Testosterone therapy and breast cancer?

To the Editor:

Schover's (1) suggestion that endogenous T and exogenous replacement regimens confer increased breast cancer risk remains, at best, conjectural. Although few epidemiological studies have inferred such an association between T and increased risk of breast cancer, such studies suffer from design limitations and T assay inaccuracies. To the contrary, findings from several recent studies suggest that T confers protective effects against breast cancer. It is counterintuitive to ascribe increased risk of breast cancer to T, as aromatase inhibitors are used in postmenopausal women after initial treatment for breast cancer to prevent recurrence, although T levels are expected to increase due to inhibition of T conversion to E_2.

Rock et al. (2) showed that T concentrations are not associated with a risk for recurrence of breast cancer. Further, Blitzer et al. (3) reviewed the clinical literature and found no evidence that exogenous T increased the risk for breast cancer, even in combination with a standard hormone replacement therapy (HT) in postmenopausal women. In a recent editorial, Burger (4) discussed the shortcomings of the Nurses Health Study with regard to increased risk of breast cancer and highlighted a number of other studies, which pointed to a protective role of T against breast cancer. Interestingly, in that study, women with breast cancer had a higher incidence of other risks for breast cancer, but the increased incidence of breast cancer was noted only in the first 5 years of the study, with a decreased incidence thereafter.

We should all be aware of the recruitment bias that may contribute to higher reporting of breast cancer risk in some studies, such as the Million Women Study in the United Kingdom. Women who exhibited some risk for breast cancer are more likely to seek clinical management and would enter into clinical trials to be followed up more closely. Burger (4) also pointed to other studies that demonstrated that addition of T to estrogen (E) therapy decreased E-stimulated breast cell proliferation, contributing to protection against breast cancer. Cox et al. (5) showed that, in postmenopausal women, common variants of the androgen receptor (AR) are not associated with a risk of breast cancer. Taken together, the data from these and other studies point to the weakness of the evidence that T is linked to increased risk of breast cancer, and reinforces the more common opinion that T may confer protection against this disease.

It is best for all to refrain from incriminating T in breast cancer risk until sufficient scientific evidence, beyond any reasonable doubt, is presented to the scientific court.

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REFERENCES

1. Schover LR. Androgen therapy for loss of desire in women: is the benefit worth the breast cancer risk? Fertil Steril 2008;90:129–40.
2. Rock CL, Flatt SW, Laughlin GA, Gold EB, Thompson CA, Natarajan L, et al, Women's Healthy Eating and Living Group. Reproductive steroid hormones and recurrence-free survival in women with a history of breast cancer. Cancer Epidemiol Biomarkers Prev 2008;17:614–20.
3. Blitzer J, Kenemans P. Mueck AO, for the "FSD education Group." Breast cancer risk in postmenopausal women using testosterone in combination with hormone replacement therapy. Maturitas 2008;59:209–18.
4. Burger HG. Should testosterone be added to estrogen–progestin therapy for breast protection? Menopause 2007;14:1–4.
5. Cox DG, Blanché H, Pearce CL, Calle EE, Colditz GA, Pike MC, et al, Breast andProstate Cancer Consortium (BPC3). A comprehensive analysis of the androgen receptor gene and risk of breast cancer: results from the National Cancer Institute Breast and Prostate Cancer Cohort Consortium (BPC3). Breast Cancer Res 2006;8(R54):1–9.

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Reply of the Authors:

I am not surprised that Drs. Guay and Traish are critical of my recent publication (1). Whether self-anointed or delegated, Guay and Traish have become Knights of the Testosterone Table, ready to smite anyone threatening their quest for the holy grail of androgen therapy. When the United States Food and Drug Administration (FDA) did not approve Proctor and Gamble's T patch for women, Guay published a commentary contesting the decision (2). When the Endocrine Society published guidelines discouraging clinicians from using the diagnosis of female androgen insufficiency or from prescribing T to treat women's sexual desire problems, Drs. Traish and Guay, with Richard Spark, published a detailed rebuttal in the *Journal of Sexual Medicine* with glowing comments from nine handpicked reviewers (3).

Dr. Guay's declared conflicts of interests in recent publications confirm that he has had research grants or participated in protocols funded by Auxilium, BioSante, Solvay, Vivus, and Cellegy and has been an advisor or consultant to Solvay, Auxilium, and Cellegy—all companies developing T products to treat female sexual dysfunction. Dr. Traish has had grants from the National Institutes of Health. I could not find evidence on whether he has had Pharma funding. The stakes are high, however. With increasing competition for shrinking federal research grants, BioSante will spend an estimated 12 million dollars on research in 2008 hoping to win FDA approval for its T gel for women, estimating that annual sales will exceed $500 million (4).

Guay and Traish label the suggestion that endogenous and exogenous T increase breast cancer risk "at best,

conjectural." The investigators of two new articless they cite disagree. Cox and colleagues state in their first paragraph "In both pre- and postmenopausal women, circulating testosterone levels are associated with increased risk of breast cancer" (5). They did not find an association between polymorphisms in the androgen receptor (AR) gene and breast cancer risk, but because of the limitations of their sample, could not exclude the gene as a susceptibility locus for premenopausal or nonwhite women.

Rock and colleagues (6) confirmed other recent studies showing that localized breast cancer is more likely to recur in survivors with higher levels of E_2. Although T levels were not directly linked to recurrence, conversion of T to E_2 may provide an indirect link, as I pointed out in my own review. Rock et al. note: "Reproductive steroid hormones are biochemically related, so teasing out independent associations from a group of compounds that are readily interconverted may not be an appropriate goal" (pp. 618).

If I were not constrained by word and reference limitations, I would debate other points raised by Guay and Traish, but my original review will have to stand for itself. I will simply end with a counterpoint to their concluding statement: Despite the lure of huge profits, it is best for all to refrain from dosing healthy women with T, given the limited evidence for its efficacy in restoring sexual desire, until sufficient scientific evidence that it does *not* increase breast cancer risk is presented to the scientific court.

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REFERENCES

1. Schover LR. Androgen therapy for loss of desire in women: is the benefit worth the breast cancer risk? Fertil Steril 2008;90:129–40.
2. Guay A. Perspectives: commentary on androgen deficiency in women and the FDA advisory board's recent decision to request more safety data. Int J Impot Res 2005;17:375–6.
3. Traish A, Guay AT. Spark RF, and the Testosterone Therapy in Women Study Group. Are the Endocrine Society's clinical practice guidelines on androgen therapy in women misguided? A commentary. J Sex Med 2007;4:1223–35.
4. Fitzhenry D, Sandberg L. Female sexual dysfunction. Nat Rev Drug Discov 2005;4:99–100.
5. Cox DG, Blanché H, Pearce CL, Calle EE, Colditz GA, Pike MC, et al, Breast and Prostate Cancer Consortium. A comprehensive analysis of the androgen receptor gene and risk of breast cancer: results from the National Cancer Institute Breast and Prostate Cancer Cohort Consortium (BPC3). Breast Cancer Res 2006;8(R54):1–9.
6. Rock CL, Flatt SW, Laughlin GA, Gold EB, Thompson CA, Natarajan L, et al, Women's Healthy Eating and Living Group. Reproductive steroid hormones and recurrence-free survival in women with a history of breast cancer. Cancer Epidemiol Biomarkers Prev 2008;17:614–20.

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Decisions to donate surplus embryos

To the Editor:

We read the paper by Kristina Hug (1) in the February 2008 issue on the factors influencing a prospective donor's future motivation to donate surplus embryos to medical research with great interest. Her article is an important synthesis of findings and is an indispensable reference for future research regarding decision making for stem cell research.

We have since reported information needs and decision making among 45 couples donating embryos for stem cell research that supports the general consensus that patients benefit from additional counseling (2). On average, couples delayed 4.8 years between the time of embryo cryopreservation and the decision to donate. Among a number of compelling findings, 96% of stem cell donors had not sought counseling in making their decision. While previous reports suggest that 90% of couples indicate an intention to seek help in deciding the fate of their embryos (3), others reported that nearly half of couples with cryopreserved embryos indicated concerns about making disposition decisions, yet none had sought formal counseling regarding this issue (4). This reveals that patients recognize the potential benefit of decision support yet are unsure how to obtain this resource.

It has been recommended that IVF programs use a mental health professional to provide couples with counseling and support in addressing embryo disposition issues at the time of cryopreservation. However, studies have suggested that such counseling may not adequately address the emotional or practical implications of cryopreserved embryos as it may be years before the couples' ultimate embryo disposition and personal feelings and attitudes can change over time. This is illustrated by the finding that 88% of those initially interested in donation to stem cell research eventually change their minds (5). Further counseling would appear to be beneficial to sort through any new issues that may impact on the decision making process. This is consistent with Dr. Hug's point on the need for counseling. She has further noted that clinics may influence embryo disposition decisions via IVF treatment experiences and relationships with staff. Given this, clinics need to recognize their potential influence and mitigate any unintentional embryo disposition biases by cultivating open communication with patients during the multiyear IVF process. The ultimate goal is to make the decision-making process clearer and easier for patients.

The issue of frozen embryo disposition continues to be significant for a growing number of couples, particularly for the complex decision of donation to stem cell research. To be effective, we need to increase our understanding of the complex issues that patients face and be prepared to assist and support them through the decision-making process, not only during the entire IVF process but potentially