Hidden in Plain Sight: The Enhancement of Health Through Bio-identical Time Released Testosterone Pellets

As a physician and scientist, I feel a moral and ethical obligation to raise awareness of a seventy year old treatment that is restoring health, vitality, and happiness to many, but currently being offered to only a few. I introduce this topic with a mixture of joy and trepidation, as it is the front end of the plow that hits the rocks! I hope this article serves as a stimulating introduction to the many benefits of bio-identical time release testosterone supplementation for treatment of what is best termed "relative androgen deficiency", or RAD. RAD occurs when the serum testosterone levels are insufficient for an individual's needs. This can be due to an absolute deficiency, a relative insufficiency (e.g. in high stress situations), or a decreased sensitivity to testosterone (along the lines of insulin resistance)[1-10]. It is a common disease of both women and men starting in their 40s and 50s, but can occur at younger ages.

RAD is outwardly manifested by a decline in one's general health and well-being (often termed "menopause" or "andropause"), and is accompanied by various physical, cognitive, and emotional disease states.[11-17] Multiple scientific studies have shown a strong correlation between low testosterone levels in men and women and their respective mortality rates.[18-21] In particular, documented correlations exist between low testosterone and heart disease[22-27], diabetes/metabolic syndrome[28-31], breast and prostate cancer[32-44], atherosclerosis[45-48], osteopenia[49-52], mild depression[11-17,52,53], fatigue[11-17,52,53], loss of muscle mass[11-17,52,53], increase in visceral fat[54], cognitive failures including spatial orientation and balance[53,56,57], loss of libido[11-17], hormone related insomnia[11-17], vaginal dryness[11,15-17], erectile dysfunction,[12,13,52-53,57,58] thermodysregulation[11-17] (hot flashes), etc. This is especially troubling as several epidemiologic studies have shown a significant drop (~20%) in male testosterone levels since the 1980s[59,60]. Unfortunately, no statistically significant data was obtained on women's testosterone levels over the past decades. I strongly suspect that whatever environmental disruptor is affecting testosterone synthesis in one sex is likely affecting the other.

The important question follows: How beneficial is testosterone supplementation for those with RAD associated symptoms and diseases? Many of the above listed diseases have been proven to be prevented, improved, or cured with bioidentical testosterone supplementation.[52,56,61-101] For example, a 2005 article in the American Journal of Cardiovascular Drugs[45] reviewing just the cardiovascular benefits finds testosterone supplementation to "reduce serum levels of the pro-inflammatory cytokines interleukin (IL)-1beta and tumor necrosis factor (TNF)-alpha, and to increase levels of the anti-inflammatory cytokine IL-10; to reduce vascular cell adhesion molecule (VCAM)-1 expression in aortic endothelial cells; to promote vascular smooth muscle and endothelial cell proliferation; to induce vasodilatation and to improve vascular reactivity,

to reduce serum levels of the pro-thrombotic factors plasminogen activator inhibitor (PAI)-1 and fibrinogen; to reduce low-density lipoprotein-cholesterol (LDL-C); to improve insulin sensitivity; and to reduce body mass index and visceral fat mass. These actions of testosterone may confer cardiovascular benefit since testosterone therapy reduces atheroma formation in cholesterol-fed animal models, and reduces myocardial ischemia in men with CHD." Conversely, when multiple researchers looked for any significant ill effects of bio-identical testosterone supplementation, they have found none after 70 years of experience and investigation[102,103].

To state the obvious (and allowing for individual genetic differences): men and women are of the same species, and therefore cellularly and biochemically nearly identical. Intracellular estrogen is critical in both sexes for survival. Evan Simpson and colleagues have reported that in women "the estrogen which is responsible for breast cancer development, for the maintenance of bone mineralization and for the maintenance of cognitive function is not circulating estrogen but rather that which is produced locally at these specific sites within the breast, bone and brain." There is a convincing body of evidence showing that all our cells requiring estrogen for proper functioning create their own estrogen intracellularly through the aromatase enzyme conversion of testosterone to estrogen[104-108]. To cling to the idea that a high circulating level of estrogen (which occurs only in one sex for a small percentage of its lifetime) is necessary for optimal health, makes no logical, biochemical, or evolutionary sense. We are the same species and both sexes produce the necessary intracellular estrogen locally, at the cellular level, from testosterone. This explains why the symptoms of male and female RAD are nearly identical, as seen in the international menopause and andropause scales[13-17]; and explains why menopause (like andropause) is most successfully treated with only steady state time release bioidentical testosterone[71.]

The ramifications of our new understanding of local estrogen production through testosterone conversion are huge. Each cell can regulate its internal estrogen concentration through "up or down regulation" of aromatase production, provided there is sufficient testosterone available. Supplementing humans with estrogen is not optimally effective at treating menopause or andropause symptoms as it fails to replace the deficient testosterone levels and fails to provide the one substrate needed to produce and regulate intracellular estrogen. Furthermore, when estrogen is *unopposed* by testosterone, it causes cellular proliferation leading to increased cancer risks - even when we are supplementing only with bio-identical estrogens[109-112]. Testosterone is a non-proliferative hormone[33,35,39,40,44,65,71,113-119]. Contrary to what we were all taught in medical school, men with low testosterone are at highest risk for prostate cancer, and more likely to have an aggressive grade prostate cancer[36-42].

Historically, the independent partial synthesis of testosterone from a cholesterol base earned Butenandt and Ruzicka the 1939 Nobel Prize for Chemistry. Testosterone has

been administered in the United States since 1938, and has been available in compressed pellet form since the 1940's. Much non-scientific "confusion" has surrounded this compound, in large part because it is not patentable. Its poor commercial viability negatively impacts research funding and limits our medical education on its uses.

The term "bio-identical" incites unnecessary prejudices. A bio-identical hormone is simply one that is molecularly identical to the hormone the human body makes, *regardless* of its synthetic derivation. In other words, it has the exact same three dimensional molecular shape and atomic composition as our "in vivo" produced hormone. As such, a "bio-identical" hormone functions at various receptor sites and inside cellular chemical pathways exactly like the in vivo produced hormone[117].

Humans are designed to fully breakdown oral ingestion of bio-identical testosterone and estrogen in their liver via the portal system before these hormones can reach systemic circulation. While evolutionarily sound, this has encouraged the pharmaceutical industry to create molecularly altered (but patentable and profitable) mimics of these hormones that bypass hepatic degradation. Unfortunately, these mimics uniformly have significant negative health effects. The only oral version of chemically altered testosterone approved for use in the US is methyl-testosterone which is known to cause irreversible liver damage[118, 119] and is converted to 17-α methyl-estradiol by aromatase. (Aromatase is present in large quantities in the fatty tissue of the GI tract.) 17-α methyl-estradiol is highly stimulatory to the breast tissue because it binds many times more strongly to estrogen receptor alpha than naturally occurring estradiol. Additionally, 17-α methyl-estradiol likely serves as an endocrine disruptor by blocking cells' androgen receptors. These combined properties may explain the increased incidence of breast cancer in women using oral methyl-testosterone (e.g. Estratest™) at an incidence *above* the increase noted from Premarin alone[110,120]. (Premarin, ethinyl estradiol, binds 18 times more strongly to beta estrogen receptors than estradiol.) Methyl-testosterone's metabolites also explain the poor efficacy of this compound when compared to parenteral bio-identical testosterone. Careful reading of the scientific literature is always necessary to decipher whether bio-identical or mimics of testosterone were used in studies, as the effects are quite different and require a different interpretation of the results[119].

Assuming you agree with the mountain of scientific evidence as to the importance of testosterone supplementation in men and women with RAD, an important question remains. How do we optimally provide appropriate steady state levels of testosterone to the cells that need it? The only reliable means of obtaining consistent steady state levels is through insertion of a highly compressed bio-identical testosterone pellets designed for steady state release[121,122]. The rapid swings and variability of serum testosterone levels when using depo-injections or transdermal creams are well

documented in pharmacodynamics studies[119,123,124]. In my practice, women receive pellet reinsertion every 3 months and men every 4 months. (The female testosterone supplementation dosage is far below the masculinization dose.) The “in office” process is quick and done under local anesthesia through a 3 millimeter skin puncture which is taped closed. The process is easily teachable to physicians who wish to learn.

As Ken Hortloff MD stated: “Evidence based medicine demands an assessment of the currently available data to decide which therapies are likely to carry the greatest benefits and lowest risks for patients.” Despite having treated hundreds of patients and studying the research publications for over a thousand hours, I am still awed by the cost effectiveness, safety, and efficacy of bio-identical testosterone pellets for men and women with relative androgen deficiency – *the most common disease of aging*.

At a time when our nation’s Medicare health expenditures are leading us toward insolvency, a therapy that increases the healthy functioning and productivity of its aging citizens should be our highest priority. We already have the answer! It has been hiding in plain sight for 70 years.

Dr. Mark Richards is a board certified plastic surgeon practicing in Rockville, Maryland and a past president of the Montgomery County Medical Society.

Competing Interests Disclaimers: In addition to providing bioidentical hormone pellet therapy to his patients, Dr. Richards provides paid instructional training to physicians on the science and practice of bioidentical pellet therapy through his association with Medinars, LLC.

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