The above letter was referred to the authors of the article in question, who offer the following reply:

To the Editor: Dr. Pugliese’s letter illustrates the confusion over the role of prostaglandins in bone resorption. Prostaglandins of the E series stimulate bone resorption in organ-culture systems. However, the activity of isolated rat and human osteoclasts is inhibited by exposure to these prostaglandins. The situation is further confused because prostaglandins are spontaneously generated in some organ-culture systems, and their production may be further provoked by certain growth factors in some culture systems but not in others. Thus, in neonatal-mouse calvaria, epidermal growth factor, transforming growth factor \( \alpha \), and transforming growth factor \( \beta \) all stimulate bone resorption indirectly by provoking endogenous prostaglandin generation in the organ cultures. However, in a widely used alternative system, the fetal-rat long-bone assay, these growth factors do not provoke prostaglandin generation. Moreover, it appears that prostaglandins may have opposite effects on bone-resorbing cells in different species. For example, they inhibit the formation of human osteoclasts from marrow-cells cultures (Roodman GD, personal communication) but stimulate the formation of mouse osteoclasts from precursors (Takahashi N: personal communication).

Cytokines such as lymphotixin and tumor necrosis factor stimulate prostaglandin generation in rodent organ-culture assays and in isolated bone cells. However, the relation between the responses seen in these assays and the responses to these factors in human bone remains unknown. We do not know whether prostaglandins play any part in the mechanism of bone resorption and hypercalcemia in humans with myeloma. However, we do know that they are not produced in sufficient amounts by cultured myeloma cells to account for the bone-resorbing activity, and that drugs that inhibit prostaglandin synthesis effectively, such as indomethacin and aspirin, have little effect on the hypercalcemia that occurs in this situation.

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To the Editor: We have treated a 45-year-old woman with metastatic melanoma with high-dose interleukin-2 alone, administered intravenously as a continuous infusion. On the first two days the patient received \( 3 \times 10^9 \) U per square meter of body-surface area, and on days 3 and 4 she received \( 6 \times 10^9 \) U per square meter. Physical and radiologic examinations revealed that the metastatic lesions were confined to the regional lymph nodes, subcutaneous tissue, and lungs. The patient had neither a history of visual impairment nor central nervous system involvement, and therefore a CAT scan of the brain and orbits was not obtained before interleukin-2 therapy. On day 4 the patient’s weight gain was 8 percent, and she had marked swelling of the subcutaneous metastases, inginal lymph nodes, and face. In addition, the patient had a marked proptosis bulbous on her right side, diplopia, and transient blurred vision. A CAT scan of the brain and orbits showed a mass in the mediastinal part of the retrobulbar region of the right eye. Treatment with interleukin-2 was ended, and corticosteroids were administered. The patient’s symptoms disappeared promptly, and she received radiation therapy (40 Gy over a period of four weeks). Six weeks after the first cycle of interleukin-2, we restarted therapy using the same dosage and schedule of administration, and the patient had no further ocular problems. Her subcutaneous and lung metastases are now in partial remission.

Another patient who received high-dose interleukin-2 therapy in the manner described above was a 57-year-old man with bone metastases from a renal-cell carcinoma. Six weeks before interleukin-2 treatment, he had completed radiation therapy for an extradural metastasis that caused spinal-cord compression. On admission to the hospital, a neurologic examination revealed no evidence of spinal-cord compression. On day 1 the patient received \( 3 \times 10^9 \) U of interleukin-2 per square meter. On day 2 his weight gain was 1 kg, and there was evidence of cord compression at the site of the previous radiation therapy. Treatment with interleukin-2 was ended and corticosteroids were given to the patient immediately. The symptoms disappeared gradually, and the patient was taken out of the study.

These phenomena are almost certainly the result of edema in the metastases consequent to an interleukin-2-induced "capillary-leak" syndrome. We would therefore counsel caution when patients are being treated with high doses of interleukin-2, if they have metastases at sites where sudden enlargement would compromise physiologic function. Both these patients responded well to our ending interleukin-2 treatment and starting corticosteroid therapy. However, prophylactic corticosteroid therapy in conjunction with interleukin-2 is not advisable; experiments in lab-
oratory animals have shown that these agents abrogate the anti-
tumor effects of interleukin-2.*

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DISPOSITION OF OOCYTES AND AGE AT MENOPAUSE

To the Editor: The recent paper by Krauss et al. on familial ovarian failure (July 15 issue)1 and the accompanying editorial2 suggest that the age at which menopause occurs is strongly influenced by the rate of atresia. Although direct proof of this hypothesis is lacking, we believe it is correct.

Using mathematical models, we have explored the effect of oocyte number at birth (OB) and rate of atresia (R) on age at menopause.3 Analysis of data collected by Block4 suggests that the variation in number of human oocytes with age is best described by an exponential equation, O(A) = OB × exp (A × R), in which OB denotes oocytes per ovary at birth (9.01×107), R denotes rate of atresia (0.127 years⁻¹), A denotes age in years, and O(A) denotes oocyte number at age A.

According to this model, a twofold decrease in OB would be associated with menopause at age 45, whereas a twofold increase in R would produce menopause at age 25. For premature menopause to occur — before the age of 40 — requires a loss of more than 70 percent of the normal OB. Conversely, a 25 percent increase in R is required for menopause to occur before the age of 40.

Clearly, the age at which menopause occurs is a more complex matter than our two-index model suggests. However, despite its simplicity, the model fits clinical observations and data from experiments with animals surprisingly well, supporting the concept that the timing of menopause is influenced more strongly by the rate of atresia than by the number of oocytes at birth.

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INFLUENCE OF FUROSEMIDE ON PARATHYROID HORMONE LEVELS IN HYPERPARATHYROIDISM

To the Editor: We have previously demonstrated that a physiologic increase in dietary calcium intake can suppress the parathyroid hormone-1,25-dihydroxyvitamin D axis in patients with primary hyperparathyroidism.* We reasoned that the converse may also be true — that is, that any maneuver that could decrease serum calcium may cause an increase in the secretion of parathyroid hormone.

We observed three women (65, 86, and 88 years of age) with primary hyperparathyroidism who had all been treated with 20 mg of furosemide per day. After the start of furosemide therapy, all three had increases in immunoreactive parathyroid hormone levels from 42 to 160, 40 to 82, and 43 to 105 ng/mL per milliliter (normal, <25), respectively, over a period of 17 to 32 months, with no notable changes in levels of blood urea nitrogen or creatinine. Two of the three patients had decreases in their serum calcium levels.

These observations led us to conduct a prospective study of five patients with primary hyperparathyroidism in four men (58, 61, 67, and 69 years of age) and one woman (63 years of age). All were instructed to follow a diet including 400 mg of calcium and 1000 mg of sodium and were treated with 40 mg of furosemide per day. The individual immunoreactive parathyroid hormone levels are shown in Figure 1.

Administration of furosemide (19 to 29 weeks) was associated with a small but significant increase in serum levels of immunoreactive parathyroid hormone. However, no notable changes in nephrogenous cyclic adenosine monophosphate, 1,25-dihydroxyvita-


Figure 1. Individual Levels of Immunoreactive Parathyroid Hormone at Base Line, during Furosemide Therapy (Peak), and Four to Six Weeks after the End of Therapy.

Five of five patients had increases in immunoreactive parathyroid hormone levels (PTH; P<0.025 by paired t-test). Mean fasting levels of serum calcium did not change significantly during or after therapy (10.5, 10.4, 10.0; P not significant).