Letters

Darvon Safety

Parts of the article, "Federal government faces painful decision on Darvon" by R. Jeffrey Smith (News and Comment, 2 Mar., p. 857) are misleading and not objective. A few remarks may add balance to the discussion.

The impression that Eli Lilly and Company has acted irresponsibly in promoting and discussing Darvon (propoxyphene hydrochloride) with physicians is clearly implied by Smith when he uses words like "Lilly . . . used to claim that . . . ," "physicians remain apparently uninformed of the true nature of the drug . . . ," and the quote that "by not calling Darvon a narcotic, Lilly was not informing physicians about its narcotic properties." These insinuations ignore the fact that pharmaceutical manufacturers must conform to Food and Drug Administration-approved labeling that requires full disclosure of a drug's therapeutic usefulness, limitations, and adverse reactions or side effects. Most of what is known about the pharmacology and metabolism of Darvon has come from research done by our own scientists. The results of their work have been published in scientific journals. Our product labeling and promotional materials have faithfully reflected new information as it has been accumulated.

Lilly has gone beyond the legal requirements. In 1976 our sales representatives contacted more than 100,000 physicians throughout the country to present new warning information that stemmed from the results of a Lilly-sponsored study. This information included warnings that Darvon should be taken only as directed and not in conjunction with alcohol or other central nervous system (CNS) depressants. All manufacturers of propoxyphene are now required to include similar warnings in their package literature. In reporting that Department of Health, Education, and Welfare (HEW) Secretary Califano ordered that warnings be sent to hospitals and physicians, Smith could have pointed out that Lilly's labeling reflected these warnings almost 3 years before.

The fact is that physicians *do* know about the measures required for the safe use of propoxyphene. Eighty-eight percent of the physicians interviewed in a nationwide survey taken earlier this year by an independent market research firm said they are aware of the warnings about the use of propoxyphene alone or in combination with other CNS drugs (including alcohol).

Smith also writes that Lilly once promoted Darvon as "the ideal alternative to codeine." We continue to promote Darvon as "the best available alternative to codeine." Physicians prescribe Darvon because their experience has taught them that, in situations where either codeine or Darvon might be appropriate, patients using Darvon do not experience the side effects that often arise when codeine is prescribed.

The analgesic efficacy of propoxyphene has clearly been established in clinical trials. The National Academy of Sciences–National Research Council's 1969 review (*1*) of propoxyphene affirmed the efficacy of 65-milligram doses of Darvon. Moreover, the previously cited survey of practicing physicians showed that 90 percent of the group found propoxyphene clinically effective in their practice.

William T. Beaver presented a scholarly analysis of the effectiveness and safety of propoxyphene to the Senate subcommittee chaired by Senator Nelson. Smith quotes excerpts not reflecting Beaver's overall position. For example, Beaver's statement that "at recommended doses propoxyphene produces an extremely low incidence of any sort of adverse effect and a virtually zero incidence of serious adverse effects" is not mentioned.

Effectiveness and safety are the two major reasons why billions of doses of Darvon have been prescribed for millions of patients. No amount of salesmanship and promotion could generate the continued sale and use of a drug that did not perform as expected by both the prescribing physician and the patient.

When one keeps in mind the many millions of patients over the past two decades who have safely received relief from pain with Darvon, the reports of dependence are so insignificant that they are nearly unmeasurable. Lilly has received only 402 reports of alleged dependence since 1957. Of the 402 reported cases of addiction, in only 122 was there sufficient evidence to support inference of propoxyphene-induced dependence.

Another significant point missed in Smith's comments came from testimony by Kenneth A. Durrin, director of the Office of Compliance and Regulatory Affairs of the Drug Enforcement Administration (DEA). Durrin questioned whether the data being gathered by DEA would support the criteria provided by law for placing propoxyphene in Schedule II of the Controlled Substances Act.

Eli Lilly and Company is convinced that the objective, full review of the safety and usefulness of Darvon ordered by Secretary Califano on 15 February will confirm that Darvon is a useful analgesic, capable of safely relieving pain.

C. W. PETTINGA
Eli Lilly and Company,
Indianapolis, Indiana 46206

Reference

1. Analgesic Drugs Panel, *National Academy of Sciences-National Research Council Drug Efficacy Study Investigation Review of Propoxyphene Hydrochloride Compound* (DESI 10996, NDA 10996, Log 27, National Academy of Sciences-National Research Council, Washington, D.C., 1969).

Tea and Tannins

Eliot Marshall's statement (News and Comment, 23 Feb., p. 731) that tea contains more tannic acid than beer is in error. In fact, tea contains *no* tannic acid. Tannic acid is a hydrolyzable tannin that yields on hydrolysis gallic acid and glucose (*1*). It is most commonly described as a pentadigalloyl glucoside with the empirical formula of $C_{76}H_{52}O_{46}$ (*2*). This material has never been reported as a component of tea in any serious work dealing with analysis of the product (*3*). Careful review of the "Federation of American Sciences [sic] for Experimental Biology" report (*4*) referred to by Marshall indicates that tannins are widely distributed in many foods, including tea, but that tannic acid is a more narrowly defined substance. The authors of this report were careful to distinguish the tannic acid under evaluation as a food additive from the tannins that are ubiquitous in plants.

Since Marshall's unreferenced statement is not unique, this "fact" appears to have entered into the domain of common, albeit erroneous, knowledge. When one considers the existing climate surrounding the safety and use of food additives, it is particularly important that what is or is not contained in a food is accurately reported.

STEVEN R. WHEELER
Product Safety and Nutrition,
Thomas J. Lipton, Inc.,
Englewood Cliffs, New Jersey 07632

References

1. V. L. Singleton and F. H. Kratzer, in *Toxicants Occurring Naturally in Foods* (National Academy of Sciences, Washington, D.C., ed. 2, 1973), pp. 309-345.
2. *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man*, vol. 10, *Some Naturally Occurring Substances* (International Agency for Research on Cancer, Lyon, 1976), pp. 253-262; A. Osol *et al.*, *United States Dispensatory* (Lippincott, Philadelphia, ed. 26, 1967), pp. 1128-1129.
3. M. A. Bockuchava and N. I. Skobeleva, in *Advances in Food Research*, C. O. Chichester, E. M. Mrak, G. F. Stewart, Eds. (Academic Press, New York, 1969), vol. 17, pp. 215-292; W. H. Stahl, in *ibid.*, vol. 11, pp. 210-262; T. Eden, *Tea* (Longmans, London, ed. 3, 1976); G. W. Sanderson, in *Structural and Functional Aspects of Phytochemistry*, V. C. Runeckles and T. C. Tso, Eds. (Academic Press, New York, 1972), pp. 247-316.
4. Select Committee on GRAS *Evaluation of the Health Aspects of Tannic Acid as a Food Ingredient* (SCOGS-48, Federation of American Societies for Experimental Biology, Washington, D.C., 1977).

Antibiotics in Feeds

Eliot Marshall (News and Comment, 23 Feb., p. 732) indirectly quotes Richard Novick and others as saying that they agreed to join the CAST (Council for Agricultural Science and Technology) task force on antibiotics in animal feeds because "we were naïve." This is scarcely true in Novick's case: while the preliminary deliberations of the task force were in progress, he published a long article in the *Journal of Commerce* (*1*) devoted to claims that agricultural use of antibiotics was dangerous and ineffective. James McGinnis telephoned Novick on 18 October 1977 and furnished him with information about the continued efficacy of antibiotics in the state of Washington ever since 1949. Novick subsequently wrote to the *New York Times* (*2*) and stated that "frequently these days little or no effect can be obtained."

Concerning the ABC news documentary on antibiotics in animal feed, American Cyanamid purchased a full page in the *New York Times* to refute it, and the head of Cyanamid, James Affleck, appeared on ABC television in rebuttal. Accuracy in Media also protested. One statement in the ABC documentary was that their reporters had seen a "whole barrel of chloramphenicol" (CM) in a feed mill in North Carolina. This turned out to be chlortetracycline. The use of CM in animal feeds is illegal; it would foster development of CM resistance in *Salmonella*.

THOMAS H. JUKES
Division of Medical Physics,
University of California, Berkeley 94720

References

1. R. Novick, *J. Commer.*, 23 Sept. 1977, p. 4.
2. ——, *New York Times*, 21 Nov. 1977, p. 36.

Pert and the Lasker Award

The National Institute on Drug Abuse (NIDA) Division of Research played a significant role in the events leading up to the flurry of current questions concerning the 1978 Lasker Award for Basic Medical Research to Hughes, Kosterlitz, and Snyder (News and Comment, 26 Jan., p. 341; Letters, 2 Mar., p. 834) (*1*).

At the 1977 39th Annual Scientific Meeting of the Committee on Problems of Drug Dependence, the NIDA Pacesetter Research Award was given to Avram Goldstein, John Hughes, Hans Kosterlitz, Eric Simon, Solomon Snyder, and Lars Terenius for the rapid development of the concept and characterization of the structure and function of enkephalins and endorphins, the endogenous morphine-like substances produced in the central nervous system. All six of the awardees had received NIDA support for the investigations leading to these discoveries.

In retrospect, we feel that it was a significant omission on our part that Dr. Candace Pert was not included. Her graduate student role was the issue at the time; subsequent increased awareness of her major contribution has led us to this revised conclusion.

Selecting recipients for prestigious awards is a complex social process in which "scientific merit," unfortunately, is often only one of many considerations. Sometimes, serious mistakes are made. This should not detract, however, from the satisfaction we can all share at the continuing dramatic progress in the opiate receptor and peptide research area.

WILLIAM POLLIN
Office of the Director,
Division of Research,
National Institute on Drug Abuse,
Rockville, Maryland 20857

References

1. J. Arehart-Treichel, *Sci. News* **115**, 120 (17 February 1979).

Erratum: In the reply by J. W. Holaday and B. H. Natelson to the technical comment entitled "Ultradian cortisol rhythms in monkeys: Synchronized or not synchronized?" (1 Dec. 1978, page 1001), the second sentence of the last paragraph should have read: "Tannenbaum and Martin (*6*) have reported a light-entrained, synchronized ultradian growth hormone rhythm in rats."

Erratum: The article "American Physical Society panel gives a long-term yes to electricity from the sun" (News and Comment, 16 Feb., p. 629) contains an error in the fourth paragraph. The first sentence in the paragraph should read: "Ehrenreich portrayed the future of solar cells as bright, calling attention to a decrease in their costs by a factor of 5 in the past 5 years and citing the prospects for further advances."

Erratum: William Beaver was erroneously identified in a recent story about Darvon (News and Comment, 2 Mar., p. 857) as a professor at George Washington University; he is actually a professor at Georgetown University.