To the Editor:

In his brief review on propylthiouracil ("Propylthiouracil Is an Old but Still Useful Drug") in the April 2011 issue of *Clinical Thyroidology*, Dr. Weissel makes one erroneous statement and one personal recommendation with which I disagree. The incorrect statement is that propylthiouracil (PTU)-related agranulocytosis is "independent of the age of the patient." The study he cited (1) and others (e.g., 2) show that it is actually older persons who are more susceptible to agranulocytosis.

The personal recommendation made by Dr. Weissel that is troubling is the statement that "PTU should be used in preference to MMI [methimazole] also in lactating mothers, since its secretion in the milk is less than that of MMI." While it is true that PTU crosses breast epithelium less well than MMI does because it is highly protein-bound and ionized at physiologic pH (3), the quantities of both drugs that an infant might ingest are, in fact, quite low. For PTU, it has been estimated that a child might ingest approximately 150 µg per day from a woman taking 200 mg of PTU three times a day (4).It has been calculated that a baby could receive 70 µg of MMI over an 8-hour period after the mother received a single 40-mg dose (5). Because this small amount conceivably could have an effect on a nursing baby's thyroid function, it was suggested that PTU might be preferred in nursing mothers (6). However, subsequent data from Azizi and colleagues (7-12) show that infants exposed to MMI in breast milk have normal thyroid function (7-9), as well as normal IQ and growth (10-12). These investigators also measured serum MMI levels by high-performance liquid chromatography in 8 infants 2 hours after they breast-fed from mothers who were taking 10 mg of MMI two or three times a day. The serum MMI levels were undetectable in 6 of the 8 babies and were at the limit of detection (0.03 µg/ml) in the other two (12). Serum MMI levels at least 10-fold higher than this are seen in serum in adults after a 10-mg oral dose (13). Therefore, there is no reason not to use methimazole in breast-feeding women, and in acknowledgment of this fact, the drug is approved for use in lactation, just like PTU, by the American Academy of Pediatrics (14).

Recent concerns raised by the American Thyroid Association and the Food and Drug Administration about potential PTU-induced hepatotoxicity have resulted in recommendations that limit the use of PTU (15,16) to individuals who cannot take MMI, persons with life-threatening thyrotoxicosis, and hyperthyroid women in the first trimester of pregnancy. Breast-feeding is not included in the indications. Because breast-feeding can last for many months or even years (17), the duration of PTU exposure of the mother could place her at increased risk for severe liver toxicity, while a safer drug (i.e., MMI) is available that would not put the baby at increased risk for adverse health consequences. While there are no case reports of infants breast-feeding from mothers taking PTU in whom hepatotoxicity subsequently developed, there are instances of babies with presumed in utero hepatotoxicity from PTU (18).

In light of the foregoing, MMI should be the drug of choice in breast-feeding women. Doses up to 40 mg per day are safe, although the minimum dose that is required to maintain normal thyroid function should be used. This was also the conclusion of a recent extensive review of the available literature (19). Interestingly, the need for an antithyroid drug in the postpartum period is associated with a decreased likelihood that a woman will breast-feed or be advised to breast-feed by a physician (20), indicating a need for greater physician education about the safety of antithyroid drugs in lactation.

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Dr. Weissel responds:

My statement on page 3, 1st paragraph was ... "The prevalence (of agranulocytosis) seems to be independent of the age of the patient and of the dose used." Dr. Cooper claims that is incorrect. Let me briefly quote from Cooper's review article (1) that I cited (contrary to Cooper's suggestion, I did not quote the 1983 paper by Cooper et al.) "Some, but not all, studies have suggested that the risk of agranulocytosis is greater in older patients and that they have a higher rate of death." In his contribution to the textbook, The Thyroid: A Fundamental and Clinical Text, Cooper states: "Elderly patients may be more susceptible to agranulocytosis" (p. 671). I conclude from this repeated cautious phrasing that the author admits uncertainty about the influence of age on this side effect of propylthiouracil (PTU). Dai et al. did not find any correlation of PTU-induced agranulocytosis with age (3).

My personal preference for PTU in lactating women troubles Dr. Cooper. My argument was—and is—that PTU is secreted less in the milk than is MMI. Cooper agrees that this is the case, but he presents a calculation that might give the impression that the infants are at risk of ingesting considerable amounts of PTU when the lactating mother's hyperthyroidism is treated with PTU. However, the mother's dose per day on which his calculation is based is extremely high. His calculation (based on a paper by Momotami et al. [4]) that a baby could receive as much as 150 µg of PTU per day is, at least in Europe, unrealistic. Doses of 600 mg per day for a lactating mother would be necessary for such concentrations, doses that are not given in Europe, where tablets contain only 20 mg in some countries (e.g., Austria). The usual starting dose of PTU in Austria is 300 mg per day for newly diagnosed hyperthyroidism. This dose is subsequently rapidly tapered to a dose of about 60 mg per day. Moreover, Momotami et al. conclude in their article: "Mothers can breast-feed while taking PTU at doses as high as 750 mg daily without adverse effects on thyroid status in their infants." I am not aware of any paper reflecting the experience of equivalent high doses of methimazole.

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