

Chapter 3

Defects of Androgen Metabolism and Androgen Mediated Disease

3A

Introduction

Significant clues leading to the development of safe and effective treatments for AGA can be found in the exploration of how androgenic hormones act to influence other pathophysiological processes. Well described studies have been conducted with eunuchs, pseudohermaphrodites, and others suffering from androgen mediated disorders. Although at first glance these disorders display many obvious differences, upon deeper exploration of the evidence, there are striking connections which bear heavily upon the central hypothesis of this dissertation.

3B

Eunuchs

Castration of men and males of other species was almost certainly the first experiment in endocrinology, and the literature on the subject is vast. In fact, the Cumming Manuscript Collection of the New York Academy of

Medicine Library contains more than 1200 references, abstracts, and documents concerning the early history of human castration.

The Skoptzy (meaning the castrated), also called the White Doves, were an 18th century Christian sect, which ranged from parts of Russia into Romania and Bessarbia, whose male members, to attain their ideal of sanctity, subjected themselves to castration. In the early years of this sect the surgical instrument of choice was a red-hot iron rod or poker (hence the expression baptism of fire) ref, but other instruments included pieces of glass, razors, and knives. When the penis and testes were removed, nails were inserted into the urethra to avoid strictures, and such men were said to urinate while sitting or squatting. This brutal practice was continued at least until 1927 (1).

Medical studies on these individuals were performed by at least three groups of investigators. At the turn of the century Pittard took physical observations of 30 Skoptzy men in 1 Romanian village and noted that, among other curious findings, they appeared to be totally free from hair loss (1). In 1907 Tandler and Grosz examined 5 Skoptzy men in Bucharest whose average age was 30 and who had been castrated between ages 5-21. Subsequently, during the German occupation of Romania in the First World War Walter Koch studied 13 Skoptzy men, all between 50 and 94 years of age.

A variety of anthropomorphic measurements were made, including a prostate examination. Androgen action is required for the development of the prostate gland during embryogenesis (2), and the prostate does not develop in men with mutations that profoundly impair the function of either the androgen receptor or of the microsomal enzyme, steroid α 5AR type 2. Furthermore, it has been understood since the 19th century that BPH does not develop in prepubertal castrates and that castration causes regression of the hyperplastic prostate.

The practice of employing eunuchs as court functionaries in China and other oriental countries goes back into prehistory (3). The procedure by which the Chinese court eunuchs were castrated in the late 19th century during the Qing dynasty was described in some detail by Stent in 1878, and subsequent descriptions by other investigators (4). However, on the basis of published interviews of surviving eunuchs, the surgical procedure, as well as the physiologic consequences, appear to have been essentially the same in all cases (5). In addition to osteomalacia consistent with the kind of bone deterioration described in post-menopausal females, gynecomastia seems to have been a common result. Wagenseil reported that 9 of 26 subjects in his 1930 Chinese eunuch study had grossly visible breast enlargement (6). He also found that all 26 had hypoplastic to nonexistent prostate tissue. And,

importantly, juvenile hairlines and hair density were maintained in all individuals.

3C

Pseudohermaphrodite studies

Disorders of androgen metabolism present excellent opportunities to develop improved understanding of the effects of androgens on human hair cycling and hair loss. Male pseudohermaphrodites with a deficiency of the enzyme 5AR raised as girls have also provided a unique opportunity for evaluation of the effects of androgenic processes in determination of gender identity. In 1979 investigators published results from their observations of 19 Dominican pseudohermaphrodites. Postpubertal psychosexual histories were obtained from 18 of these 19 subjects. Investigators noted that, at birth, the subjects presents with a markedly bifid scrotum that appeared labia-like. There is a clitoris-like phallus and a urogenital sinus with a blind vaginal pouch. The testes are in the abdomen, inguinal canal or scrotum.

However, during puberty, under the influence of normal plasma levels of testosterone, definite virilization occurs. The voice deepens, and affected subjects develop a muscular habitus. There is substantial growth of the phallus, and the scrotum becomes rugated and hyperpigmented. In most subjects, the

testes descend into the scrotum if they have not already done so. There is no gynecomastia. The subjects have erections, and there is ejaculate from the urethral orifice on the perineum. They are capable of intromission but, because of the position of the urethra, are incapable of insemination (7). These subjects are therefore testosterone-exposed and testosterone-responsive boys born with female-appearing external genitalia and raised as girls.

Thus, at birth the defect is limited to incomplete differentiation of the male external genitalia; masculinization of the internal structures is normal. Especially noteworthy were the findings that at puberty, virilization occurs with the exception of a scanty or absent beard, lack of temporal recession of hairline, and a small to absent prostate. These among other facts led McGinley to her key hypothesis.

Because of the virilization at puberty, and despite marked ambiguity of the external genitalia at birth, they hypothesized that the affected individuals would not have a disorder of T biosynthesis. The male puberty without breast development and with complete spermatogenesis also precluded a defect due to impaired androgen action. These investigators proposed, rather, that the abnormality was due most likely to a defect in the metabolism of T at the target tissue, that is, biotransformation of T to 5 α DHT by the enzyme 5AR (8).

To define a defect in 5AR activity, these investigators measured plasma T and 5aDHT levels in four affected males by a double isotope derivative technique. In the affected males the plasma T concentration ranged from 470 to 960 ng per 100 mL, which was within the normal male range of 300 to 1200 ng per 100 mL (8). However, DHT concentrations were 16, 17, 21, and 29 ng per 100 mL, which were below the normal male range of 40 to 80 ng per 100 mL. The ratio of plasma T to DHT in normal males was approximately 14/1, and in the affected males it was approximately 40/1 (8).

In two affected males, the percentage conversion of T to 5aDHT was measured during continuous infusion of radioactive T. The percentage conversion was 0.48 and 0.85, and was approximately one-sixth of the reported normal range of 3.5 to 7.0 (8).

The above assays reflect a defect in 5a reduction resulting in the decreased conversion of T to DHT. From the clinical presentation of ambiguous external genitalia with normal male internal structures and the biochemical data demonstrating Δ^4 -steroid 5a-reductase deficiency with decreased DHT formation, the investigators hypothesized that during embryogenesis, and again at puberty, both T and DHT are necessary for complete male external differentiation and development (9). T secreted in utero

by the testes acts directly on the Wolfian ducts to cause differentiation to the vas deferens, epididymis, and seminal vesicles; but in the urogenital sinus and urogenital tubercle, T functions as a prohormone, where its conversion to DHT results in differentiation of the external genitalia and prostate. The anabolic events at puberty, in particular the increase in muscle mass, the growth of the phallus and scrotum, and the voice change, appear to be mediated by T and occur in the affected males (10). Importantly, however, prostate growth, facial hair, temporal recession of the hairline, and acne do not occur all of which appear to be mediated by DHT (11).

As noted, during their prepubertal period, the individuals affected by this disorder of androgen metabolism were raised as females. However, they began to realize they were different from other girls in the village between 7 and 12 years of age, when they did not develop breasts, when their bodies began to change in a masculine direction and when masses were noted in the inguinal canal or scrotum. For these subjects, the change to a male-gender role primarily occurred either during puberty or in the post-pubertal period, after the subjects became convinced they were men, and thus, began experiencing sexual interest in women. Of the 18 subjects, 17 had successfully changed to a male-gender identity and 16 to a male-gender role.

This paper suggests that when the sex of rearing is contrary to the testosterone-mediated biologic sex, the biology prevails if the normal androgen-induced activation of puberty is permitted to occur. Eighteen subjects were unambiguously raised as females, yet despite the female assignment of rearing, 17 subjects changed to a male-gender identity and 16 to a male-gender role during or after puberty. Thus, it appears that the extent of androgen (i.e. testosterone) exposure has far more effect in determining male-gender identity than does either phenotype at birth, or gender assignment during prepubertal rearing. It must also be noted that those effected by this disorder present a complete absence of any signs of AGA.

3D

Botanicals and Anabolic Steroid Usage

“A third clue”

Androgens secreted or administered in abnormally large amounts can cause development of male characteristics in the female and precocious sexual development in the male. Conversely, hypogonadism of the male (inadequate testicular function) leads to retarded sexual development and retention of

feminine bodily characteristics (eunuchoidism), which can sometimes be remedied by administration of androgenic steroids.

Several esters of testosterone are commonly used by injection for this purpose. Many orally active analogs of testosterone are also available in which activity is greatly enhanced, and often the ratio of androgenic activity to anabolic activity is shifted markedly in favor of the latter.

This ratio primarily determines the therapeutic value of these compounds as anabolic agents. They are used together with growth hormone to promote growth in children in whom physical development is retarded. They are also used to promote physical recovery from debilitating diseases. Their reported use by some athletic competitors in sports has been decried.

It has been anecdotally reported that prostate enlargement and premature hair loss for males genetically susceptible to baldness can be ameliorated by the herb Saw Palmetto Berry Extract (60-320 mg per day). Increased levels of DHT in steroid users have been implicated in the pathogenesis of these conditions. These reports initially led us to consider the potential efficacy of this, and other botanicals, in the treatment of androgenetic alopecia.

3E

Pathophysiology of Benign Prostatic Hyperplasia

Causes, incidence, and risk factors:

Benign prostatic hyperplasia (BPH), a non-malignant abnormal enlargement of the prostate gland, affects almost all men to some degree as they age and can cause a significant disruption of lifestyle due to urinary outflow obstructive and irritative symptoms. This disorder shares a remarkable degree of hormonal processes with AGA. It has also been shown responsive to drugs and agents used to treat AGA. BPH is characterized by large, discrete nodules formed in the periurethral region of the prostate. These nodule may narrow the urethra sufficiently to cause full or partial obstruction.

An accumulation of estrogen in the aging prostate, along with increased conversion of testosterone to its more active metabolite, dihydrotestosterone (DHT), seems to induce this aberrant hyperplasia. Fatty acid deficiencies, zinc deficiency, and amino acid deficiencies may also contribute to the disease process.

The specific etiology of BPH is unknown. However, it has been noted that eunuchs, (individuals born male who have been castrated), do not develop

this disorder. Furthermore, after castration, benign prostatic hyperplasia has been observed to regress.

Since the presence of normal testicular function appears to be necessary for the development of BPH, it is believed that the hyperplastic tissue metabolizes the androgenic hormones differently than normal prostate tissue. Although by definition this tissue is benign, progressive growth of the tumor may cause significant obstruction of the urethra and interfere with the normal flow of urine.

The incidence of BPH increases with advancing age. BPH is so common, that it is believed all men will develop benign prostatic hyperplasia if they live long enough. Some degree of BPH is present in 80% of all men over 40 years old and this figure increases to 95% of all men 80 years old (figure 14).



Figure 14: Incidence of histological BPH increases as a male ages.

3F

Symptoms:

Less than half of all men with BPH show any symptoms of the disease, which may include urinary hesitancy, weak urine stream, nocturia, pain on urination, hematuria, urinary retention, and increased urinary frequency.

3G

Signs and tests:

- A digital rectal exam will reveal an enlarged, soft prostate. Urine flow rate may be measured (men with BPH have a rate less than 10 ml per second). Post-void residual volume may be measured. An IVP (Intravenous Pyelogram) may be done to confirm the diagnosis or look for blockage. Urinalysis may be useful in order to check for blood or infection. Urine should be cultured if signs of infection are present. Prostatic-specific antigen blood test has also become part of the diagnostic standard of care. And finally, a cystoscopy should be done based on significant positive findings with less invasive tests.

3H

Treatment:

The choice of an appropriate treatment is based on the severity of symptoms, the extent to which they affect lifestyle, and the presence of any other medical conditions. Treatment options include watchful waiting, various drug therapies aimed at decreasing the size of the prostate or reducing the severity of symptoms, and several surgical methods to remove or compress the enlarged prostate.

3I

Medications:

Alpha 1 blockers

Current medical therapy may involve a trial use of alpha 1-blockers (doxazosin, prazosin, and terazosin), which are also used to treat hypertension. Peripheral vasodilation is the primary mechanism of action of alpha1-blockers. They inhibit post-synaptic alpha1-receptors on smooth muscle of veins and arteries. The alpha1-receptors are also abundant in the smooth muscle of the bladder neck and prostate. Antagonism of these receptors causes relaxation of the bladder muscle, which then results in increased urinary flow rates and relief of symptoms of BPH. (12)

These medications may be useful in the treatment of BPH because they relax the muscles of the bladder neck, allowing easier urination. Of the people treated with alpha 1-blocker medications, 74 percent reported an improvement in symptoms.

3J

Finasteride

This drug has recently been approved for treatment of BPH. Finasteride lowers prostate hormone levels, thus reducing the size of the prostate. This drug has been shown to increase the urine flow rate and decrease the symptoms of BPH. It may take up to 6 months before one notices a significant improvement in symptoms. However, potential side effects related to use of finasteride include decreased sex drive (3.3%) and impotence (2.5 - 3.7%).

3K

Finasteride and BPH

The development of the human benign prostatic hyperplasia clearly requires a combination of testicular androgens and aging. Although the role of androgens as the causative factor for human benign prostatic hyperplasia is debated, they undoubtedly have at least a permissive role. The principal prostatic androgen is DHT. Although not elevated in human benign prostatic hyperplasia, DHT levels in the prostate remain at a normal level with aging, despite a decrease in the plasma testosterone. DHT is generated by reduction of testosterone.

As mentioned earlier, two isoenzymes of 5alpha-reductase have been discovered. Type 1 is present in most tissues of the body where 5alpha-reductase is expressed and is the dominant form in sebaceous glands. Type 2 5AR is the dominant isoenzyme in genital tissues, including the prostate. Finasteride is a 5AR inhibitor that has been used for the treatment of BPH. At doses prescribed clinically, its major effect is through suppression of type 2 5alpha-reductase, as it has been shown to have a much lower affinity for the type 1 isoenzyme. Finasteride suppresses DHT by about 70% in serum and by as much as 85-90% in the prostate. The remaining DHT in the prostate is likely to be the result of type 1 5AR.

Two large international multicenter phase III trials have been published documenting the safety and efficacy of finasteride in the treatment of human

benign prostatic hyperplasia (13). Combining these two studies, randomized, controlled data are available for 12 months. Noncontrolled extension of these data from a subset of patients, who elected to continue drug treatment for 3, 4 or 5 years, are also available. These studies demonstrate that long-term medical therapy with finasteride can reduce clinically significant endpoints such as acute urinary retention or the need for surgery. According to the meta-analysis of six randomized clinical trials with finasteride, finasteride is most effective in men with clinically hyperplastic prostates. A more effective dual inhibitor of type 1 and 2 human 5AR may lower circulating DHT to a greater extent than finasteride and show advantages in the treatment of human benign prostatic hyperplasia and other disease states that depend on DHT. Clinical evaluation of potent dual 5alpha-reductase inhibitors may help define the relative roles of human type 1 and 2 5alpha-reductase in the pathophysiology of benign prostatic hyperplasia and other androgen-dependent diseases.

Finasteride has recently been reformulated from 5 mg (Proscar™/indication BPH) to 1 mg dosage (Propecia™/indication AGA) after it was discovered, quite by accident, that individuals being treated for BPH with finasteride were showing an abatement of hair loss associated with AGA (14).

Other Medications

Antibiotics may also be prescribed to treat chronic prostatitis, which commonly accompanies BPH. Some men note symptom relief after a course of antibiotics.

3M

Surgery:

Surgery is usually indicated for men with symptoms of incontinence, hematuria, urinary retention, and recurrent UTIs. The choice of a specific surgical procedure is usually based on the severity of symptoms and the size and shape of the prostate gland.

Surgical treatment options include transurethral resection of the prostate (TURP), transurethral incision of the prostate (TUIP), and open prostatectomy. Various studies are underway to evaluate the effectiveness of other treatments, such as hyperthermia, thermal therapy, prostatic stents, and hormonal therapy.

3N

Conclusions

Several lines of evidence examined in this chapter have converged to support the view that both circulating testosterone and the modifying enzyme, 5AR, have profound effects on androgen metabolism and provide insight into the role of these compounds in hair loss. First, the absence of circulating testosterone (and therefore, DHT) in males castrated prior to puberty has been shown to prevent AGA in later life, suggesting that this metabolism is key to the pathogenesis of male pattern hair loss. Secondly, in a group of male pseudohermaphrodites with inherited defects in the 5AR gene, the inability to convert circulating testosterone to its active metabolite, DHT, also led to the preservation of the juvenile hair line. These two examples demonstrate that whether the disturbance in androgen metabolism results from either the absence of substrate (T), active metabolite, DHT, or dysfunction of the enzyme 5AR, at least one phenotypic consequence is consistent and reproducible - terminal hair density as well as juvenile hairlines remain intact in such individuals.

In contrast, a third and critical observation was noted in bodybuilders who were self-administering anabolic steroids that excessive levels of circulating T and therefore DHT had the opposite effect of the first two examples – that of acceleration of hair loss due to upregulation of the hormonal processes which result in AGA.

Collectively, these lines of converging evidence pointed to a common theme among disorders resulting from dysregulation of the conversion of T to DHT, and led the author to the central hypothesis of this dissertation.

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