THE ROUTE OF ANDROGEN PRODUCTION – TO CLINICAL CASTRATION – TO SURGICAL CASTRATION/ORCHIECTOMY

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DISCLAIMER: Please recognize that I am not a Medical Doctor. I have been an avid student researching and studying prostate cancer as a survivor and continuing patient since 1992. I have dedicated my retirement years to continued research and study in order to serve as an advocate for prostate cancer awareness, and, from a activist patient's viewpoint, to voluntarily help patients, caregivers, and others interested develop an understanding of prostate cancer, its treatment options, and the treatment of the side effects that often accompany treatment. There is absolutely no charge for my mentoring – I provide this free service as one who has been there and hoping to make your journey one with better understanding and knowledge than was available to me when I was diagnosed so many years ago. Readers of this paper must understand that the comments or recommendations I make are not intended to be the procedure to blindly follow; rather, they are to be reviewed as my opinion, then used for further personal research, study, and subsequent discussion with the medical professional/physician providing your prostate cancer care.

What we speak of "Androgen" regarding hormone treatment for prostate cancer we are primarily speaking of the hormone Testosterone. Androgen/testosterone is the fuel for the growth of prostate cells, and that means both healthy prostate cells as well as cancerous prostate cells.

With most androgen produced in the testicles, "androgen deprivation therapy" (aka Clinical Castration) for prostate cancer is often prescribed when usual treatment methods of surgical removal, radiation, or freezing of the prostate have not proved effective in eradicating all prostate cancer cells. This is an attempt at explaining the pathway in testicular production of androgen/testosterone

CLINICAL CASTRATION:

- The hypothalamus is the start of the process releasing pulses of LHRH (Luteinizing Hormone Releasing Hormone). This signals the pituitary gland to release the two hormones FSH (follicle-stimulating hormone – FSH helps

control the production of sperm) and LH (luteinising hormone stimulates Leydig cells in the testes to produce testosterone which acts locally to support sperm production).

- LH then travels from the pituitary gland in the blood stream where it then binds to the Leydig cells and is involved in testosterone release into the bloodstream and into the prostate gland.

- In the prostate gland are 5Alpha Reductase (5AR) enzymes that convert the testosterone to dihydrotestosterone (DHT), a powerful stimulant to prostate cell growth, and if prostate cancer cells are in development, an increased growth and proliferation of those cells. As an added note, when prostate cancer cells are not totally removed by surgical removal of the gland, or radiation to the gland and its periphery, or freezing of the gland, DHT, if not inhibited continues as a powerful stimulant to their growth. The prescribing of a 5AR "inhibitor" may inhibit the conversion of testosterone to DHT in those cancerous cells and if not causing apoptosis (death) of those cells, may at least arrest their continued development. Avodart/dutasteride is the preferred 5AR inhibitor, with Proscar/finasteride an alternative.

The Activity of Clinical Castration:

- When LHRH *agonists* (Lupron, Zoladex, Eligard, Trelstar, Vantas) are prescribed, their "activity" is to flood the pituitary gland in order to cause increased production of LH. By doing so this also causes a surge of testosterone production that overloads receptors in the pituitary resulting in a shutdown of Leydig cell testosterone production in the testicles. This "surge" can last for up to two weeks, with a result from that surge causing a "flare" effect that can cause discomfort, feeling of nausea, as well as pain if metastases are present. Prescribing of an anti-androgen (either bicalutamide/Casodex, flutamide/Eulexin, or nilutamide/Nilandron) to begin a week before the initial injection of an LHRH agonist and continuing over two weeks beyond can ease the flare effect.

- When the GnRH *antagonist* Firmagon is prescribed, its activity is to totally shut off receptors in the pituitary gland blocking LHRH pulses from the hypothalamus, thus preventing LH activity, resulting in a shutdown of testicular testosterone production. Since there is no surge of testosterone production with this medication, the "flare" effect does not occur.

SURGICAL CASTRATION:

An alternative to Clinical Castration is Surgical Castration, the removing of the testicles, thus another method of preventing testicular production of testosterone. Since some men are bothered by the absence of the testicles, prosthetic testicles can be inserted before the surgical incision is closed so that an outward appearance of the scrotum, as well as the personal "feel," looks the same as pre-orchiectomy.

Surgical Castration/Orchiectomy, removes the testicles, thus preventing testicular production - the primary production of likely over 90% of testosterone - however an orchiectomy does NOT stop all production of testosterone. The adrenal glands are another area of metabolized testosterone production, albeit to a much lower extent than testicular, but with the reduction of testosterone from clinical or surgical castration, the adrenal glands react with more production of testosterone than usual.

In view of adrenal gland testosterone, the testosterone level should still occasionally be checked to make sure that level remains at "castrate" levels near or below 20ng/dl..

Many physicians as well as patients assume that with the patient having an orchiectomy his production of testosterone is halted. As noted above, not so. As Medical Oncologist Stephen B. Strum, M.D., FACP, notes "The therapy the physician selects to deprive the tumor cell population of androgen may have consequential effects on the course of PC. For example, work by Sciarra et al has shown that 37% of men undergoing orchiectomy have a reflex increase in the production of the adrenal androgen precursor androstenedione. Androstenedione is metabolized within the prostate cell (both benign and malignant prostate cells) into testosterone (see Insights July 1999, pp 3-4 and October 2000, page 4). If the physician assumes that orchiectomy has resulted in a castrate testosterone (< 20ng/dl) and does not monitor the serum testosterone, almost 40% of these patients

face a significant risk of disease progression. If progressive PC occurs, it would likely be assumed to be a reflection of androgen independent PC. In fact, it may be due to the reflex stimulation of the pituitary-adrenal axis due to the lack of testosterone — the production of androstenedione — and the subsequent conversion of this androgen precursor to testosterone within the prostate cell. The body tries to maintain balance or homeostasis in regard to testosterone and in doing so uses its backup systems.”