Patients were treated with an MMI dosage that was gradually tapered to maintain the euthyroid state. In some cases the MMI dosage was increased when the serum thyroid hormone levels were not declining. If a patient had fever, MMI was immediately discontinued and the white-cell count was measured.

**RESULTS**

In all, 28 of 6658 patients (0.4%) had agranulocytosis; 30 (0.5%) neutropenia, and 650 (10%) minor side effects resulting in a switch to other treatments. In all, 5950 patients (89%) had follow-up for more than 1 year. The patients who could be followed for at least 1 year and others who had side effects during the observation period were selected as study subjects. As a result, 2087 subjects were treated with 30 mg/day of MMI and 2739 were treated with 15 mg/day of MMI.

Agranulocytosis developed in 17 patients (0.8%) in the 30-mg group, and 6 patients (0.3%) in the 15-mg group (P<0.01, comparing the prevalence of agranulocytosis in the two groups) (Figure 1). When severe agranulocytosis was defined as a neutrophil count less than 200 per microliter, there were 11 such patients (0.5%) in the 30-mg group and 3 (0.1%) in the 15-mg group (P<0.05).

Neutropenia occurred in 16 patients (0.8%) in the 30-mg group and 7 (0.3%) in the 15-mg group (P<0.05). Of the 33 patients (2%) affected with agranulocytosis and neutropenia, 33 (1.6%) were in the 30-mg group and 13 (0.5%) were in the 15-mg group (P<0.001).
When the group treated with more than 20 mg/day of MMI was compared with those treated with less than 15 mg of PTU, 22 (0.7%) of 3174 patients had agranulocytosis in the high-dose group, and 6 (0.2%) of 3484 patients had agranulocytosis in the low-dose group (Figure 2). No patients treated with less than 10 mg/day of MMI had agranulocytosis, and 3 had neutropenia.

CONCLUSION Methimazole-induced agranulocytosis in patients with Graves’ disease is more likely with a daily dose of 30 mg than with 15 mg.

COMMENTARY
The initial treatment of Graves’ disease varies according to geographic location. Nonetheless, antithyroid drugs are the initial therapy of choice for the majority of patients with Graves’ disease treated in Europe and Japan and elsewhere in Asia (1, 2). Although the superiority of either PTU or MMI is not fully established (3), MMI is in many ways better than PTU. For example, with MMI serious toxicity is less common, adherence rates to treatment are higher, and the thyroid hormones levels fall faster as compared with PTU (4, 5). Moreover, MMI is generally preferred when antithyroid drugs are given to prepare a patient for radioiodine therapy or surgery.

Yet, PTU is still the drug of choice during pregnancy as a consequence of the rare reports of birth defects, especially MMI-related aplasia cutis, that occur in women treated with MMI during the first trimester. In addition, PTU is most commonly recommended for patients with life-threatening thyrotoxicosis, mainly because of the reduction of T3 production, although the clinical response to this effect is difficult to prove.

The most important issue concerning the choice of antithyroid drugs is the occurrence of life-threatening complications. MMI has less toxicity than PTU, especially when prescribed in lower doses (6, 7). In contrast, PTU can produce life-threatening hepatotoxicity that seems especially severe in children and has been reported to occur in pregnant women and in the fetus (7). A recent editorial by Cooper and Rivkees (7) suggests that approximately 4000 pregnant women per year would be expected to be treated with antithyroid drugs, most of whom would be treated with PTU, according to current practice guidelines. They also estimated that 15 adults with Graves’ disease will develop severe PTU-related hepatotoxicity and that each year one or two individuals with Graves’ disease in the United States will die or require a liver transplant after PTU exposure. Although MMI also can cause liver injury, it typically produces serious cholestatic dysfunction rather than severe hepatocellular inflammation. Cooper and Rivkees (7) concluded that considering the intricacies of care and risks involved for a pregnant women with thyrotoxicosis, treatment with radioactive iodine or surgery before pregnancy should be strongly considered for women who desire future pregnancy.

Agranulocytosis is the other life-threatening complication of antithyroid drugs that is of great concern. In this issue of Clinical Thyroidology, Takata et al. suggest that although a few studies suggest that agranulocytosis is related to the dose of MMI, the data are sparse (8).

The study by Takata et al. of 2087 subjects treated with 30 mg/day of MMI and 2739 treated with 15 mg/day of MMI found that the prevalence of agranulocytosis in the 30-mg group was almost fivefold greater than that in the 15-mg group (P<0.01). Likewise, the prevalence of agranulocytosis plus neutropenia was also about fivefold greater in the 30-mg group as compared with that in the 15-mg group (P<0.001). The authors’ conclusions that MMI-induced agranulocytosis is dose-related is underpinned by their large study, which provides robust evidence to support this conclusion. Considering both the effectiveness of MMI and the risk of serious side effects with larger doses, the authors recommend 15 mg/day of MMI as the starting dose for the treatment of Graves’ disease. This makes sense.