ARTICLE

==========

"...simultaneous treatment of intact...rats with testosterone and estradiol-17beta for 16 weeks consistenly induced a putative precancerous lesion, termed dysplasia, in the dorsolateral prostate of all animals. Since treatment of rats with androgen alone did not elicit the same response, we concluded that estrogen played a critical role in the genesis of this proliferative lesion." Shuk-mei Ho and M. Yu, in "Selective increase in type II estrogen-binding sites in the dysplastic dorsolateral prostates of Noble rats," Cancer Research 53, 528-532, 1993.

==========

Prostate Cancer

It was noticed several decades ago that estrogen causes the prostate gland to enlarge in experimental animals, but by then an oversimplified view of the sex hormones was already well established, that led people to say that "estrogen causes the female organs to grow, and testosterone causes the male organs to grow." Logically extending this mistaken idea led many of the same people to suppose that the "hormones of one sex would inhibit the growth of the reproductive organs of the other sex."

When a friend of mine was told he had prostate cancer, though he had had no symptoms, and should receive large doses of estrogen, I reviewed the literature, to see whether his doctor might have seen something I had neglected. Since that time, I have found it necessary to use quotation marks around the phrases "medical research" and "medical science," because there is a certain kind of "research" performed within the medical profession which is peculiar to that profession.

When I read through the studies cited by the current articles as the basis for using estrogen to treat prostate cancer, I saw that the decisive "research" had consisted of mailing a questionnaire to physicians asking them if they thought it was reasonable to administer estrogen to these patients on the basis of its opposition to testosterone, which was considered to be responsible for the growth of the prostate gland. Many physicians answered the questionnaire affirmatively.

If the questioner's purpose was to determine his legal status in using a treatment, his research method was appropriate, to see whether the treatment seemed reasonable to others in the profession. Legally, a physician is safe if he can count on others to testify that his practice is standard. Unfortunately, for generations his study of the opinions of his peers became the "evidence" of the value of the estrogen treatment. Phrases such as "it is indicated," "treatment of choice," and "standard practice" are used in medicine, as part of the pseudo-scientific mystique of the profession. Physicans who attempt to base their practice on methods that have a sound scientific basis are likely to find that they are violating the norms of their profession.

More than 25 years ago, when I started pointing out that deliberate

misrepresentation had been involved in the continued designation of estrogen as "the female hormone," used as a basis for "hormone replacement therapies," I saw that it was hard for people to sustain a critical attitude toward language. Language is prior to judgment, law, science, reason. Those who define the terms set the rules.

By the mid-1980s, some studies had shown that estrogen treatment didn't prolong the survival of prostate cancer patients at all, but it was argued that the patients who received estrogen were happier than those who didn't.

Apparently, many physicians who were experts in conventional cancer treatment hadn't been impressed by the happiness of their patients who were receiving estrogen, because a survey at a conference of physicians found that many of them would choose to have no treatment if they learned they had prostate cancer. And more recently, there have been recommendations that older patients shouldn't be treated aggressively, because their cancers are usually so slow growing that they are likely to die of something else related to old age.

In spite of the articles I showed my friend, and my warning that estrogen can cause strokes and heart attacks, he decided to take the estrogen treatment. Within a few days he began suffering from asthma and disturbed sleep. Then he had a series of strokes and died.

Since it was known that estrogen treatment was dangerous for men, and that it increases blood clotting and vascular spasms, there had to be some overriding belief that led to its general use in treating prostate cancer. That belief seems to be that "estrogen, the female hormone, opposes testosterone, the male hormone, which is responsible for the growth--and therefore for the cancerization--of the prostate gland." Everything is wrong with that sentence, but you can find every part of the belief present and functioning in the medical literature. Just to give some context to the association of growth and cancerization, I should mention that Otto Warburg observed that all of the carcinogenic factors he studied caused tissue atrophy before cancer appeared. Another important contextual point is that every hormone does many things, and every endocrine gland produces multiple hormones.

Since the time of Brown-Sequard and Eugen Steinach, it has been accepted that declining testicular function is a common feature of aging, and testosterone was probably the first hormone that was clearly found to decrease consistently with aging. (Vermeulen, et al., 1972, 1979.)

It has seemed odd to many people that enlargement of the prostate should occur mainly in older men, if testosterone is the hormone that causes its growth, and estrogen is antagonistic to its growth. The nature of the growth of the old man's prostate is very different from its natural growth in youth.

It was also recognized decades ago that estrogen rises in men during old age (Pirke and Doerr, 1975), as it rises in stress, disease, malnutrition, and hypothyroidism (which are also associated with old age). Estrogen is produced in fat (Siiteri, and MacDonald, 1973, Vermeulen, 1976) which tends to increase with age, when thyroid and progesterone are deficient. The conversion of testosterone to estrogen occurs in the testicle itself, but this conversion is also inhibited by the favorable hormonal environment of youth. The active thyroid hormone, T_3, declines with aging, and this necessarily lowers production of pregnenolone and progesterone. Increasingly, in both sexes, it appears that DHEA may rise during stress as a result of a deficiency of thyroid,

progesterone, and pregnenolone.

In 1786, John Hunter reported that castration causes a decrease in the size of the prostate gland, and by the end of the 19th century castration was being advocated for treating enlargement of the prostate. In aging men, the prostate gland (both central and peripheral zones) atrophies, and it is within the atrophic gland that cancer cells can be found. Nodular, noncancerous enlargement may occur, with or without cancer. In 1935, an autopsy study showed carcinoma in the prostates of 30% of men by the age of 50. Proliferation of ductal and epithelial tissue is closely associated with prostate cancer, a situation similar to that of the cancerous or precancerous breast. (Simpson, et al., 1982; Wellings, et al., 1975; Jensen, et al., 1976.) The high probability of "epitheliosis" in association with cancer was seen in women in their early 40s, and in women over 60. (Simpson, et al.) (Epitheliosis just refers to an exaggerated proliferation of epithelial cells, the cells covering all surfaces, including the lining of glands, and things as simple as irritation and vitamin A deficiency can cause these cells to proliferate.) In the breast, the proliferative epitheliosis is clearly caused by estrogenic stimulation. The antagonism between estrogen and vitamin A in controlling epithelial proliferation (and possibly other cell types: Boettger-Tong and Stancel, 1995) is clear wherever it has been tested; vitamin A restrains epithelial proliferation. (Wherever estrogen is a factor in the development of abnormal tissue, vitamin A supplementation would seem beneficial.)

In aging women and men, as the breasts and prostate atrophy, their estrogen/antiestrogen ratio increases.

In men with prostate cancer, the fluid secreted by the prostate contains significantly more estradiol than the fluid from men without cancer (Rose, et al., 1984). This is analogous to observations made in women with breast cancer.

The pituitary hormones have diverse functons, including effects on epithelial tissues, other than their "classical" functions. Growth hormone, ACTH (Lostroh and Li, 1957), and ACTH with prolactin (Tullner, 1963) stimulate prostate growth. Prolactin--which is increased by estrogen--stimulates growth of the rat's lateral prostate (Holland and Lee, 1980), and stimulates the growth of human prostate epithelial cells in vitro (Syms, et al., 1985). LH (luteinizing hormone) increases when progesterone or testosterone is deficient, and growth hormone and prolactin (which are closely associated in evolution) both increase under a variety of stressful situations, and with estrogenic stimulation. Prostate cancer patients who had higher levels of LH and lower testosterone died most quickly. (Harper, et al., 1984.) Also, a high ratio of testosterone to estradiol or of testosterone to prolactin corresponded to better survival (Rannikko, et al., 1981.) Considered separately, patients with higher testosterone levels had a better prognosis than those with lower levels, and patients with lower growth hormone levels did better than those with higher growth hormone levels. (Wilson, et al., 1985.) Has anyone ever tried testosterone therapy for prostate cancer? Or, more practically, a generalized antiestrogenic therapy, using thyroid, progesterone, and pregnenolone? Other drugs (naloxone, bromocriptine, gonadotropin-releasing hormone agonists, and anti-growth hormone druges, e.g.) are available to regulate the pituitary hormones, and might be useful therapeutically or preventively. (See Blaakaer, et al., 1995.) Biskind and Biskind's work (1944) with ovarian tumors might be relevant to both testicular and prostate cancer.

Abnormal patterns of pituitary hormones reflect stress and hormonal imbalance, but they are also directly involved in widespread changes in tissue content of glycoproteins. The prostate is specialized to secrete large amounts of mucin. The endocrine physiology of prostate mucin secretion is poorly understood, but it is likely that there are interactions between growth-regulatory and secretion-regulatory systems.

In recent years, prostate cancer has been one of the fastest increasing kinds of cancer, and it isn't apparent that increased treatment has had an effect in lowering the death rate. The postwar baby-boom (following the baby-bust of the great depression) created an abnormal age-structure of the population, that has been used to argue that the war against cancer is being won. Increasing environmental estrogens are known to cause many reproductive abnormalities, and their contribution to prostate cancer would get more attention if estrogen's role in prostate disease were better known. Environmental estrogens are clearly responsible for genital deformities and sterility in many species of wild animals, but when the causal link is made between estrogens and human abnormalities, the estrogen industry sends its shills in to create controversy and confusion. Even the effects of estrogens in sewage, known for decades, are treated as State Secrets: "There had been reports of hermaphroditic fishes in one or two rivers, and government investigators had been studying them since the late 1970s. But no one had been aware of the work because it was classified." (Lutz, 1996.)

Testicular cancer is easy to diagnose, and its incidence has clearly increased (100% in white men, 200% in black men) since 1950. Undescended testicles, urethral abnormalities, etc., similar to those seen in DES sons and in wild animals, have also increased. So the tremendous increase in the death rate from prostate cancer during the same time has a meaningful context.

Although the animal studies showed that estrogen treatment promotes enlargement of the prostate, it was possible to suppose that the human prostate's growth might be stimulated only by testosterone, until tests were done in vitro to determine the effects of hormones on cell division.

In human prostate slices, several hormones (including insulin, and probably prolactin) stimulated cell division; testosterone did not, under these experimental conditions. (McKeehan, et al., 1984.) Contrary to the stereotyped ideas, there are suggestions that supplementary androgens could control prostate cancer (Umekita, et al., 1996), and that antagonists to prolactin and estrogen might be appropriately used in hormonal therapy (for example, Wennbo, et al., 1997; Lane, et al., 1997).

By the age of 50, men often show an excess of both prolactin and estrogen, and a deficiency of thyroid and testosterone. This is the age at which enlargement of the prostate often becomes noticeable.

Estrogen's role in prostate growth and cancerization is clear: "...simultaneous treatment of intact...rats with testosterone and estradiol-17beta for 16 weeks consistenly induced a putative precancerous lesion, termed dysplasia, in the dorsolateral prostate of all animals. Since treatment of rats with androgen alone did not elicit the same response, we concluded that estrogen played a critical role in the genesis of this proliferative lesion." (Ho and Yu.)

Progesterone and pregnenolone also decline in aging men. Several studies using synthetic progestins have shown that they effectively shrink the hypertrophic prostate, and the saw palmetto remedy for prostate enlargement has been reported to contain pregnenolone, or

something similar to it. These materials might be expected to reduce conversion of testosterone or other androgens to estrogen.

The prostaglandins were discovered in prostatic fluid, where they occur in significant concentrations. They are so deeply involved with the development of cancers of all sorts that aspirin and other prostaglandin inhibitors should be considered as a basic part of cancer therapy. The prostaglandins have local and systemic effects that promote cancer growth. ("The prostaglandins and related eicosanoids synthesized from polyunsaturated fatty acid precursors have been implicated as modulators of tumor metastasis, host immunoregulation, tumor promotion, and cell proliferation." Hubbard, et al., 1988.)

Estrogens cause elevation of free fatty acids, and there are many interactions between the unsaturated fatty acids and estrogen, including their metabolism to prostaglandins, and their peroxidation. Estrogen's roles as free-radical promoter, DNA toxin, carcinogen, tumor promotor, modifier of tissue growth factors, anti-thymic hormone, etc., as well as its local effects on the prostate gland, have to be kept in mind. Most of the interest in studying estrogen's contributions to prostate cancer relates to the existence of estrogen receptors in various parts of the prostate. While that is interesting, it tends to distract attention from the fact that many of estrogen's most important actions don't involve the "receptors." A direct excitatory action on prostate cells, and indirect actions by way of the pituitary, pancreas, thyroid, adrenal, fatty acids, prostaglandins, histamine and circulation are probably essential parts of the cancerization process.

The unsaturated fatty acids, but not the saturated fatty acids, free estrogen from the serum proteins that bind it, and increase its availability and activity in tissue cells.

Thyroid supplementation, adequate animal protein, trace minerals, and vitamin A are the first things to consider in the prevention of prostate hypertrophy and cancer. Nutritional and endocrine support can be combined with rational anticancer treatments, since there is really no sharp line between different approaches that are aimed at achieving endocrine and immunological balance, without harming anything.

Avoiding tissue atrophy is very closely related to promoting healthy regeneration. These processes require efficient energy production, and an appropriate balance between stimulation and resources. Growth hormone is sometimes recommend to correct tissue atrophy, but the evidence seems reasonably clear that it is a factor in the promotion of tumefaction of the prostate. The only study I have seen suggesting that it might be beneficial in prostatic cancer was a 14 day experiment done in female rats. Numerous publications suggest that blocking growth hormone is beneficial in treating prostate cancer; in future newsletters I will be discussing the evidence that growth hormone, like estrogen, cortisol, and unsaturated fats, tends to promote degenerative changes of aging - **Growth hormone: Hormone of Stress, Aging, and Death?**

REFERENCES

M.C. Audy, et al., "17beta-Estradiol stimulates a rapid Ca2+ influx in LNCaP human prostate cancer cells," Eur. J. Endocrionol.135, 367-373, 1996.

M. S. Biskind and G. S. Biskind, "Development of tumors in the rat ovary after transplantation into the spleen," Proc. Soc. Exp. Biol. Med. 55, 176-179, 1944.

J. Blaakaer, et al., "Gonadotropin-releasing hormone agonist suppression of ovarian tumorigenesis in mice of the W^x/W^v genotype," Biol. of Reprod. 53, 775-779, 1995.

Clinton, SK Mulloy AL, Li SP, Mangian HJ, Visek WJ, J Nutr 1997 Feb;127(2):225-237 "Dietary fat and protein intake differ in modulation of prostate tumor growth, prolactin secretion and metabolism, and prostate gland prolactin binding capacity in rats."

J. R. Drago, "The induction of Nb rat prostatic carcinomas," Anticancer Res. 4, 255-256, 1984.

J. Geller, et al., "The effect of cyproterone acetate on adenocarcinoma of the prostate," Surg. Gynec. Obst. 127, 748-758, 1968.

J. Geller, J. Fishman, and T. L. Cantor, "Effect of cyproterone acetate on clinical, endocrine and pathological features of benign prostatic hypertrophy," J. Steroid Biochemistry 6, 837-843, 1975.

Ho, Shuk-mei, and M. Yu, "Selective increase in type II estrogen-binding sites in the dysplastic dorsolateral prostates of Noble rats," Cancer Research 53, 528-532, 1993. "...simultaneous treatment of intact...rats with testosterone and estradiol-17beta for 16 weeks consistenly induced a putative precancerous lesion, termed dysplasia, in the dorsolateral prostate of all animals. Since treatment of rats with androgen alone did not elicit the same response, we concluded that estrogen played a critical role in the genesis of this proliferative lesion."

M. E. Harper, et al., "Carcinoma of the prostate: relationship of pretreatment hormone levels to survival," Eur. J. Cancer Clin. Oncol. 20, 477-482, 1984.

J. M. Holland and C. Lee, "Effects of pituitary grafts on testosterone stimulated growth of rat prostate," Biol. Reprod. 22, 351-355, 1980.

W. C. Hubbard, et al., "Profiles of prostaglandin biosynthesis in sixteen established cell lines derived from human lung, colon, prostate, and ovarian tumors," Cancer Research 48, 4770-4775, 1988. "The prostaglandins and related eicosanoids synthesized from polyunsaturated fatty acid precursors have been implicated as modulators of tumor metastasis, host immunoregulation, tumor promotion, and cell proliferation."

Izes JK, Zinman LN, Larsen CR, Urology 1996 May;47(5):756-759 "Regression of large pelvic desmoid tumor by tamoxifen and sulindac," "A 54-year-old man was evaluated for symptoms of bladder outlet obstruction. Evaluation revealed a 10 by 9.8-cm tumor composed of bland, fibroblastic, poorly cellular material adjacent to the prostate. Administration of a course of antiestrogen (tamoxifen) and a nonsteroidal anti-inflammatory agent (sulindac) resulted in prompt relief of symptoms and a slow decrease in the size of the tumor as measured by computed tomography. After 54 months of therapy, the tumor was undetectable clinically and dramatically reduced in size as seen on computed tomography. Data on the natural history of desmoid tumors and the efficacy of various therapeutic strategies are reviewed.

Jungwirth A, Schally AV, Pinski J, Halmos G, Groot K, Armatis P, Vadillo-Buenfil M., Br J Cancer 1997;75(11):1585-1592, "Inhibition of in vivo

proliferation of androgen-independent prostate cancers by an antagonist of growth hormone-releasing hormone."

Kroes R; Teppema JS Development and restitution of squamous metaplasia in the calf prostate after a single estrogen treatment. An electron microscopic study. Mol Pathol, 1972 Jun, 16:3, 286-301.

Lane KE, Leav I, Ziar J, Bridges RS, Rand WM, Ho SM, Carcinogenesis 1997 Aug;18(8):1505-1510 "Suppression of testosterone and estradiol-17beta-induced dysplasia in the dorsolateral prostate of Noble rats by bromocriptine." "We, and others, have previously described the histological changes that occur in the prostate gland of intact Noble (NBL) rats following prolonged hormonal treatment. Dysplasia, a pre-neoplastic lesion, develops specifically in the dorsolateral prostates (DLPs) of NBL rats treated for 16 weeks with a combined regimen of testosterone (T) and estradiol-17beta (E2) (T + E2-treated rats). Concurrent with DLP dysplasia induction, the dual hormone regimen also elicits hyperprolactinemia, in addition to an elevation of nuclear type II estrogen binding sites (type II EBS), no alteration in estrogen receptors (ER), and marked epithelial cell proliferation in the dysplastic foci. The aim of this study was to investigate whether the dual hormone action is mediated via E2-induced hyperprolactinemia. Bromocriptine (Br), at a dose of 4 mg/kg body wt per day, was used to suppress pituitary prolactin (PRL) release. Serum PRL levels were lowered from values of 341 +/- 50 ng/ml in T + E2-treated rats to 32 +/- 10 ng/ml in Br co-treated animals. The latter values were comparable to those in untreated control rats. In addition, Br co-treatment effectively inhibited the evolution of dysplasia (six out of eight rats) and the often associated inflammation (five out of eight rats) in most animals. In contrast, Br co-treatment did not suppress the T + E2-induced type II EBS elevation nor alter ER levels in the DLPs of these rats, when compared with T + E2-treated rats. These data extend the many previous studies that have detailed marked influences of PRL on rat prostatic functions. However, the current study is the first to implicate PRL in prostatic dysplasia induction in vivo."

I. Leav, et al., "Biopotentiality of response to sex hormones by the prostate of castrated or hypophysectomized dogs: Direct effects of estrogen," Am. J. Pathol., 93, 69-92, 1978.

H. C. Levine, et al., "Effects of the addition of estrogen to medical castration on prostatic size, symptoms, histology and serum prostate specific antigen in 4 men with benign prostatic hypertrophy," J. Urol. 146, 790-93, 1991.

Diana Lutz, The Sciences, January/February 1996.

W. L. McKeehan, et al., "Direct mitogenic effects of insulin, epidermal growth factor, glucocorticoid, cholera toxin, unknown pituitary factors and possibly prolactin,but not androgen, on normal rat prostate epithelial cells in serum-free, primary cell culture," Cancer Res. 44(5), 1998-2010, 1984.

Nevalainen MT, Valve EM, Ingleton PM, Nurmi M, Martikainen PM, Harkonen PL, J Clin Invest 1997 Feb 15;99(4):618-627 "Prolactin and prolactin receptors are expressed and functioning in human prostate." "The highest density of prolactin receptors was detected in the secretory epithelial cells by immunohistochemistry. Finally, we report that prolactin is locally produced in human prostate epithelium, as evidenced by marked prolactin immunoreactivity in a significant portion of prostate epithelial cells, with parallel expression of prolactin mRNA in human

prostate. Collectively, these data provide significant support for the existence of an autocrine/paracrine loop of prolactin in the human prostate and may shed new light on the involvement of prolactin in the etiology and progression of neoplastic growth of the prostate."

A. J. Lostroh and C. H. Li, "Stimulation of the sex accessories of hypophysectomised male rat by non-gonadotrophin hormones of the pituitary gland," Acta endocr. Copenh. 25, 1-16, 1957.

F. B. Merk, et al., "Multiple phenotypes of prostatic glandular cells in castrated dogs after individual or combined treatment with androgen and estrogen," Lab. Invest. 54, 42-46, 1986.

Pirke, K.M. and P. Doerr, "Age related changes in free plasma testosterone, dihydrotesterone, and oestradiol," Acta endocr. Copenh. 89, 171-178, 1975

S. Rannikko, et al., "Hormonal patterns in prostatic cancer 1. Correlation with local extent of tumour, presence of metastases and grade of differentiation," Acta endocr. Copenh. 98, 625-633, 1981.

P. H. Rolland, et al., "Prostaglandins in human breast cancer: Evidence suggesting that an elevated prostaglandin production is a marker of metastatic potential for neoplastic cells," J. Natl. Cancer Inst. 64, 1061-1070, 1980.

D. P. Rose, et al., "Hormone levels in prostatic fluid from healthy Finns and prostate cancer patients," Eur. J. Cancer clin. Oncol. 20, 1317-1319, 1984.

L. M. Schuman, et al., "Epidemiologic study of prostatic cancer: Preliminary report," Cancer Treat. Rep. 61, 181-186, 1977.

Siiteri, P.K. and P. C. MacDonald, "Role of extraglandular estrogen in human endocrinology," In Handbook of Physiology, section 7, Endocrinology Vol II (Eds. S. R. Geiger, et al.,) pp. 615-629, Williams & Wilkins, Baltimore.

H. W. Simpson, et al., "Bimodal age-frequency distribution of epitheliosis in cancer mastectomies, Cancer 50, 2417-2422, 1982; S. R. Wellings, et al., "Atlas of subgross pathology of the human breast with special reference to possible precancerous lesions," J. Nat. Cancer Inst. 55, 231-273, 1975; H. M. Jensen, et al., "Preneoplastic lesions in the human breast," Science, N.Y. 191, 295-297,1976.

Sugimura Y, Sakurai M, Hayashi N, Yamashita A, Kawamura J., Prostate 1994;24(1):24-32 "Age-related changes of the prostate gland in the senescence-accelerated mouse." "Wet weight and numbers of ductal tips in ventral and dorsolateral prostate glands in senescence accelerated-prone (SA-P) mice were significantly smaller than those of senescence accelerated-resistant (SA-R) mice, although the changes of patterns of gross ductal morphology were virtually identical in these groups. High incidence of stromal hyperplasia with fibrosis and inflammation was observed...." "These data suggest that the aging process occurs heterogeneously within the prostate gland, and that SA-P mice may be an important model for the study of age-related changes in the prostate gland."

W. W. Tullner, "Hormonal factors in the adrenal-dependent growth of the rat ventral prostate," Nat. Cancer Inst. Monograph 12, 211-223, 1963.

Umekita Y, Hiipakka RA, Kokontis JM, Liao S, Proc Natl Acad Sci U S A 1996 Oct 15;93(21):11802-11807 "Human prostate tumor growth in

athymic mice: inhibition by androgens and stimulation by finasteride," "When the human prostate cancer cell line, LNCaP 104-S, the growth of which is stimulated by physiological levels of androgen, is cultured in androgen-depleted medium for > 100 passages, the cells, now called LNCaP 104-R2, are proliferatively repressed by low concentrations of androgens. LNCaP 104-R2 cells formed tumors in castrated male athymic nude mice. Testosterone propionate (TP) treatment prevented LNCaP 104-R2 tumor growth and caused regression of established tumors in these mice. Such a tumor-suppressive effect was not observed with tumors derived from LNCaP 104-S cells or androgen receptor-negative human prostate cancer PC-3 cells. 5 alpha-Dihydrotestosterone, but not 5 beta-dihydrotesto- sterone, 17 beta-estradiol, or medroxyprogesterone acetate, also inhibited LNCaP 104-R2 tumor growth. Removal of TP or implantation of finasteride, a 5 alpha-reductase inhibitor, in nude mice bearing TP implants resulted in the regrowth of LNCaP 104-R2 tumors. Within 1 week after TP implantation, LNCaP 104-R2 tumors exhibited massive necrosis with severe hemorrhage. Three weeks later, these tumors showed fibrosis with infiltration of chronic inflammatory cells and scattered carcinoma cells exhibiting degeneration. TP treatment of mice with LNCaP 104-R2 tumors reduced tumor androgen receptor and c-myc mRNA levels but increased prostate-specific antigen in serum- and prostate-specific antigen mRNA in tumors. Although androgen ablation has been the standard treatment for metastatic prostate cancer for > 50 years, our study shows that androgen supplementation therapy may be beneficial for treatment of certain types of human prostate cancer and that the use of 5 alpha-reductase inhibitors, such as finasteride or anti-androgens, in the general treatment of metastatic prostate cancer may require careful assessment."

A. Vermeulen, "Testicular hormonal secretion and aging in males," in Benign prostatic hyperplasia (J. T. Grayhack, et al., eds), pp. 177-182, DHEW Publ. No. (NIH) 76-1113, 1976.

A. Vermeulen, et al., "Testosterone secretion and metabolism in male senescence," J. Clin. Endocr. Metab. 34, 730-735, 1972.

A. Vermeulen, et al., "Hormonal factors related to abnormal growth of the prostate," in Prostate Cancer (D. S. Coffey and J. T. Issacs, eds). UICC Technical Workshop Series, Vol 48, 81-92, UICC, Geneva.

S. Zuckerman and J. R. Groome, "The aetiology of benign enlargement of the prostate in the dog," J. Pathol. Bact. 44, 113-124, 1937.

B. Zumoff, et al., "Abnormal levels of plasma hormones in men with prostate cancer: Evidence toward a 'time-defense' theory," The Prostate 3, 579-588, 1982.

M. Wehling, "Non-genomic steroid action--take a closer look, it's not rare!" Eur. J. of Endorinol. 135, 287-288, 1996.

Wennbo H, Kindblom J, Isaksson OG, Tornell J., Endocrinology 1997 Oct;138(10):4410-4415. "Transgenic mice overexpressing the prolactin gene develop dramatic enlargement of the prostate gland," "An altered endocrine status of elderly men has been hypothesized to be important for development of prostate hyperplasia. The present study addresses the question whether increased PRL expression is of importance for development of prostate hyperplasia in mice. Three lines of PRL transgenic mice were generated having serum levels of PRL of approximately 15 ng/ml, 100 ng/ml, and 250 ng/ml, respectively. These mice developed dramatic enlargement of the prostate gland,

approximately 20 times the normal prostate weight and they had a 4- to 5-fold increased DNA content. Histologically, the prostate glands in the transgenic mice were distended from secretion, and the amount of interstitial tissue was increased. The levels oftestosterone and IGF-I were increased in the PRL transgenic animals. In mice overexpressing the bovine GH gene, displaying elevated IGF-I levels, the prostate gland was slightly larger compared with normal mice, indicating that the effect of PRL was not primarily mediated through elevated plasma IGF-I levels. "The present study suggests that PRL is an important factor in the development of prostate hyperplasia acting directly on the prostate gland or via increased plasma levels of testosterone."

^^^ Top ^^^