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Editorial Comment on: Shifting the Paradigm of Testosterone and Prostate Cancer: The Saturation Model and the Limits of Androgen-Dependent Growth

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For >65 yr, it has been accepted that prostate cancer (PC) growth is modulated by androgens and that castration causes PC regression. Recently, several studies [1–3] have shown controversial data on the relationship between serum testosterone (T) concentrations and PC. An increased risk of PC was associated with low serum T levels [1], and tumors arising in a low-T environment appeared to be more aggressive [2]. The clinical hypothesis is that low serum T levels may be a potential predictor of PC risk and PC aggressiveness in a screening program [4]. These data conflict with the long-standing concern that an increase in serum T level can increase the risk of PC.

Morgentaler and Traish [5] present a critical revision of the traditional view of T and PC. They use a saturation model that is consistent with regression of cancer when T is reduced to castrate levels but lacks observed growth when serum T is increased [5]. The saturation model starts from the observation that PC growth is sensitive to variation in serum T concentrations at or below the castrate range and is insensitive to T variation above this concentration.

Considering the actual interest in using T replacement therapies in men, a new definition of the relationship between T and PC is of considerable importance. Evidence supports the hypothesis that T administration in hypogonadal men without PC does not increase the risk for PC growth if T levels are normalized [1–3]. The dangerous message that could develop from this saturation model [5] is that continuous T administration associated with elevated T serum

levels cannot produce a risk for PC growth, with or without PC disease. This hypothesis may produce clinical applications not supported by significant scientific evidence.

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Editorial Comment on: Shifting the Paradigm of Testosterone and Prostate Cancer: The Saturation Model and the Limits of Androgen-Dependent Growth

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In Roman mythology, Janus was the god of gates and doors. He was usually depicted with two heads looking in opposite directions and was frequently used to symbolize changes and transitions, such as the progression from one vision to another. This idea perfectly illustrates the saturation model proposed by Morgentaler and Traish in the current issue of *European Urology* [1].

Indeed, many of us still regard testosterone through Charles Huggins's eyes and consider it to be a key promoter of prostate cancer progression only because its abrupt suppression induces metastatic prostate cancer to shrink. But is this view enough to sustain our common-sense understanding that testosterone promotes or even causes prostate cancer?

Although urologists still diabolize testosterone, endocrinologists, rheumatologists, and cardiologists attract more and more of our attention to its virtues, especially with regard to metabolic and cardiovascular health [2].

This paradigm is an interesting one for the physician counseling a man who was successfully treated for localized prostate cancer and who suffers from late-onset hypogonadism. What puts him more at risk: a high-testosterone-promoting cancer or a low-testosterone-promoting cardiovascular disease? Considering the extensive use of hormone therapy in early prostate cancer, it seems that urologists have some difficulties seeing the man around the prostate, although they should be aware of the lack of efficacy in that setting [3,4].

Morgentaler and Traish's saturation model provides a nice rational background in which to move away from our unwarranted fear of testosterone in prostate cancer [1]. This article should help urologists to understand that treating middle-age men with localized disease requires getting rid of those fears and developing a holistic view of men's health that encompasses balancing the risks and benefits of adjusting testosterone to normal values.

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