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THE AUTHOR REPLIES: In response to the comments by Raskauskas, the degree to which the polycystic ovary syndrome is associated with an increased risk of endometrial cancer is controversial.¹ Nonetheless, I agree that it is prudent to provide treatment to prevent endometrial disease.

Standard practice to prevent endometrial cancer in anovulatory women is either to induce withdrawal bleeding with a progestin every 1 to 3 months or to provide treatment with an oral contraceptive pill. Treatment with metformin is associated with an increased frequency of ovulation, resulting in at least six ovulatory menses per year in 55 to 85% of treated women.² This frequency of ovulatory menses is consistent with the current standard of care for the prevention of endometrial cancer. My review emphasizes that once an improvement in menstrual cyclicality is achieved with metformin, it is important to document that the menses are ovulatory. If ovulation followed by menstrual bleeding occurs at least every 2 to 3 months, then additional treatment with a progestin or an oral contraceptive pill should not be necessary. If ovulation is not satisfactorily improved, I recommend treatment with periodic progestin or an oral contraceptive pill while treatment with metformin is continued.

In response to Fiskens's comments, metformin's primary action is to inhibit hepatic glucose production. However, using the hyperinsulinemic-euglycemic clamp, Diamanti-Kandarakis and colleagues showed that metformin increases insulin-stimulated glucose disposal in normoglycemic women with the polycystic ovary syndrome.³ If we define an insulin sensitizer by its ability to enhance glucose disposal during treatment with insulin, then this observation supports the idea

that metformin is an insulin-sensitizing drug, albeit a weak one.

Space limitations precluded a discussion of all coexisting conditions related to insulin resistance in patients with the polycystic ovary syndrome, including nonalcoholic fatty liver disease, discussed by Targher et al., and sleep apnea. Although nonalcoholic fatty liver disease is associated with the polycystic ovary syndrome, it is not known to have a role "in the development and progression" of the disorder. Many women with the polycystic ovary syndrome present with mild elevations in serum hepatic aminotransferase levels, and it is my experience that these values often revert to the normal range during treatment with metformin. This is not surprising, given the literature linking insulin resistance to nonalcoholic fatty liver disease and the reported amelioration of the signs and symptoms of nonalcoholic fatty liver disease after treatment with insulin-sensitizing drugs.⁴

Mascitelli and colleagues raise the interesting possibility that metformin may enhance insulin sensitivity by inhibiting intestinal absorption of iron. This is not a known effect of metformin, and the hypothesis warrants testing.

John E. Nestler, M.D.

Virginia Commonwealth University
Richmond, VA 23298-0111
jnestler@mcvh-vcu.edu

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Major Depressive Disorder

TO THE EDITOR: In their review article, Belmaker and Agam (Jan. 3 issue)¹ examine several mechanisms involved in depressive disorders, but they do not mention evidence that androgen-deprivation therapy, which is frequently used in the

management of prostate cancer, can cause major depression.² The mechanisms underlying this association may include loss of sexual potency, fatigue, cognitive impairment, and changes in body composition, which lead to deterioration of a

patient's perception of his body.³ A direct effect of testosterone, however, cannot be ruled out. A cross-sectional study of the relation between testosterone levels and depressive symptoms in 856 community-dwelling older men showed that depression was inversely associated with bioavailable testosterone independently of age, weight change, and physical activity.⁴ Bioavailable estradiol was not associated with depressed mood.

Andrea Saini, M.D.

San Luigi Gonzaga Hospital
10043 Orbassano, Italy

Mara Ardine, M.D.

San Lorenzo Hospital
1022 Carmagnola, Italy

Alfredo Berruti, M.D.

University of Turin
10043 Orbassano, Italy
alfredo.berruti@gmail.com

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dual energy x-ray absorptiometry in patients with prostate cancer without apparent bone metastases given androgen deprivation therapy. *J Urol* 2002;167:2361-7.

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TO THE EDITOR: Belmaker and Agam indicate that a person must feel sad to be depressed. The American Medical Association monograph *Major Depressive Disorder in Primary Care*¹ notes on page 5 that many depressed people do not feel blue but instead present with symptoms such as "fatigue, insomnia, gastrointestinal distress or musculoskeletal pain." On page 4, it is noted that depression is correctly diagnosed by primary care physicians at the time of presentation in only 22% of patients who present with primarily physical symptoms.

Thomas C. Long, M.D.

Thomas C. Long and Associates
South Barrington, IL 60010
tomclong@comcast.net

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Case 40-2007: A Man with Weakness in the Hands

TO THE EDITOR: In the Case Record involving a 38-year-old man with multifocal motor neuropathy, discussed by Triggs and Cros (Dec. 27 issue),¹ Triggs emphasizes that it is important to distinguish multifocal motor neuropathy from amyotrophic lateral sclerosis or other motor neuron diseases because it responds favorably to immunotherapy. He mentions that plasma exchange, cyclophosphamide, and intravenous immune globulin are all beneficial. However, only treatment with intravenous immune globulins has been shown to be beneficial in randomized, controlled trials.² Cyclophosphamide has been reported to be effective but only anecdotally, and its toxicity precludes long-term use, which is usually necessary in patients with multifocal motor neuropathy. Plasma exchange is a well-established therapy in other immune-mediated neuropathies, such as chronic inflammatory demyelinating neuropathy, but has not been shown to be effective in patients with multifocal motor neuropathy and may lead to deterioration with respect to symptoms.³⁻⁵

Elisabeth A. Cats, M.D.

W-Ludo van der Pol, M.D., Ph.D.

Leonard H. van den Berg, M.D., Ph.D.

University Medical Center Utrecht
3584 CX Utrecht, the Netherlands
e.cats@umcutrecht.nl

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THE DISCUSSANT REPLIES: I agree with Cats and colleagues that plasma exchange has not been shown to be effective in multifocal motor neuropathy. In describing therapy for multifocal motor