogen Risk Assessment nor the Food and Drug Administration's (FDA's) basic law (the Delaney clause of the Food, Drug and Cosmetic Act) recognize this reality. The dissonance between these laws and scientific reality causes much distress to scientists in these two agencies; they appear to be doing their best to circumvent the most absurd consequences.

Also obscured by the controversy is the change that has occurred in the strategies for testing chemicals. Our understanding of the impact of mitotic rate on cancer risk (most prominently evident from the work of Cohen and Leon Ellwein) implies that chronic toxicity testing needs to include tests that gather information about this response to exposure. Identification of instances where critical metabolic pathways differ strongly among species implies inclusion of metabo-

lism and pharmacokinetics testing. In fact, the National Toxicology Program has modified the design of its tests to include these kinds of data. Testing required by the FDA and the EPA for registration of new food additives and pesticides, as well as for industrial chemicals generally, is flexible enough to include such measurements, should the sponsors wish to obtain the data.

No toxicologist of my acquaintance would ever advocate doing away with chronic toxicity testing altogether. For substances with widespread, long-term human exposure, the cost in time, expense, and animal lives seems justified. However, most toxicologists want to conduct chronic tests using designs that return the most information for the expenditure. Clearly, the traditional "MTD carcinogenicity bioassay," the source of most of the results analyzed by Ames and Lois Gold, is not an efficient design. In bringing to public view the scientific deficiencies in those tests, Ames has performed a public service.

JAMES D. WILSON
Monsanto Company,
800 North Lindbergh Boulevard,
St. Louis, MO 63167

The statement attributed by Marx to I. B. Weinstein that "some types of synthetic compounds, including halogenated hydrocarbons such as PCB [polychlorinated biphenyl], are not found in nature" is misleading if not erroneous. Such chemicals have been isolated and characterized from marine and terrestrial sources for decades. Indeed, the general chemical structure of the ancient Egyptian dye from mollusks, Tyrian Purple, which is a brominated indole, has been known since 1909 (*1*). Moreover, a myriad of chlorinated, brominated, and iodinated hydrocarbons, aliphatic and aromatic, are produced and secreted by numerous species of sea creatures, such as sponges, algae, mollusks, sea slugs, sea hares, tunicates, and others(*2*). Nearly 100 halogenated compounds have been identified in the edible Hawaiian red alga *Asparagopsis taxiformis* (*3*), and several polychlorinated phenolic compounds have been found in Australian terrestrial lichen (*4*). The simplest chlorinated hydrocarbon, chloromethane, was recently isolated from alga (*5*), and this chemical was previously known to be synthesized by wood-rotting fungus (*6*). In fact, it has been estimated that the global emission of chloromethane (5×10^6 tons per year) is largely from the marine and terrestrial biomass and that man-made emissions are insignificant by comparison (*5, 6*). The precursor of the herbicide 2,4-D, 2,4-dichlorophenol, is the sex pheromone of the female lone star tick (*Amblyomma americanum*) (7), and another polychlorinated aromatic compound, rebeccamycin, having powerful antitumor properties, is present in the bacteria *Nocardia aeroligenes* (*8*). Even the halogen fluorine is present in some plant carboxylic acids (*9*). The list goes on.

This is not a trivial point, since environmental hysterics seize upon and propagate such ignorance and imprecision to further their causes. Scientists should be accurate and vigilant in their presentation of chemical issues to an already badly informed and confused public.

GORDON W. GRIBBLE
Department of Chemistry,
Dartmouth College,
Hanover, NH 03755

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Kidney Transplantation: Overlooked Pioneer

I read with interest Joseph Palca's article "Overcoming rejection to win a Nobel Prize" (News & Comment, 19 Oct., p. 378). While the article was well done and factual, there was an unfortunate omission in the description of the sequence of events that led from the work of Robert Schwartz and William Dameshek to the use of 6-mercaptopurine and azathioprine in kidney transplantation. Roy Calne (now Sir Roy Calne) first used 6-mercaptopurine in kidney transplants in dogs; he then went to work with Joseph Murray in Boston, where he introduced azathioprine to prevent transplant rejection in dogs. That history is recorded in my Nobel lecture (Articles, 7 Apr. 1989, p. 41).

There is no question that Joseph Murray deserves the Nobel Prize for his pioneering work in kidney transplantation. However, one should not overlook the highly important contribution of Roy Calne to the eventual success of that therapeutic procedure involving unrelated donors.

GERTRUDE B. ELION
Wellcome Research Laboratories,
Burroughs Wellcome Co.,
3030 Cornwallis Road,
Research Triangle Park, NC 27709