Testosterone

Testicular action was linked to circulating blood fractions – now understood to be a family of androgenic hormones – in the early work on castration and testicular transplantation in fowl by Arnold Bethold (1803–1861). Research on the action of testosterone received a brief boost in 1889, when the Harvard professor Charles-Edouard Brown-Séquard (1817–1894), then in Paris, self-injected subcutaneously a “rejuvenating elixir” consisting of an extract of dog and guinea pig testicle. He reported in The Lancet that his vigor and feeling of wellbeing were markedly restored but, predictably, the effects were transient (and likely based on placebo), and Brown-Séquard’s hopes for the compound were dashed. Suffering the ridicule of his colleagues, work on the mechanisms and effects of androgens in human beings was abandoned by Brown-Séquard and succeeding generations of biochemists for nearly 40 years.

The trail remained cold until the University of Chicago’s Professor of Physiologic Chemistry, Fred C. Koch, established easy access to a large source of bovine testicles - the Chicago stockyards – and to students willing to endure the ceaseless toil of extracting their isolates. In 1927, Koch and his student, Lemuel McGee, derived 20mg of a substance from a supply of 40 pounds of bull testicles that, when administered to castrated roosters, pigs and rats, remasculinized them. The group of Ernst Laqueur at the University of Amsterdam purified testosterone from bovine testicles in a similar manner in 1934, but isolation of the hormone from animal tissues in amounts permitting serious study in humans was clearly not feasible until three European pharmaceutical giants — Schering (Berlin, Germany), Organon (Oss, Netherlands) and Ciba (Basel, Switzerland) — began full-scale steroid research and development programs in the 1930’s.

The Organon group in the Netherlands were the first to isolate and identify the hormone in a May 1935 paper "On Crystalline Male Hormone from Testicles (Testosterone)" by Karoly Gyula David, E. Dingemanse, J. Freud and Ernst Laqueur. They named the hormone testosterone, from the stems of testicle and sterol, and the suffix of ketone. The structure was worked out by Schering’s Adolf Butenandt (1903–1995).

The chemical synthesis of testosterone was achieved in August that year, when Butenandt and G. Hanisch published a paper describing "A Method for Preparing Testosterone from Cholesterol." Only a week later, the Ciba group in Zurich, Leopold Ruzicka (1887–1976) and A. Wettstein, announced a patent application in a paper "On the Artificial Preparation of the Testicular Hormone Testosterone (Androsten-3-one-17-ol)." These independent partial syntheses of testosterone from a cholesterol base earned both Butenandt and Ruzicka the joint 1939 Nobel Prize in Chemistry. Testosterone was identified as 17beta-hydroxandrost-4-en-3-one ($C_{19}H_{28}O_2$), a solid polycyclic alcohol with a hydroxyl group at the 17th carbon atom. This also made it obvious that additional modifications on the synthesized testosterone could be made, i.e., esterification and alkylation.

The partial synthesis in the 1930’s of abundant, potent testosterone esters permitted the characterization of the hormone’s effects, so that Kochakian and Murlin (1936) were able to show that testosterone raised nitrogen retention (a mechanism central to anabolism) in the dog, after which Charles Kenyon’s group was able to demonstrate both anabolic and androgenic effects of testosterone propionate in eunuchoidal men, boys, and women. The period of the early 1930’s to the 1950’s has been called “The Golden Age of Steroid Chemistry”, and work during this period progressed quickly. Research in this golden age proved that this newly synthesized compound — testosterone — or rather family of compounds (for many derivatives were developed in the 1940’s, 50’s and 60’s), was a potent multiplier of muscle, strength, and wellbeing.

Testosterone Production

Natural

Like other steroid hormones, testosterone is derived from cholesterol. The largest amounts of testosterone are produced by the testes in men. It is also synthesized in smaller quantities in women by the thecal cells of the ovaries, by the placenta, as well as by the zona reticularis of the adrenal cortex in both sexes.

In the testes, testosterone is produced by the Leydig cells. The male generative glands also contain Sertoli cells which require testosterone for spermatogenesis. Like most hormones, testosterone is supplied to target tissues in the blood where much of it is transported bound to a specific plasma protein, sex hormone binding globulin (SHBG).

Artificial

Testosterone is synthesizable in almost unlimited quantities. Furthermore, there are two possible modifications

on it, giving it further abilities. First, it can be esterified, permitting a long-lasting effect when injected into the body. Second, it can be alkylated, permitting oral intake instead of injection.

Esterification
The C-17 hydroxyl group testosterone can be esterified, or altered by the substitution of an acid group for the hydroxyl group at the C17 position. Esterification lowers the water solubility of the molecule and increases its lipid solubility, permitting a sterile oil-based injectible with testosterone to form a “depot” in the muscle, from which it is gradually released. Esterification temporarily deactivates the steroid molecule, because the presence of the large acid chain prevents the steroid from binding to androgen receptor (AR) molecules within muscle cells that promote protein synthesis. But, as the esterified steroid is gradually leached from the oily depot into the blood, esterases (acid-cleaving molecules) replace the acid chain with a hydroxyl group as in the virgin molecule, permitting the steroid to bind to AR. The overall effect of esterification is to extend the steroid’s half-life, ease its administration, and alter its anabolic/androgenic ratio (A/AR), or the degree to which it affects striated muscle vs. sexual organ tissues such as the testes or prostate.

Alkylation
The second importance of the hydroxyl side chain at the C-17 position is that it can not only be esterified, but it can also be alkylated (by substitution of an ethyl or methyl group for the hydroxyl group). Alkylation permits oral steroids, the so-called “17-aa” or alkylated family of androgens such as methyltestosterone, which can be taken up by the digestive tract, and so be easily administered in pill form.

Virilizing and anabolic effects on humans
In general, androgens promote protein synthesis and growth of those tissues with androgen receptors. Testosterone effects can be classified as virilizing and anabolic effects, although the distinction is somewhat artificial, as many of the effects can be considered both.

* Anabolic effects include growth of muscle mass and strength, increased bone density and strength, and stimulation of linear growth and bone maturation.
* Virilizing effects include maturation of the sex organs, particularly the penis and the formation of the scrotum in unborn children, and after birth (usually at puberty) a deepening of the voice, growth of the beard and axillary hair. Many of these fall into the category of male secondary sex characteristics.

Testosterone effects can also be classified by the age of usual occurrence. For postnatal effects in both males and females, these are mostly dependent on the levels and duration of circulating free testosterone.

Prenatal androgen effects
Most of the prenatal androgen effects occur between 7 and 12 weeks of gestation.

* Genital virilization (midline fusion, phallic urethra, scrotal thinning and rugation, phallic enlargement); although the role of testosterone is far smaller than that of Dihydrotestosterone.
* Development of prostate and seminal vesicles

Early infancy androgen effects
Early infancy androgen effects are the least understood. In the first weeks of life for male infants, testosterone levels rise. The levels remain in a pubertal range for a few months, but usually reach the barely detectable levels of childhood by 4-6 months of age. The function of this rise in humans is unknown. It has been speculated that "brain masculinization" is occurring since no significant changes have been identified in other parts of the body.

Early postnatal effects
Early postnatal effects are the first visible effects of rising androgen levels in childhood, and occur in both boys and girls in puberty.

* Adult-type body odour
* Increased oiliness of skin and hair, acne
* Pubarche (appearance of pubic hair)
* Axillary hair
* Growth spurt, accelerated bone maturation
* Fine upper lip and sideburn hair

Advanced postnatal effects
Advanced postnatal effects begin to occur when androgen has been higher than normal adult female levels for

months or years. In males these are usual late pubertal effects, and occur in women after prolonged periods of heightened levels of free testosterone in the blood.

* Phallic enlargement (including clitoromegaly)
* Increased libido and frequency of erection or clitoral engorgement
* Pubic hair extends to thighs and up toward umbilicus
* Facial hair (sideburns, beard, moustache)
* Chest hair, periareolar hair, perianal hair
* Subcutaneous fat in face decreases
* Increased muscle strength and mass
* Deepening of voice
* Growth of the adam's apple
* Growth of spermatogenic tissue in testes, male fertility
* Growth of jaw, brow, chin, nose, and remodeling of facial bone contours
* Shoulders widen and rib cage expands
* Completion of bone maturation and termination of growth. This occurs indirectly via estradiol metabolites and hence more gradually in men than women.

Adult testosterone effects
Adult testosterone effects are more clearly demonstrable in males than in females, but are likely important to both sexes. Some of these effects may decline as testosterone levels decline in the later decades of adult life.

* Maintenance of muscle mass and strength
* Maintenance of bone density and strength
* Libido and clitoral engorgement/penile erection frequency.
* Mental and physical energy
* Excessive testosterone in males can lead to an increased risk of prostate cancer although some recent studies suggest that the role of testosterone has less of a potentiating effect on prostate cancer, but that estrogen has more of a role.

Effects on the brain
As testosterone affects the entire body (often by enlarging; men have bigger hearts, lungs, liver, etc.) the brain is also affected by this "sexual" advancement; the enzyme aromatase converts testosterone into estradiol that is responsible for masculinization of the brain in a male fetus.

There are some differences in a male and female brain (the result of different testosterone levels); a clear difference is the size, the male human brain is on average larger, however in females (who do not use testosterone as much) the corpus callosum is proportionally larger. This means that the effect of testosterone is a greater overall brain volume, but a decreased connection between the hemispheres.

Animal models of the effects of supraphysiological doses of testosterone suggest that it alters aggression, sexual behaviors, anxiety, reward, and learning and the neurotransmitter systems and brain areas that underlie these behaviors. A number of studies and reviews have linked testosterone use in humans to significant psychiatric disturbances including depression, psychosis, and aggression. Experimental evidence suggests that supraphysiologic doses of testosterone may lead to mania in a small number of men. Depressive symptoms have been noted particularly during AAS withdrawal. At least one study suggests that testosterone users are more likely to die of suicide or homicide than amphetamine or heroin users and to die younger than non-using weightlifting controls. There is gathering support from animal research for a model in which testosterone and others steroids use cause increased hypothalamic activation, euphoria, and energy, which most users find pleasant, but which might also cause increased distractibility and for some morphs into mania or into depression during drug abstinence. This activation may lead to threat-wariness and irritability, resulting in greater aggression. There is limited evidence for a steroid-withdrawal syndrome, but a multidimensional model of steroid withdrawal – combining physical, affective and cognitive dimensions – could possibly be worked out if data were available. There is evidence for a testosterone-aggression expectancy effect, which could account for many of the results found in the research, and it is also possible that the root cause of observed dysphoria may lie elsewhere (e.g., with ergo/thermogenics used concurrently).

Human literature suggests that attention, memory, and spatial ability are key cognitive functions affected by testosterone, though the literature is rather sparse. Preliminary evidence suggests that low testosterone levels may be a risk factor for cognitive decline and possibly for dementia of the Alzheimer’s type, a key argument in Life Extension Medicine for the use of testosterone in anti-aging therapies. Much of the literature, however, suggests a curvilinear or even quadratic relationship between spatial performance and circulating testosterone,

where both hypo- and hypersecretion of circulating androgens have negative effects on cognition and cognitively-modulated aggressivity, as detailed above.

Mechanism
The effects of testosterone in humans and other vertebrates occur by way of two main mechanisms: by activation of the androgen receptor (directly or as DHT), and by conversion to estradiol and activation of certain estrogen receptors.

Free testosterone (T) is transported into the cytoplasm of target tissue cells, where it can bind to the androgen receptor, or can be reduced to 5?-dihydrotestosterone (DHT) by the cytoplasmic enzyme 5-alpha reductase. DHT binds to the same androgen receptor even more strongly than T, so that its androgenic potency is about 2.5 times that of T. The T-receptor or DHT-receptor complex undergoes a structural change that allows it to move into the cell nucleus and bind directly to specific nucleotide sequences of the chromosomal DNA. The areas of binding are called hormone response elements (HREs), and influence transcriptional activity of certain genes, producing the androgen effects. It is important to note that if there is a 5-alpha reductase deficiency, the body (of a human) will continue growing into a female with testicles.

Androgen receptors occur in many different vertebrate body system tissues, and both males and females respond similarly to similar levels. Greatly differing amounts of testosterone prenatally, at puberty, and throughout life account for a share of biological differences between males and females.

The bones and the brain are two important tissues in humans where the primary effect of testosterone is by way of aromatization to estradiol. In the bones, estradiol accelerates maturation of cartilage into bone, leading to closure of the epiphyses and conclusion of growth. In the central nervous system, testosterone is aromatized to estradiol. Estradiol rather than testosterone serves as the most important feedback signal to the hypothalamus (especially affecting LH secretion). In many mammals, prenatal or perinatal "masculinization" of the sexually dimorphic areas of the brain by estradiol derived from testosterone programs later male sexual behavior.

The human hormone testosterone is produced in greater amounts by males, and less by females. The human hormone estrogen is produced in greater amounts by females, and less by males. Testosterone causes the appearance of masculine traits (i.e deepening voice, pubic and facial hairs, muscular build, etc.) Like men, women rely on testosterone to maintain libido, bone density and muscle mass throughout their lives. In men, estrogens simply lower testosterone, decrease muscle mass, stunt growth in teenagers, introduce gynecomastia, increase feminine characteristics, and decrease susceptibility to prostate cancer.

Therapeutic use

Routes of administration
There are many routes of administration for testosterone. Forms of testosterone for human administration currently available in North America include injectable (such as testosterone cypionate or testosterone enanthate in oil), oral, buccal, transdermal skin patches, and transdermal creams or gels. In the pipeline are "roll on" methods and nasal sprays.

Indications
The original and primary use of testosterone is for the treatment of males who have too little or no natural endogenous testosterone production—males with hypogonadism. Appropriate use for this purpose is legitimate hormone replacement therapy, which maintains serum testosterone levels in the normal range.

However, over the years, as with every hormone, testosterone or other anabolic steroids has also been given for many other conditions and purposes besides replacement, with variable success but higher rates of side effects or problems. Examples include infertility, lack of libido or erectile dysfunction, osteoporosis, penile enlargement, height growth, bone marrow stimulation and reversal of anemia, and even appetite stimulation. By the late 1940s testosterone was being touted as an anti-aging wonder drug (e.g., see Paul de Kruif's The Male Hormone). Decline of testosterone production with age has led to a demand for Androgen Replacement Therapy.

To take advantage of its virilizing effects, testosterone is often administered to female-to-male transsexual men as part of the hormone replacement therapy, with a "target level" of the normal male testosterone level. Like-wise, male-to-female transsexual women are sometimes prescribed drugs [anti-androgens] to decrease the level of testosterone in the body and allow for the effects of estrogen to develop.

Women use testosterones to treat low libido, often a symptom or outcome of hormonal contraceptive use. Women may also use testosterone therapies to treat or prevent loss of bone density, muscle mass and to treat certain kinds of depression and low energy state. Women on testosterone therapies may experience an increase in weight without an increase in body fat due to changes in bone and muscle density. Most undesired effects of testosterone therapy in non-transgendered women (the majority) may be controlled by hair-reduction strategies, acne prevention, etc.

There is a myth that exogenous testosterone can more or less definitively be used for male birth control. However, the vast majority of physicians will agree that to prescribe exogenous testosterone for this purpose is inappropriate. But, perhaps more important, many men found this, in first-hand experience, to be untrue or at least, unreliable.

Some drugs specifically target testosterone as a way of treating certain conditions. For example, finasteride inhibits the conversion of testosterone into dihydrotestosterone (DHT), a metabolite which is more potent than testosterone. By lowering the levels of dihydrotestosterone, finasteride may be used for various conditions associated with androgens, such as benign prostatic hyperplasia (BPH) and androgenetic alopecia (male-pattern baldness).

Adverse effects
Exogenous testosterone supplementation comes with a number of health risks. Fluoxymesterone and methyltestosterone are synthetic derivatives of testosterone. In 2006 it was reported that women taking Estratest, a combination pill including estrogen and methyltestosterone, were at considerably heightened risk of breast cancer.

Athletic use
Testosterone may be administered to an athlete in order to improve performance, and is considered to be a form of doping in most sports. There are several application methods for testosterone, including intramuscular injections, transdermal gels and patches, and implantable pellets.

Anabolic steroids (of which testosterone is one) have also been taken to enhance muscle development, strength, or endurance. They do so directly by increasing the muscles' protein synthesis. In result muscle fibers become larger and repair faster than the average person. After a series of scandals and publicity in the 1980s (such as Ben Johnson's improved performance at the 1988 Summer Olympics), prohibitions of anabolic steroid use were renewed or strengthened by many sports organizations. Testosterone and other anabolic steroids were designated a "controlled substance" by the United States Congress in 1990, with the Anabolic Steroid Control Act.

Changes during aging
Testosterone levels decline gradually with age in human beings. The clinical significance of this decrease is debated (see andropause). There is disagreement about if and when to treat aging men with testosterone replacement therapy. The American Society of Andrology's position is that testosterone therapy "is indicated when both clinical symptoms and signs suggestive of androgen deficiency and decreased testosterone levels are present". The American Association of Clinical Endocrinologists says "Hypogonadism is defined as a free testosterone level that is below the lower limit of normal for young adult control subjects. Previously, age-related decreases in free testosterone were once accepted as normal. Currently, they are not considered normal....Patients with low-normal to subnormal range testosterone levels warrant a clinical trial of testosterone."

There isn't total agreement on the threshold of testosterone value below which a man would be considered hypogonadal. (Currently there are no standards as to when to treat women.) Testosterone can be measured as "free" (that is, bioavailable and unbound) or more commonly, "total" (including the percentage which is chemically bound and unavailable). In the United States, male total testosterone levels below 200 to 300 ng/dl from a morning sample are generally considered low. However these numbers are typically not age-adjusted, but based on an average of a test group which includes elderly males with low testosterone levels. Therefore a value of 300 ng/dl might be normal for a 65 year old male, but not normal for a 30 year old. Identification of inadequate testosterone in an aging male by symptoms alone can be difficult. The signs and symptoms are non-specific, and might be confused with normal aging characteristics, such as loss of muscle mass and bone density, decreased physical endurance, decreased memory ability and loss of libido.

Replacement therapy can take the form of injectable depots, transdermal patches and gels, subcutaneous pellets and oral therapy. Adverse effects of testosterone supplementation include minor side effects such as acne and oily skin, and more significant complications such as increased hematocrit, exacerbation of sleep

apnea and acceleration of pre-existing prostate cancer growth. Exogenous testosterone also causes suppression of spermatogenesis and can lead to infertility. It is recommended that physicians screen for prostate cancer with a digital rectal exam and PSA (prostate specific antigen) level prior to initiating therapy, and monitor hematocrit and PSA levels closely during therapy.

Large scale trials to assess the efficiency and long-term safety of testosterone are still lacking. Many caution against embracing testosterone replacement therapy because of lessons from the female hormone replacement therapy trials, where initially promising results were later refuted by larger studies. Still, testosterone replacement therapies in women to treat/prevent osteoporosis have yet to show the risks now shown with estrogen replacement therapies.