The Endocrine System and Steroids

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The casual use of anabolic steroids is becoming more widespread in a 20th century culture that focuses on fitness and youth. Not only have professional athletes used steroids, but college students, high school students and even some middle school students have used steroids as performance-enhancing aids. But the appeal of steroids is shadowed by possible negative side effects often dismissed by the general population.

Essentially, the most abused steroids are manufactured compounds chemically related to the male sex hormone testosterone. This hormone generates two side effects—secondary male sexual characteristics, such as a deepening voice and increased body hair, and secondly, accelerated muscle growth.

In order to understand the threat of steroid misuse, this article will present a detailed discussion of the endocrine system and selected hormones as a preface to the use and misuse of steroids.

The functions of the human body are regulated by two methods: nerve impulses and information transmitted by the spinal cord and brain (Figure 1) as well as the endocrine system, a network of nine glands that secrete chemicals called hormones. (Figure 2) These hormones are responsible for various functions, including resistance to stress, use of food for energy, and reproduction. Simply, these chemical secretions, or hormones, modify activity within cells, and this modification causes a change.[34, 35]

The ductless endocrine glands convey their secretions to specific sites via the capillaries. Hormones are circulated in the blood throughout the body but affect only specific organs or tissues, often termed target organs or target tissues.[34] Hormones, such as insulin, may have multiple target sites, whereas other hormones, such as aldosterone, focus on a single target organ, the kidneys.[34] (Table 1)

There are three classifications of hormones: amines, proteins and steroids.[34] Amines are simple hormones and include thyroxine produced by the thyroid gland, and epinephrine and norepinephrine, generated by the adrenal medulla gland.[34] Proteins are also hormones. They exist as chains of amino acids and include insulin produced by the pancreas. Steroid hormones represent the third group and include cortisol and aldosterone generated by the adrenal cortex, estrogen and progesterone from the ovaries, and testosterone from the testes. Figure 3 illustrates many of the glands and associated hormones in the human endocrine system.[34, 35]

HOW HORMONES FUNCTION

Initially, the body signals a need for action on a specific target organ. A particular endocrine gland is alerted to increase hor-

TABLE 1. THE MAJOR ENDOCRINE GLANDS AND THEIR RESPECTIVE HORMONES

GLAND	HORMONE	TARGET TISSUE	OUTCOME
Adrenal Cortex	Mineralcortoids (aldosterone)	Kidney	Increases the rate of sodium absorption. Increases retention of water.
	Glucocorticoids (cortisol)	Most tissues	Increases levels of blood glucose. Inhibits inflammation/immune response.
	Androgens and estrogens	Most tissues	Only small quantities secreted. Majority produced by testes and ovaries.
Adrenal Medulla	Epinephrine, norepinephrine	Heart, liver, blood vessels	Assists with stress. Increases heart rate and blood pressure, increases blood to skeletal tissue and level of glucose in blood.
Hypothalamus	Releasing and inhibiting	Anterior lobe of pituitary	Signals production or reduction of specific hormones.
Ovaries	Estrogens	Widespread	Maintains female reproduction organs and menstrual cycle. Generates secondary sexual traits.
	Progesterone	Uterus, breast	Readies uterus for pregnancy. Promotes development of mammary gland. Promotes menstrual cycle.
Pancreas	Glucagon	Liver	Increases glycogen breakdown and causes increase in glucose level in blood.
	Insulin	Widespread, liver, skeletal muscle, adipose	Reduces level of glucose in blood, stimulates glucose storage as glycogen, and produces adipose.
Parathyroid	Parathyroid (PTH)	Bone, kidney, digestive tissue	Promotes blood calcium, increases absorption of calcium and reduces calcium lost in urine.
Pineal	Melatonin	Hypothalamus	Inhibits gonadotropin-releasing hormone. Regulates sleep functions.
Pituitary (anterior lobe)	Growth (GH)	Widespread	Promotes synthesis of protein
	Thyroid-stimulating	Thyroid gland	Increases thyroid hormone secretion; increases size of thyroid gland.
	Adrenocorticotropic (ACTH)	Adrenal cortex	Increases secretion of adrenocortical hormones, e.g. cortisol.
	Follicle-stimulating (FSH)	Ovarian follicles, tubules of testis	Promotes follicle maturation and estrogen secretion (F); promotes spermatogenesis (M).
	Luteinizing (LH)	Ovary Testis	Ovulation. Promotes production of progesterone. Produces testosterone.
	Prolactin	Mammary	Signals milk production.
Pituitary (posterior lobe)	Antidiuretic (ADH)	Kidney	Increases reabsorption of water.
	Oxytocin	Mammary, uterus	Increases contraction of uterus. Signals ejection of milk.
Testes	Testosterone	Widespread	Maintains male reproductive organs and produces secondary male sexual traits.
Thymus	Thymosin	Immune response tissues	Develops immune system and maintains functions.
Thyroid	Thyroxine and triiodothyronine	Widespread	Increases rate of metabolism. Critical to development.

mone production, which may directly effect the target organ or indirectly stimulate a secondary endocrine gland that impacts the target organ. Once the effects on the target organ are reached, the stimuli in the blood decrease and the secretion of hormone is correspondingly reduced. This negative feedback is repeated in glands again and again all over the body.

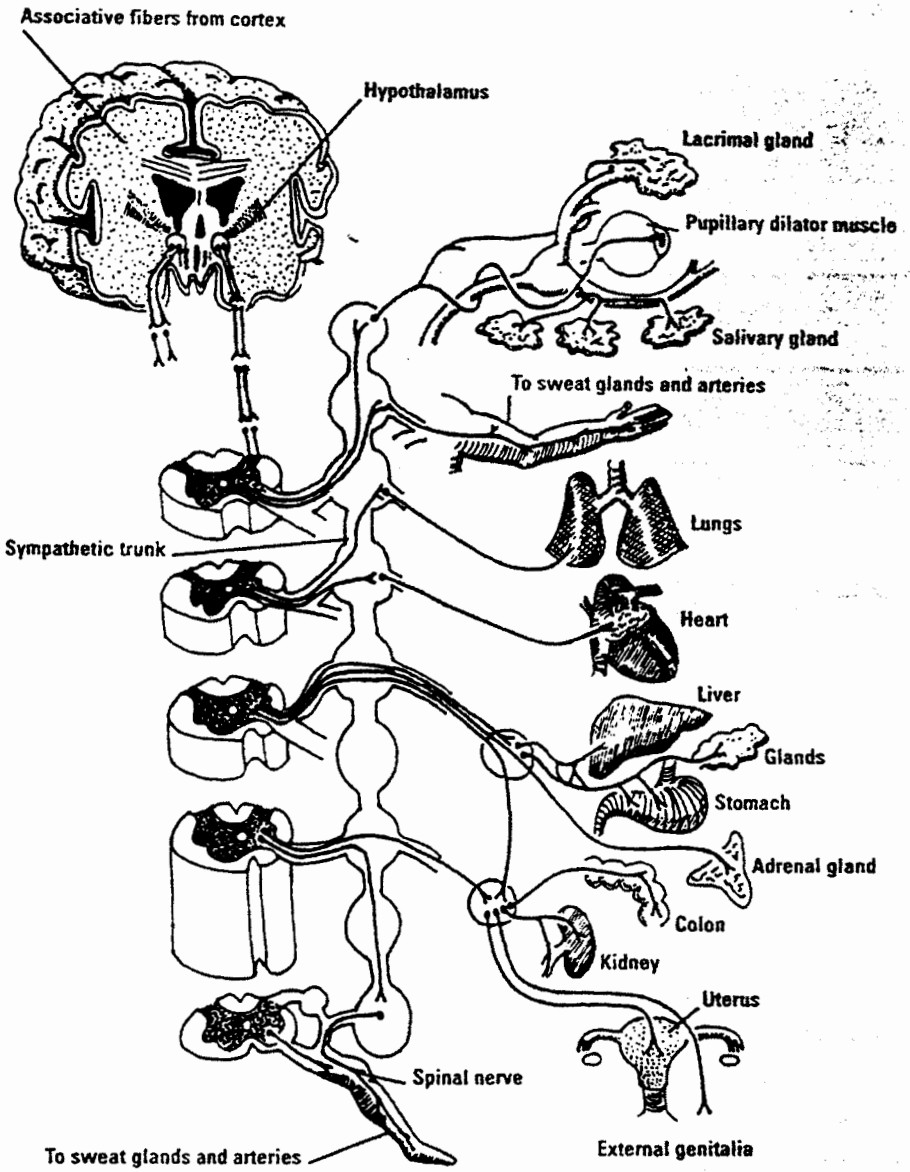

FIGURE 1—Sympathetic and parasympathetic nerve pathways to the various organs of the human body.

For example, when an individual exercises and begins to sweat profusely, the body's water content is reduced, and fluids become more salty. This saltiness signals the receptors in the hypothalamus to produce the antidiuretic hormone (ADH). In turn, messages to the posterior pituitary gland, which stores the hormone, signal the need to release more ADH. More ADH increases the reabsorption of water by kidney tubules and decreases the quantity of urine produced. Ultimately, the body's water is being conserved.[34]

THE PITUITARY GLAND

Many bodily functions are regulated by the pituitary gland, which is located on a portion of the sphenoid bone and is approximately 1 cm in size. (Figure 4)[34] Its two major components are the posterior pituitary gland and the anterior pituitary gland. (Figure 5) Besides secreting the hormone ADH, the posterior pituitary gland also stores the hormone oxytocin, which stimulates the contraction of the uterus at the end of pregnancy and stimulates the release of milk from the mammary glands.[15]

However, the anterior pituitary gland and its hormones are the focus of the remainder of this article. Six hormones are produced by the anterior pituitary gland: growth hormone (GH), thyroid-stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), prolactin, follicle-stimulating hormone (FSH), and luteinizing hormone (LH-female, ICSH-male). (Figure 3) Respectively, their targets are bones and organs, thyroid, adrenal cortex, breasts, testes and ovaries.[34] Some of their functions encompass growth, milk production, ovulation, and sperm production. (Table 1)

These six hormones are regulated by releasing hormones secreted in the hypothalamus. From the hypothalamus, the releasing hormones travel through the hypophyseal portal veins to another capillary network in the anterior pituitary gland where they are absorbed and stimulate secretion of these anterior pituitary hormones.[34, 35]

One of the important targets of the pituitary gland—the adrenal glands and related hormones—regulate metabolic processes (salt metabolism), production of sex hormones and production of fibrous tissue throughout the body.[34, 35]

THE ADRENAL GLANDS

The adrenal gland is superior to each kidney and composed of two parts: an outer layer, the adrenal cortex, and an inner layer, the adrenal medulla. (Figure 6) Each secretes very different hormones that perform different functions. The adrenal cortex is critical to life, but the adrenal medulla may be removed without consequence.[35]

In stress situations, such as in aerobic exercise or athletic competition, the hypothalamus sends impulses to the adrenal medulla to secrete two hormones: epinephrine and norepinephrine. Primarily, they prepare the body for "flight or fight" and charge the body for physical action. Secreted in small amounts, norepinephrine causes vasoconstriction in the skin, viscera and skeletal muscles, and raises blood pressure. Stored in larger amounts, the hormone epinephrine acts on the cardiovascular and pulmonary systems, as well as a variety of metabolic processes. It increases heart rate and force of contraction, dilates bronchioles, decreases peristalsis, increases conversion of glycogen to glucose in the liver, and speeds up both the use of fat for energy and the rate of cellular respiration.[34]

The adrenal cortex, the outer layer of the gland, produces steroid hormones, primarily cortisol and aldosterone. Cortisol affects metabolism and the release of stored fuels, while aldosterone acts on the kidneys and influences sod um and potassium balance in the body. Control of the adrenal cortex is affected by the adrenocorticotropic hormone (ACTH) that is produced by the anterior pituita gland. (Figure 7)

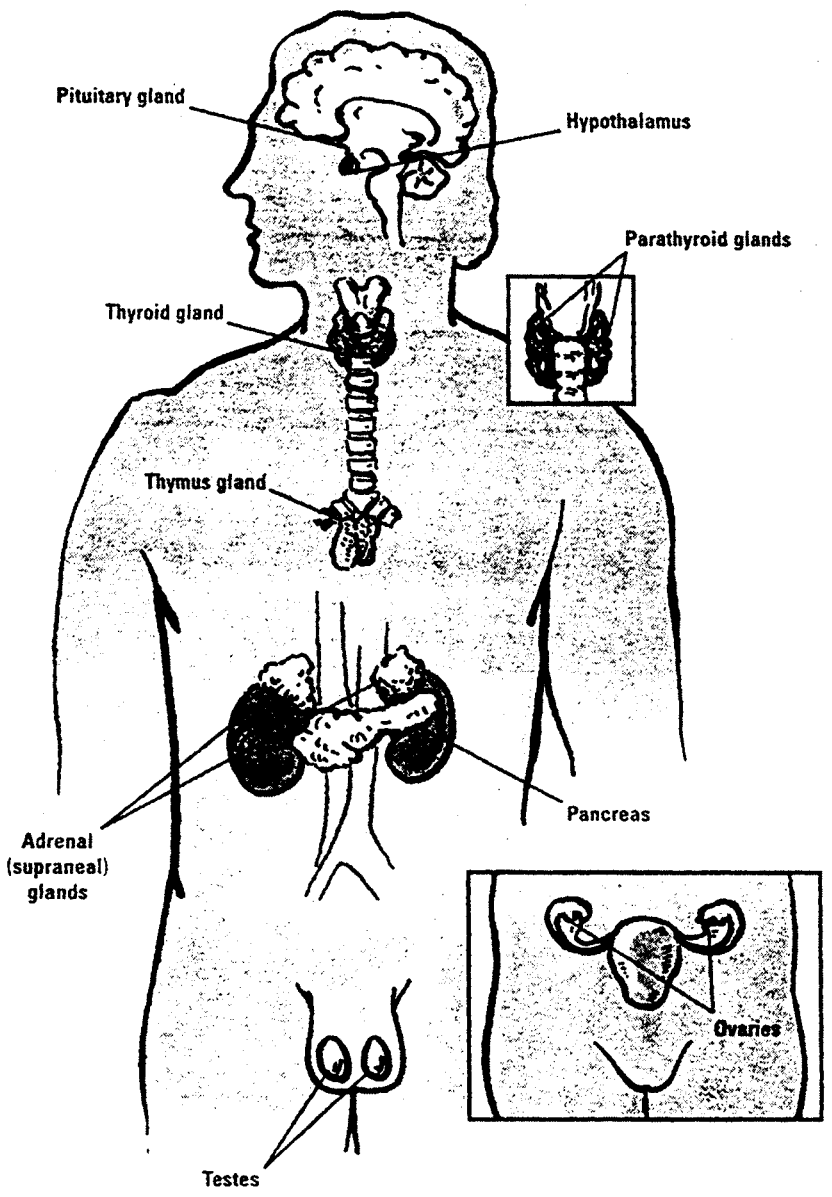

FIGURE 2—Major glands in the endocrine system.

Adrenocorticotropic secretion is regulated by another hormone, corticotrophin releasing hormone (CRH), which is produced by the hypothalamus and transmitt to the anterior pituitary by the portal vessels. ACTH affects the adrenal cortex in two ways. First, it stimulates metabolism and, second, it controls all adrenocortica especially cortisol secretion.[34]

ANATOMY OF THE ADRENAL CORTEX

The adrenal cortex is divided into three zones, and each manufactures a different class of steroid hormone. The outer layer, the Zona Glomerulosa, produces aldosterone, also known as a mineralocorticoid; the inner layer, Zona Fasciculata, produces cortisol, also called glucocorticoid; and the innermost area, Zona Reticularis, produces androgens. (Figure 8)

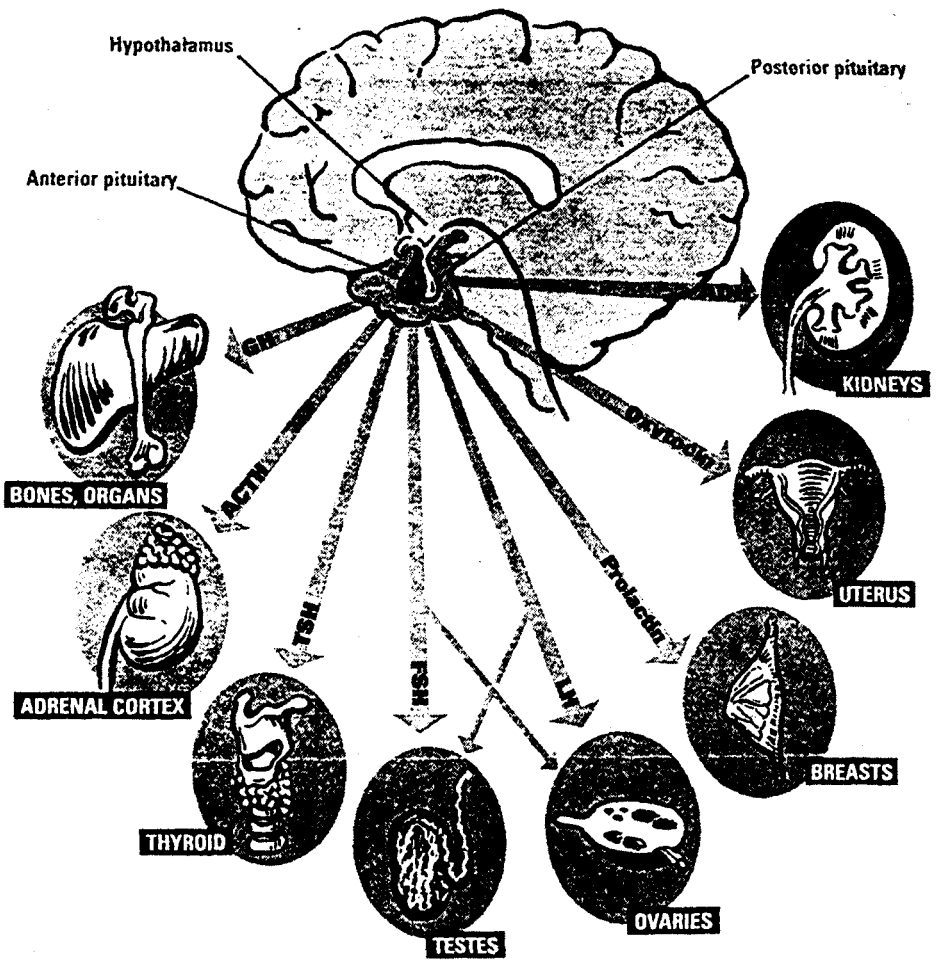

FIGURE 3—Hormones generated by the pituitary and their target organs.

PRIMARY HORMONES OF THE ADRENAL CORTEX

Aldosterones are hormones that increase the blood sodium and decrease blood potassium during periods of physical exertion. While sweating, the human body loses salt and blood pressure drops. Low blood pressure in the nephron of the kidney causes the kidney to release renin. The renin signals the production of a vasoconstrictor, angiotensinogen, and blood pressure subsequently rises. The angiotensinogen promotes aldosterone secretion which conserves sodium and water. This indirect effect of aldosterone means that normal blood volume and blood pressure remain relatively constant. Essentially, aldosterone maintains normal blood levels of sodium and potassium and contributes to the maintenance of normal blood pH, blood volume and blood pressure.[32, 34]

Cortisol is secreted in any type of physiological stress situation, including disease, physical injury, hemorrhage, anger, exercise and hunger. Cortisol has an anti-inflammatory effect. When inflammation occurs, damaged tissue within the body releases histamine that makes capillaries more permeable. Although more enzymes break down damaged tissue, they may also cause destruction of healthy tissue.[34]

Cortisol blocks the effects of histamine and stabilizes lysosomal membranes, preventing excessive tissue destruction. Under normal secretion, cortisol seems to limit the inflammation process to what is useful for tissue repair and prevent excessive tissue destruction. Abnormal secretion or excess cortisol decreases the immune response, making the body susceptible to infection and decreases the healing of damaged tissue. Cortisol secretion is controlled by the hormone ACTH from the anterior pituitary gland. In turn, the gland is stimulated by corticotropin releasing hormone (CRH) from the hypothalamus.

The innermost layer of the adrenal cortex secretes small amounts of androgens, the male sex hormone, that exert masculinizing effects, or estrogen, the female sex hormone. The adrenal gland also secretes two other hormones, dehy-

dehydroepiandrosterone (DHEA) and testosterone, which is primarily produced by the testes. In female adrenal glands, androgens may contribute to the sex drive and other sexual behavior. Female androgens may also be converted into the hormone estrogen by other body tissues. This transformation is significant when ovarian estrogen diminishes during menopause. Adrenal androgens also contribute to growth spurts occurring during puberty.[34,35]

ANABOLIC STEROIDS

As we have seen, naturally occurring hormones or steroids in the body can generate very positive side effects demanded in specific situations, including balance of blood volume, increasing heart rate, conservation of fluids, to name just a few. However, when the side effects become the goal, and artificial means, such as anabolic steroids, are used to enhance these objectives of physical performance, negative effects may occur.[41]

Muscle-growing or "anabolic" steroids, also produce male sexual characteristics (androgens) to some degree. The difference between the many anabolic compounds is based upon the ratio of androgenic to anabolic results.[11,23,27]

In 1939, steroids were believed to improve physical performance,[33] and before WWII, they were administered to further healing and hasten recovery. Observers noticed that the moods of steroid users varied quickly. During the war, rumors circulated widely of German soldiers consuming steroids to boost their strength and hostility. In the 1960s, steroids were medically prescribed to increase strength, vigor, appetite, and weight. Adult women, young women, children and preschoolers were observed for any evidence of hirsutism, acne or voice change.[33] (Table 2)

Today, athletes use steroids to enhance their lean body mass, increase strength, heighten aggressiveness and reduce recovery time between workouts. Limited evidence is available to support these practices, but medical ethics has prohibited exhaustive testing of steroids in controlled studies, because the dosages involved are considered dangerous.

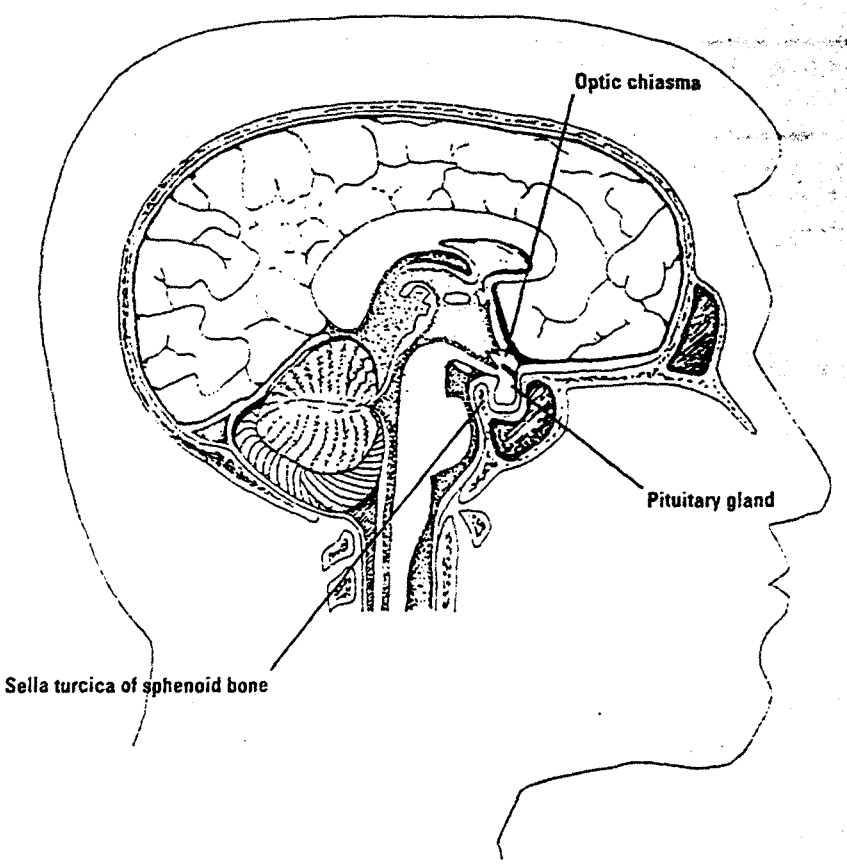

FIGURE 4—Anterior and posterior pituitary glands lie on a portion of the sphenoid bone.

Three distinct types of steroid use are practiced: stacking, cycling and pyramiding.[33] Stacking involves the simultaneous use of several different steroids to optimize the muscle growth effects and reduce the secondary sexual characteristics. Cycling describes a repetitive sequence of drugs alternately taken over a period of six to 12 weeks. Theoretically, cycling prevents the user from developing a tolerance to steroids. Pyramiding involves taking low doses of the drugs and increasing the

amounts for several weeks, then decreasing the dosage to zero before competition. Often, steroid abusers combine all three approaches.

Multiple surveys indicate approximately 7 percent of high school males and 1 percent of high school females use steroids. When the National Collegiate Athletic Association announced a drug testing program, steroids were detected in only about 1 percent of the athletes. However, when the International Olympic Committee

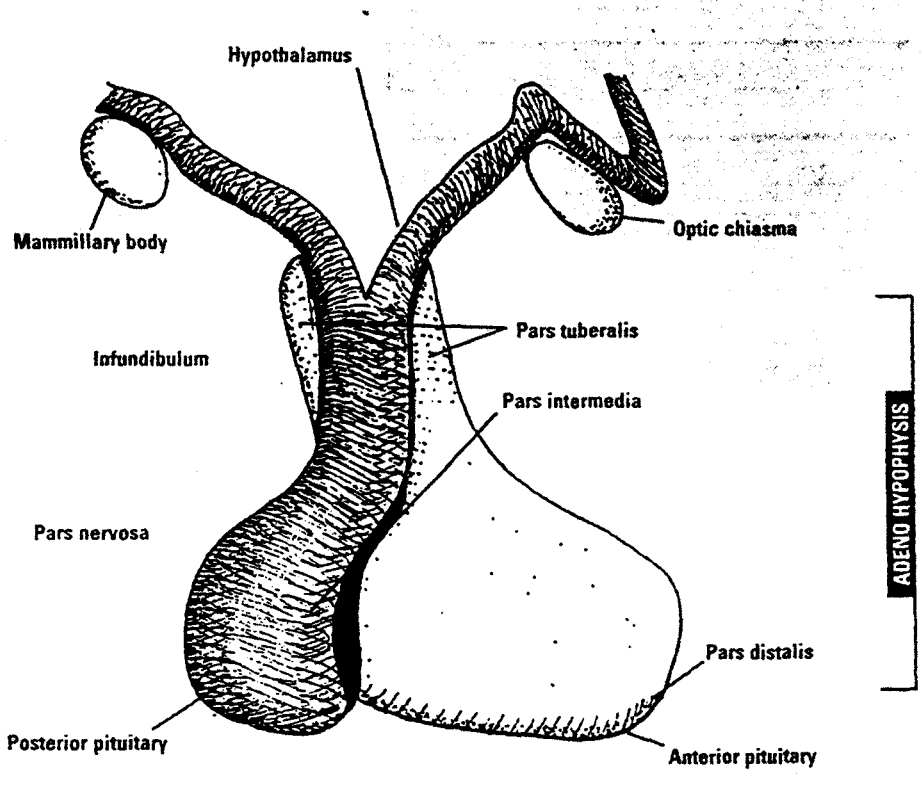

FIGURE 5—Anterior and posterior pituitary glands.

administered a surprise test for steroids, the results showed that 50 percent of the athletes tested positive for steroids.[24,33,34]

How steroids are metabolized

Approximately 5 percent of testosterone originates in the adrenal glands and the remainder is synthesized in the testes. Acetate stored in the testes produces cholesterol. In turn, this cholesterol synthesizes testosterone. In the mitochondria, the cholesterol changes into pregnenolone, and it moves to the endoplasmic reticulum where a three-step process results in testosterone.[27] Once testosterone is produced, it immediately circulates in the bloodstream. Approximately half attaches to a glycoprotein, produced in the liver, the sex-hormone-binding globulin (SHBG), and the remainder loosely binds to albumin.[33]

When administered orally, nearly half of the testosterone will be metabolized by the liver on the first pass.[33] Consequently, very large doses are required to generate any therapeutic effect. Approximately 90 percent of a dose of testosterone will be excreted in the urine as the glucuronic or sulfuric acid conjugates.[33]

Legitimate considerations for androgens involve testicular failure and metastic breast cancer with bone involvement. Anabolic steroids, such as Winstrol®, are prescribed only for hereditary angioedema.[1,2,4] Substances that demonstrate both androgenic and anabolic results are also indicated for treatment of deficient red cell production, such as aplastic anemia and myelofibrosis.[33]

Banned Steroids

In 1990, the Anabolic Steroids Control Act regulating the control of anabolic steroids was passed and created an increase in the importation of illegal substances. The depressant, gamma hydroxybutyric acid (GHB), became popular in the early 1990s when bodybuilders believed that it would promote the release of growth hormone. While

the average dose is only a few grams, large quantities can cause nausea, vertigo, seizures and respiratory depression.[33]

Steroids can be taken both orally and by injection, and serious athletes favor injection. However, while they demonstrate the most dramatic effects, they also are responsible for the most severe side effects, such as liver cancer (hepatic tumors and jaundice), cardiovascular disease (hypercholesterolemia, arrhythmias, stroke and cardiomyopathy), psychological (depression) and sexual (sterility). Common steroids, including prednisone and dexamethasone are available in oral forms and as topic creams and lotions for psorasis, allergic reactions and skin disease. The most popular drugs are testosterone (not a steroid) and human growth hormone.[39,40,41] (Table 3)

TABLE 2 SYMPTOMS OF STEROID ABUSE

Muscular hypertrophy
Decreased pituitary and adrenal function
Increased susceptibility to infection
Peptic ulcer disease
Psychological disturbances including suicidal tendencies
Osteoporosis
Pre-pubertal penile enlargement
Post-pubertal testicular atrophy
Oligospermia
Impotence
Gynocomastia
Deepening of the voice in women
Hirsutism and male pattern baldness in women
Acne
Premature closure of epiphyseal plates
Sodium and potassium imbalances
Decrease in glucose tolerance
Increase in LDL and decrease in HDL

TABLE 3 COMMERCIAL STEROIDS[33]

Steroids administered by injection:

Deca-Durbolin (Nandrolone decanoate)
Depo-Testosterone (Testosterone cypionate)
Delatestryl (Testosterone enanthate)
Durabolin (Nandrolone phenpropionate)
Oreton (Testosterone propionate)
Primobol (Methenolone enanthate)

Oral agents:

Anadrol-50 (Oxymetholone)
Anavar (Oxandrolone)
Dianabol (Methandrostenolone)
Halotestin (Fluoxymesterone)
Maxibolin (Ethylestrenol)
Metandren (Methyltestosterone)
Nibal (Methenolone acetate)
Nilevar (Norethandrolone)
Winstrol (Stanozolol)

Physical Effects

Steroid abuse generates several negative side effects, including liver disease, cardiovascular disease, neurological problems and musculoskeletal disease.[33] In 1952, a direct link between peliosis and anabolic steroid use was made. Small, scattered, cystic blood pools present throughout the liver, and possibly the spleen, lymph nodes and bone marrow are also involved. Although the cause of peliosis is still under investigation, one recent autopsy indicated that one third of the patients who used steroids had peliosis. Seventeen alkylated androgens have been involved in all of the studies of peliosis and steroid cases.[33]

Cholestatic jaundice is also attributed to these same 17 steroids. It is characterized by the accumulation of bile in the canaliculi without showing necrosis or inflammation. Estimates of frequency range from 1 percent to 17 percent. While the evidence of a direct relationship appears firm, the specific proof of causality has not been found.[33]

The occurrence of hepatic tumors and the use of alkylated androgens also demonstrates a relationship. Hepatocellular adenomas appear like normal hepatocytes but androgen-

related adenomas are usually larger and can range in size from a few millimeters to several centimeters in diameter.[33] These adenomas may show irregular nuclei and acini formation but are usually benign and regress when androgen use is discontinued. However, the possibility of adenoma changing to carcinoma remains a possibility.[3,5,6]

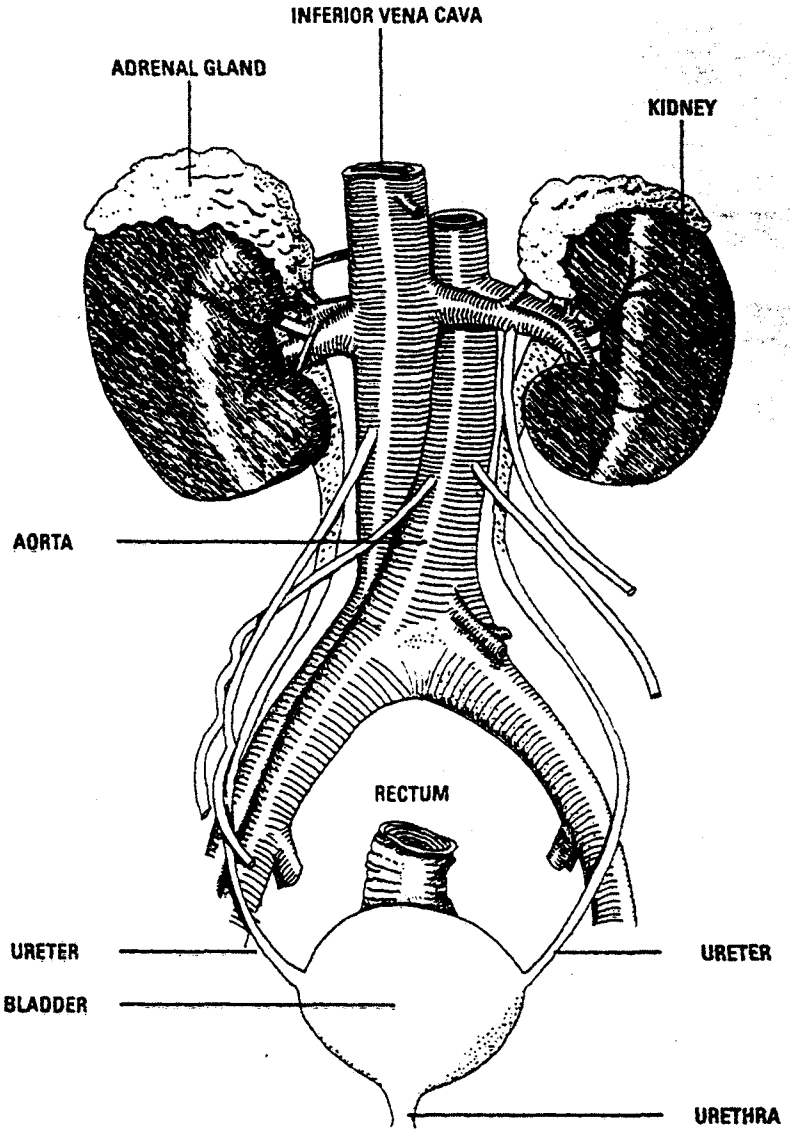

FIGURE 6—Adrenal gland relative to the kidney.

Young steroid users have also experienced myocardial infarction, arrhythmic death and stroke. Reports have described the hearts of athletes as anatomically different, and anabolic androgens directly impact cardiac growth, myocyte metabolism and platelet function. Animal studies indicate that testosterone increases the presence of thromboxane. In turn, clots could result. Myocardial hypertrophy and fibrosis are produced in other animal studies and, again, present strong possibilities for arrhythmic death.[33,38,40,41]

Studies have found instances of infarction when a weightlifter consumed both aspirin and testosterone simultaneously.[36] Another weightlifter who used steroids showed arterial thrombosis.[37]

If steroid abusers are more susceptible to thrombosis and infarction, one possible cause may be a 50 percent decrease in their high-density lipoprotein levels and a corresponding increase in their low-density lipoprotein levels.[33] This change produces an increase in cholesterol (hypercholesterolemia), which can lead to hyperinsulinemia (associated with atherogenesis).[33, 40, 41]

Cardiomyopathy presents another possibility as a cause for sudden death in athletes. Animals in experimental research studies that were given methandrostenolone showed myocyte necrosis, cellular edema and mitochondrial swelling.[38,39] Whether anabolic steroids negate cardiac improvement from endurance training is still being debated. However, research has proven that animals' hearts experience morphologic change after the administration of steroids. These changes, such as modulation of increased collagen production, mitochondrial disruption and a reduction in myocyte capillary supply, are specific to steroid use and vary from the physiologic changes produced by exercise.[33]

If similar changes occur in human hearts, then some deaths attributed to cardiac arrest could be explained. In one case report, a 21-year old weightlifter who had a history of steroid abuse (nandrolone and testos-

terone) died unexpectedly. Results showed renal hypertrophy and hepatosplenomegally and biventricular hypertrophy with chamber dilation. The heart weighed 530 grams but the valves and coronary arteries were within normal ranges. Extensive fibrosis was evident in the subendocardium and the central parts of the left ventricle and intraventricular septum. A particular area of fibrosis exceeded more than 8 cm.[40,41]

Such physical conditions may be caused by muscle fiber hypertrophy that is not accompanied by the necessary increases in the blood supply. Ultimately, small infarctions may result. Fibrosis occurs when these infarctions heal. Other physiologic causes may be identified eventually. However, fibrotic material has conduction properties unlike normal muscle and fibrotic tissue may be a strategic factor involved in cardiac arrhythmias.[33]

Steroid-caused psychiatric disorders are frequently observed and have been used as a defense in murder trials. In one study of 41 steroid abusers, 22 percent showed affective disorders (aggressive behavior and depression) and 12 percent experienced psychosis. In other instances, men taking steroids committed violent crimes, including murder, and returned to their normal personalities after cessation. Domestic abuse has also been attributed to the use of steroids.[33]

Controlled studies have proven a direct correlation between mood disorders and steroid use. In one research study, two groups took high and low doses of methyltestosterone.[33] Participants involved in the high dosage study demonstrated mood changes including euphoria, irritability, mood swings and confusion. In another research study, steroid-abusing athletes and non-steroid using participants were compared for physical and psychiatric data. The steroid-abusing athletes showed more frequent gynecomastia, decreased mean testicular strength, and higher cholesterol. In addition, a high percentage of the steroid users demonstrated evidence of mood disorders, including mania, hypomania or major depression.[33]

There is little evidence beyond animal studies to relate steroid abuse to musculoskeletal disease. Animals conditioned to exercise that have been administered anabolic steroids have a reduced number of capillaries per muscle fiber while the amount of fatty and connective tissue in their muscles has increased.[34] The hypertrophied muscles will not have an efficient exchange of respiratory gases and eventually patchy fiber necrosis could result.[41]

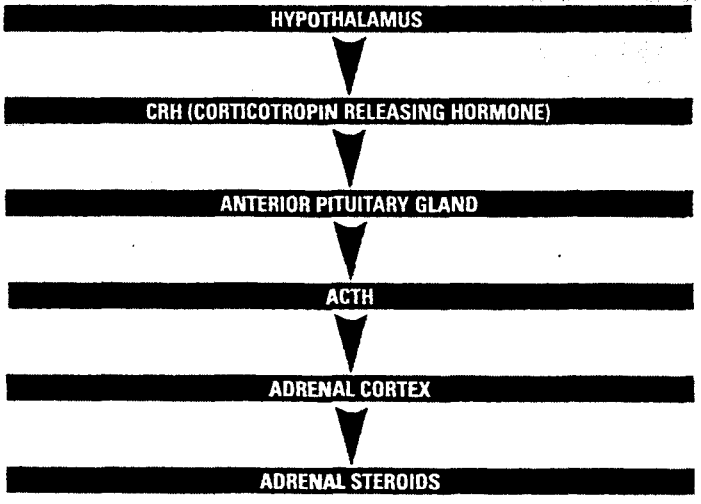

FIGURE 7—Pathway of adrenocorticotropic hormone (ACTH)

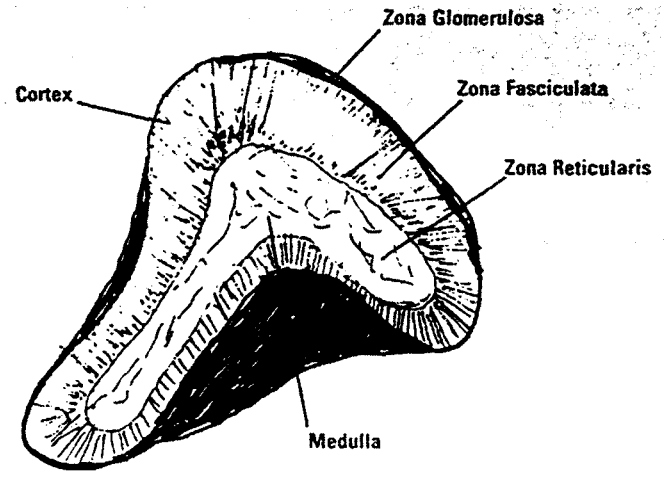

FIGURE 8—Adrenal cortex: the three zones.

CONCLUSION

Body builders and athletes who use high doses of steroids experience difficulty with any type of surgical repair for injuries. Surgery may need to be delayed as much as six to seven weeks to allow the patient to metabolize the synthetic steroids and allow a return of the body's natural production of

steroid hormones. Otherwise, a fatal risk of adrenal suppression during surgery is a possible risk.

It is vital to educate all levels of the population regarding the harmful consequences of steroid abuse. Additional research studies need to be initiated, and standardized testing for the presence of steroids must be created. A discussion regarding the priorities of health versus physical prowess and personal attributes would be beneficial, especially to children and young adults. ⚠

ABOUT THE AUTHORS

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