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Historical Article

A BRIEF HISTORY OF TESTOSTERONE

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ABSTRACT

Purpose: We explore the history of testosterone in the context of medical and scientific developments.

Materials and Methods: A review of the scientific and historical literature was conducted.

Results: The origins and effects of testosterone have been recognized throughout the history of humankind. Hunter performed testicular transplantation experiments in 1767 while studying tissue transplantation techniques, and almost a century later Berthold linked the physiological and behavioral changes of castration to a substance secreted by the testes. Brown-Séquard gave birth to the field of organotherapy in 1889 when he announced that his auto-injection of testicular extracts resulted in rejuvenated physical and mental abilities. Steinach and Niehans expanded upon Brown-Séquard's work with rejuvenation treatments involving vasoligation, tissue grafts and cellular injections. In 1935 David et al isolated the critical ingredient in organotherapeutic treatments, testosterone.

Conclusions: The effects of the powerful hormone testosterone continue to inspire research and controversy 65 years later.

KEY WORDS: testosterone, hormones, testis, brown-sequard syndrome

ANCIENT ENDOCRINOLOGY

The circumstances whereby a neolithic farmer in Asia Minor discovered that castration of animals improved their domestication will never be known but the effects of testosterone and its primary source have been crystal clear for at least 6,000 years. As classical thinkers, including Aristotle, Hippocrates, Lucretius, Celsus and Galen, tried to establish how things worked in health and disease, a humoral basis of biological function must have seemed logical and realistic. The western mind constructed a model of 4 humors in perfect balance and the eastern mind favored a yin and yang paradigm, seeking some unifying hypothesis to inform theory. The sources of imbalance in the humors, or of yin and yang, were related variously to the stars, moon, weather, diet, mood or injury. These ideas largely comprised much of the conceptual basis of medical practice during several millennia until only recently. A specific organ based humoral excess, as recognized by that neolithic farmer, fit nicely into the humoral paradigm. After castration all sorts of other manipulations were brought to bear on perceived humoral disproportions and imbalances. Diet, purging, change of climate and bleeding held powerful positions in medical practice well into the 19th century. However, by that time the conceptual basis of medicine was broadening with the germ theory, physiology and organ basis of pathology.

19TH CENTURY FORAYS

John Hunter (1728–1793) performed deliberate testicular transplantation in 1767, transferring the testis of a cock into the abdominal cavity of a hen.[1] The testis adhered to the intestine or peritoneum but produced no noticeable systemic change in the recipient. However, Hunter, was more interested in the techniques of tissue transplantation than the effects. He did not publish any findings, and evidence of the experiment exists only in notes taken at his lectures.[2]

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In 1849 Arnold Berthold (1801–1863) had the advantages of 19th century science to link the physiological and behavioral changes of castration to a substance secreted by the testes.[3] In roosters castration routinely produced regression of the comb and wattle. Returning the testes of castrated roosters to the abdominal cavity, Berthold found that the characteristic regression did not occur. Since the severed testicles were no longer connected to nerves, he concluded that the testes must affect behavioral and sexual characteristics by secreting a substance into the bloodstream.

Charles Edouard Brown-Séquard (1817–1894), the son of a Philadelphia seaman and a woman of Mauritian-French descent, investigated endocrine pathology for several decades (fig. 1). His 1856 study on the effects of extirpation of the adrenal glands in animals was a milestone.[4] He became convinced that in addition to the testes, the thyroid, adrenal, pancreas, liver, spleen and kidneys contained secretions that could be useful in treating disease.[5] Brown-Séquard further piqued mainstream scientific interest in the chemical contents of the testes with his famous auto-experimentation. On June 1, 1889, before the Sociète de Biologie in Paris, Brown-Séquard reported that he had increased his physical strength, mental abilities and appetite by self-injection with an extract derived from the testicles of dogs and guinea pigs.[6] Although never substantiated, this claim prompted researchers around the world to pursue the new field of organotherapy, injecting testicular derivatives and transplanting human or animal testicles into patients to treat epilepsy, tuberculosis, diabetes, paralysis, gangrene, anemia, arteriosclerosis, influenza, Addison's disease, hysteria and migraine.[7] By the end of 1889 more than 12,000 physicians were administering Brown-Séquard's fluid, and manufacturing chemists were making fortunes selling the new "Elixir of Life."[8,9] In the United States in particular physicians uneducated in the techniques and inherent risks of animal injections exploited the public fervor, putting many patients at risk for infection and inflammation.[10]

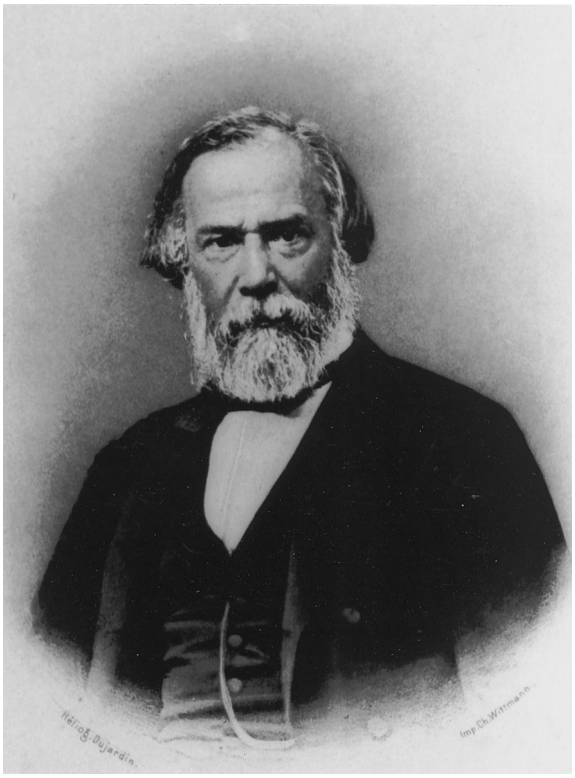

FIG. 1. Charles Edouard Brown-Séquard's auto-injection of testicular extracts led to development of organotherapy. Photogravure by Heliog Dujardin.

HORMONE—A 20TH CENTURY NEOLOGISM

In 1902 William Bayliss (1860–1924) and Ernest Starling (1866–1927), professors from the Department of Physiology at University College in London, recovered a unique substance from an extract of duodenal mucosa.[11] When injected into the bloodstream this substance, which they called secretin, stimulated the secretion of water and bicarbonate by a denervated pancreas. Like Berthold, Bayliss and Starling suggested that chemical secretion rather than nervous control was responsible for the physiological occurrences they observed. Furthermore, Bayliss and Starling postulated that blood borne messengers with targets far from the tissues of origin might regulate many other functions. These substances were ambiguously referred to as "chemical messengers" until William B. Hardy (1864–1934), a Cambridge physiologist, proposed the name hormone during a visit to Bayliss and Starling's laboratory. Hardy derived the term from a Greek word meaning "I arouse to activity," in the sense of "setting something in motion."[12,13] Starling used the word hormone for the first time on June 20, 1905 while giving a Croonian Lecture at the Royal College of Physicians of London.[14] The term made its first printed appearance on August 5, 1905 when Starling's address was published in the Lancet.[15]

REJUVENATION IN PRACTICE

Following in the footsteps of Brown-Séquard, Viennese physiologist Eugen Steinach (1861–1944) studied the rejuvenating effects of vasoligation in older animals. In 1920 Steinach concluded that unilateral vasoligation of the ductus deferens produced an increased hormonal production after cessation of the secretory output of the gonads. His "autoplastic" treatment for "middle-aged, listless individuals" became a popular surgical procedure during the next 2 decades. Patients who underwent the "Steinach operation" included Sigmund Freud, and Irish poet and Nobel prize winner William Butler Yeats. Steinach also grafted testicular tissue between the peritoneal muscles and claimed similar results.[16,17]

A Swiss genitourinary surgeon, Paul Niehans (1882–1971), claimed to have performed more than 50,000 "cellular therapy" treatments. Niehans envisioned the replacement of organ transplantation by the injection of viable cells, and he built this concept into a comprehensive system of treatment. Under functioning organs were treated with cells of the same organ, and cells of the antagonistic organ were injected in cases of over function. Niehans' 1960 book *Introduction to Cellular Therapy* describes this technique as "a method of treating the whole organism on a biological basis, capable of revitalizing the human organism with trillions of cells by bringing to it those embryonic or young cells which it needs."[18] Although he worked with a wide variety of endocrine preparations, much of Niehans' work focused on testicular secretions. He contended that the injection of testicular cells increased the long-term excretion of testosterone derivatives. His patients included Pope Pius XII, Bernard Baruch and Aristotle Onassis.[19]

ISOLATION OF TESTOSTERONE

The pharmaceutical industry was anxious to capitalize on the popularity of organotherapy despite its dubious effectiveness. Competition resulted in a race among 3 research teams for the isolation of the testicular hormone. Adolf Butenandt, a chemistry student from the University of Marburg with a doctorate from Göttingen, influenced by the work of his professor Aor Windaus (1876–1959) on cholesterol, began to explore the sex hormones. Windaus, professor of chemistry at Göttingen, received the 1928 Nobel prize in chemistry for his steroid and vitamin work. Butenandt isolated the first pure sex hormone, estrone, in 1929 from the urine of pregnant women. He then isolated 15 mg. of a pure substance from an immense quantity of policemen urine, variously reported as 15,000[20] to 25,000[21,22] l. Butenandt identified this product as androsterone (andro = male, ster = sterol, one = ketone),[23] and presented its discovery at a Hamburg chemical meeting on October 23, 1931. His ideas for the structure of androsterone were confirmed in 1934 when Leopold Ruzicka (1887–1976), a chemist in Zurich, synthesized the hormone.

Testes proved to contain a more powerful androgenic factor. In 1935 Kàroly Gyula David, E. Dingemanse, J. Freud and Ernst Laqueur, backed by the Organon Company in Oss, The Netherlands, published the now classic paper, "On Crystalline Male Hormone from Testicles (Testosterone)," coining a name for the newly identified hormone (testo = testes, ster = sterol, one = ketone).[24] The synthesis of testosterone came later that year when the journal *Zeitschrift fuer Physiologische Chemie* received "A Method for Preparing Testosterone from Cholesterol" by Butenandt and G. Hanish, funded by the Schering Corporation in Berlin. Just 1 week after Butenandt's article appeared, *Helvetica Chimica Acta* published "On the Artificial Preparation of the Testicular Hormone Testosterone (Andro-sten-3-one-17-ol)" by Ruzicka and A. Wettstein,[25] and the researchers applied for a patent. Ruzicka and Butenandt were offered the 1939 Nobel prize for chemistry for their work but Butenandt was forced by the Nazi government to decline the honor.[20]

TESTOSTERONE TODAY

Biologically synthesized testosterone is produced in the Leydig cells of the testes, adrenal glands and other peripheral sites. A series of enzymes convert the side chain at C-17 of the cholesterol precursor to a hydroxyl group, transfer a double bond from C-6 to C-4 and oxidize the hydroxyl group at C-3 to a carbonyl group (fig. 2).[26] Secretion is controlled by a negative feedback mechanism involving luteinizing hormone (LH) and follicle-stimulating hormone (FSH), tropic hormones synthesized by the anterior pituitary gland. Like

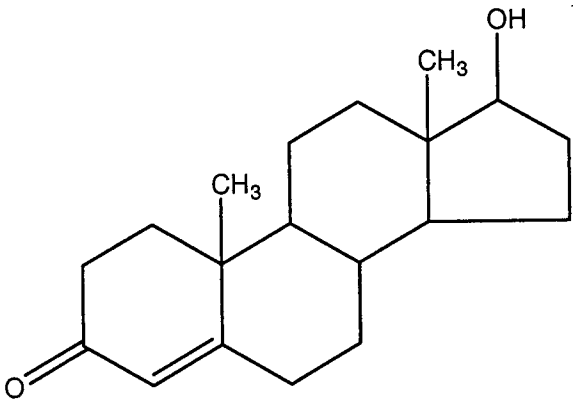

FIG. 2. Molecular structure of testosterone, steroid hormone, includes lipid soluble cholesterol nucleus and polar hydroxyl side chain.

all steroid hormones, testosterone stimulates the synthesis of specific proteins by crossing the cell membrane and binding with a receptor in the nucleus, activating particular genes. Testosterone production begins early in the development of the human fetus, and determines sexual differentiation during an early "sensitive period" in month 3 or 4 of pregnancy.[27]

Early in the 20th century some researchers supported a hormonal theory of sexuality, which supposed that the ratio of male-to-female sex hormones determined human sexual preference. Testosterone treatments were frequently prescribed as therapy for male homosexuals, and in the United States at least 11 homosexual men received transplants of testicular tissue extracted from heterosexual men. However, the ability of hormones to alter sexual preference was never scientifically established.[28] Attempts to correlate testosterone levels and aggression have been made by studying the biochemistry of criminals. Although extremely high testosterone levels correspond to increased aggressive behavior, social and educational factors correlate far more strongly with delinquent behavior.[29] Testosterone treatments have been used to treat certain metastatic breast tumors in women, despite virilizing side effects. Body builders epicentered on the west coast experimented with testosterone supplements in the 1940s and 1950s, spawning the black market that supplies drugs to today's estimated 1 million steroid abusers in the United States.[7]

In recent years the influence of testosterone on physical well-being has once again become a focus of research attention. In particular, the safety and effectiveness of testosterone therapy in treating erectile dysfunction are subjects of controversy. For patients with castrate or near castrate testosterone levels, hormone replacement has been shown to increase libido, improve erectile function and maintain secondary sexual characteristics. However, patients with erectile dysfunction and normal testosterone levels or mild hypotestosteronemia have not shown any consistent improvement in erectile function as a result of testosterone therapy. Although testosterone replacement recipients show significant increases in sexual interest, arousal, frequency of sex acts and nocturnal erections, erectile function may not correlate strongly with testosterone, particularly in men with near normal testosterone levels. Nonetheless, testosterone treatment is widely used to treat erectile dysfunction.[30]

CONCLUSIONS

Although the name testosterone is only 65 years old, the hormone that it identifies has been a focus of scientific interest for almost 150 years and its distinct effects have been obvious throughout the history of mankind. Its influence on physical and sexual development and its potentially therapeutic properties continue to inspire new research and controversy.

REFERENCES

1. Schultheiss, D., Bloom, D. A., Wefer, J. et al: Tissue engineering from Adam to the zygote: historical reflections. World J Urol, **18:** 84, 2000
2. Setchell, B. P.: The testis and tissue transplantation: historical aspects. J Reprod Immunol, **18:** 1, 1990
3. Berthold, A.: Transplantation der Hoden. Arch Anat Physiol Wissensch, 42, 1849
4. Jay, V.: A portrait in history: the extraordinary international career of Dr. Brown-Séquard. Arch Pathol Lab Med, **123:** 662, 1999
5. Haas, L. F.: Charles Edouard Brown-Séquard (1818–94). J Neurol Neurosurg Psychiatry, **64:** 89, 1998
6. Brown-Séquard, C. E.: The effects produced on man by subcutaneous injections of liquid obtained from the testicles of animals. Lancet, **2:** 105, 1889
7. Hoberman, J. M. and Yesalis, C. E.: The history of synthetic testosterone. Sci Am, **272:** 76, 1995
8. Tattersall, R. B.: Charles-Edouard Brown-Séquard: double-hyphenated neurologist and forgotten father of endocrinology. Diabet Med, **11:** 728, 1994
9. Hansen, B.: New images of a new medicine: visual evidence for the widespread popularity of therapeutic discoveries in America after 1885. Bull Hist Med, **73:** 629, 1999
10. Borrell, M.: Brown-Séquard's organotherapy and its appearance in America at the end of the nineteenth century. Bull Hist Med, **50:** 309, 1976
11. Fleming, P. R.: The other Bloomsbury set: Bayliss, Starling and Thomas Lewis. Int J Microcirc Clin Exp, **14:** 91, 1994
12. Sawin, C. T.: Hormonology. N Engl J Med, **280:** 388, 1969
13. Peart, S. W.: Humors and hormones. Harvey Lect, **73:** 259, 1979
14. Lechago, J.: The endocrine cells of the digestive tract: general concept and historic perspective. Am J Surg Pathol, **11:** 63, 1987
15. Starling, E. H.: The Croonian Lectures on the correlation of the functions of the body. Lancet, **2:** 339, 1905
16. Dixon, B.: Medicine and the media: tissue therapy. Br J Hosp Med, **22:** 512, 1979
17. Schultheiss, D., Denil, J. and Jonas, U.: Rejuvenation in the early 20th century. Andrologia, **29:** 351, 1997
18. Niehans, P.: Introduction to Cellular Therapy. New York: Pageant, p. 9, 1960
19. Billingham, R. E. and Neaves, W. B.: Paratransplantation and tissue therapy. Perspect Biol Med, **22:** 320, 1979
20. Daintith, J. and Gjertsen, D. *Oxford Dictionary of Scientists.* Oxford: Oxford University Press, p. 468, 1999
21. Kochakian, C. D.: History, chemistry and pharmacodynamics of anabolic-androgenic steroids. Wien Med Wochenschr, **143:** 359, 1993
22. Tausk, M.: Androgens and anabolic steroids. In: *Discoveries in Pharmacology. Haemodynamics, Hormones, and Inflammation.* Edited by M. J. Parnham and J. Bruinvels. Amsterdam: Elsevier, vol. 2, pp. 307–319, 1984
23. Butenandt, A. and Hanisch, G.: Uber Testosterone. Umwandlung des Dehydro-Androsterons in Androstendiol und Testosteron; ein Weg zur Darstellung des Testosterons aus Cholestrin. Hoppe Seylers Z Physiol Chem, **237:** 89, 1935
24. David, K., Dingemanse, E., Freud, J. et al: Uber krystallinisches mannliches Hormon aus Hoden (Testosteron) wirksamer als aus harn oder aus Cholesterin bereitetes Androsteron. Hoppe Seylers Z Physiol Chem, **233:** 281, 1935
25. Ruzicka, L. and Wettstein, A.: Sexualhormone VII. Uber die kunstliche Herstellung des Testikelhormons. Testosteron (Androsten-3-on-17-ol.). Helv Chim Acta, **18:** 1264, 1935
26. Voet, D. and Voet, J. G.: *Biochemistry.* New York: John Wiley & Sons Inc., p. 703, 1995
27. Kalat, J. W.: *Biological Psychology.* New York: Brooks/Cole, pp. 298–306, 1998
28. Oudshoorn, N.: *Beyond the Natural Body: An Archaeology of Sex Hormones.* London: Routledge, pp. 56–59, 1994
29. Nassi, A. J. and Abramowitz, S. I.: From phrenology to psychosurgery and back again: biological studies of criminality. Am J Orthopsychiatry, **46:** 591, 1976
30. Loughlin, K. R., Morales, A. and Carson, C. C.: Point and counterpoint: should testosterone be used to treat sexual dysfunction? Contemp Urol, **12:** 12, 2000