

Demonstrated Ability of Penile Erection in Castrate Men with Markedly Low Titers of Urinary Androgens.

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Sexual abilities have been described in castrate men (Rowe and Lawrence,¹ Lange,² McCullagh and Renshaw,³ Kolle⁴), but the possibility of some degree of stimulation by androgens from extragonadal sources has remained largely an undetermined factor. After removal of both testes men continue to excrete appreciable quantities of urinary androgens (Gallagher and associates,⁵ Callow and co-workers,⁶ Hamilton and colleagues;⁷ see summary of literature by last authors), and in a rare case the amount excreted is within the range observed in normal men (Callow and co-workers⁶). There is evidence that an androgenic substance found in the urine of normal and castrate men, dehydroisandrosterone, may be derived from secretions of the adrenal glands (Callow,⁸ Fraser and associates⁹).

Feinier and Rothman¹⁰ attempted to define the quantity of urinary androgens in a 53-year-old castrate who claimed erectile

ability, but the description of their findings seems confusing. They reported an entire absence of androgens in the urine, although, as indicated above, some quantity of these substances is found almost invariably with the use of adequate methods of extraction and assay. Description of their technic was omitted. They commented that neither testosterone nor androsterone was present in extracts obtained apparently from 3,000 cc of urine, an odd statement since testosterone has never been found in urine. It would have been difficult to identify specific compounds present in this small quantity of urine, and since the extract appears to have been used for assay in capons, it is doubtful that the authors intended to imply that the isolation of compounds was attempted.

The present communication pertains to 2 men castrated for 13 and 18 years, respectively, who demonstrated during repeated examinations a pronounced degree of erectile ability despite the absence of any considerable stimulation by androgens from extragonadal sources, as indicated by low titers of urinary androgens and supranormal values for urinary gonadotropins.

This marked capacity for penile erection distinguished these men from 6 other members of a group of 8 eunuchs all of whom have been studied during periods of one to 5 years with repeated physical examinations and bioassay of urinary androgens, estrogens, and gonadotropins. In view of the difficulties encountered in evaluating the sexual status in castrate men, especially with regard to the reliability of the history obtained from the patient and the interplay of psychogenic and endocrine factors, daily records have been kept by each person, tabulating the number, duration and completeness of erections, and the performance of intercourse. These records were

¹ Rowe, A., and Lawrence, C., *Endocrinology*, 1928, **12**, 591.

² Lange, L., *Die Folgen der Entmannung Erwachsener*, pp. 178, George Thieme, Leipzig, 1934.

³ McCullagh, E., and Renshaw, J., *J. A. M. A.*, 1934, **103**, 1140.

⁴ Kolle, *J. A. M. A.*, 1935, **105**, 1051.

⁵ Gallagher, T., Peterson, D., Dorfman, R., Kenyon, A., and Koch, F., *J. Clin. Invest.*, 1937, **16**, 695.

⁶ Callow, N., Callow, R., and Emmens, C., *J. Endocrinol.*, 1940, **2**, 88.

⁷ Hamilton, J., Dorfman, R., and Hubert, G., *J. Lab. and Clin. Med.*, 1942, **27**, 917.

⁸ Callow, R. K., *Proc. Roy. Soc. Med.*, 1938, **31**, 841.

⁹ Fraser, R., Forbes, A., Albright, F., Sulko-witch, H., and Reifenshtein, E., Jr., *J. Clin. Endocrinology*, 1941, **1**, 234.

¹⁰ Feinier, L., and Rothmann, T., *J. A. M. A.*, 1939, **113**, 2144.

collected weekly and where possible were compared with statements obtained from their partners in intercourse.

The methods and results of bioassays of urinary androgens, estrogens, and gonadotropins, which were made in collaboration with Drs. R. I. Dorfman, H. R. Catchpole, and G. R. Hubert, are described in detail elsewhere (Hamilton, Dorfman, and Hubert;¹¹ Catchpole, Hamilton, and Hubert¹¹). During intervals in which urine was collected the patients were ambulatory and in good health. Determinations of androgenic and estrogenic substances were made upon pooled samples of urine each of which represented collections made for 4 consecutive 24-hour periods and preserved with toluene. Within 2 weeks after collection the specimens were extracted with benzene in a continuous extractor according to the method of Gallagher and associates.¹² The growth of combs in day-old chicks (Dorfman and Greulich¹²) was used in assays of androgenic activity, which are expressed in international units (I.U.), the unitage of activity being that evoked by 0.1 mg of androsterone. A minimum of 15 and usually 20 animals was used for each assay. Determinations are held to be accurate within $\pm 25\%$.

The alkali soluble fraction of the urinary extract was assayed for estrogenic activity in adult spayed female mice. The results are expressed in international units (I.U.), one unit being equal to the reaction elicited by 0.1 μ g of estrone. The accuracy of the method is considered to be $\pm 50\%$.

Values for gonadotropic substances were determined separately in samples of urine each collected over a period of 24 hours. One cc of toluene was added to each specimen which was kept chilled until extracted within 24 to 48 hours by the method described by Freed and Hechter.¹³ Bioassay was performed separately on each daily sample,

utilizing changes in the uterine weight of 21- to 23-day-old mice in accordance with Catchpole's modification¹⁴ of the technic described by Levin and Tyndale.¹⁵ The values are defined in terms of a mouse unit (M.U.), which is that amount of substance that under standard conditions doubles the ratio of uterine weight/body weight in 21- to 23-day-old female mice of our stock.

Abstracts from the case histories are as follows:

Case one was a 43-year-old man who, when 25 years of age, had been castrated surgically because of suspected cancer. He stated that penile erections had occurred in the years prior to castration and had continued to appear throughout the years subsequent to orchidectomy.

The patient was a man of medium build with pale, finely wrinkled skin and a tendency to obesity. Deposits of fat were evident over the mammæ, trochanters, pubis, and lower abdomen. Muscular prominences and ridges were not obvious, and the contour of the face, trunk, and limbs was smooth. Hair over the body was scant, consisting of a few silky strands in the axilla, and isolated hairs of the terminal type on the chin and on the inner side of the lower and upper leg. Terminal hairs about an inch in length were distributed sparsely over the pubis.

The external genitalia had not regressed to an eunuchoid state, but the scrotum and the glans and shaft of the penis were poorly distinguished by ruddiness or pigmentation from skin of the thigh. The penis measured 9 cm in length when flaccid. The scrotum had only slight rugosity and when cooled did not become deeply furrowed. Upon rectal palpation the prostate was felt to be small and non-edematous. No secretion was obtained upon massage of the prostate. Urethroscopy and urological examination revealed no condition that seemed to be related to erectile ability of the penis.

¹¹ Catchpole, H., Hamilton, J., and Hubert, G. *J. Clin. Endocrinology*, 1942, **2**, 181.

¹² Dorfman, R., and Greulich, W., *Yale J. Biol. and Med.*, 1937, **10**, 80.

¹³ Freed, S., and Hechter, O., *Endocrinology*, 1936, **20**, 396.

¹⁴ Catchpole, H., *Somatic and Endocrine Studies of Puberal and Adolescent Boys*, *Monographs Soc. Res. Child Development*, 1943, **7**, pp. 43-62.

¹⁵ Levin, L., and Tyndale, H., *Endocrinology*, 1937, **21**, 619.

TABLE I.

The titers of urinary hormones of the men described in this article are typically eunuch-like in that the values for androgens and estrogens are subnormal and those for urinary gonadotropins are supranormal.

Subjects (Type and No.)	Citation	Androgens		Estrogens		Gonadotropins	
		No. days tested	Avg (I.U.)	No. days tested	Avg (I.U.)	No. days tested	Avg (M.U.)
Case 1		5	8	4	28	10	130
Case 2		4	11	4	15	10	40
Eunuchs	(2) 16	18+	1.66 and 5.8 (per liter)	18+	30 and 45 (per liter)		
	(2) 7, 11	4	9 and 3	4	11 and 5	10	50 and 60
Normal men	(4) 5	39-45	63-68	39-45	90-120		
	(5) 17					30-120	8, 11, 12, 15 and 25

When the patient stood undressed before examination was begun, erection of the penis occurred until the organ attained an angle of about 80°. The penis did not appear to be flushed during erection and the glans was of a light gray color. The shaft of the penis was firm throughout its length and resistant to strong downward pressure. The erection persisted for slightly more than a minute, then slowly subsided.

During examination at later periods complete erections were observed on several occasions. The patient stated that this phenomenon occurred quite commonly and in some circumstances when he was unaware of external stimulation.

The average daily titers of urinary androgens and estrogens were lower than in normal men, whereas those of urinary gonadotropins were supranormal (Table I). On 2 of the days in which urine was collected for extraction and assay of hormones, erections were observed. The results obtained with routine urinary and blood analyses were not remarkable. On 3 occasions the BMR was -5, -10, and 7.

Case two was a 39-year-old man whose testes and scrotum had been removed surgically after accidental traumatic injury at the age of 26 years. Other than phenomena known to accompany castration (see Ham-

ilton¹⁸), some of which have been described in Case 1, there was little of special interest revealed upon clinical and laboratory examination. The penis was 10 cm in length in a flaccid state. No fluid was obtained with prostatic massage.

Complete penile erection occurred at the first examination upon inspection of a small inguinal hernia and during 2 of a subsequent series of examinations. The erections were maintained for periods of a minute or longer, during which time the skin of the penis remained rather light in color and the glans was a pale gray.

The history related by the patient was in agreement with that obtained separately from his wife to the effect that intercourse had been carried out 2 or 3 times weekly previous to castration and during all 13 years since castration. Intercourse during the next 6 months as tabulated from records kept daily was carried out one to 4 times per week. The sexual interest shown by this patient appeared to be considerable according to the history obtained from the man, his wife, and a third party concerned. The patient claimed that orgasms occurred but that the ejaculate consisted of only about a drop of fluid.

The titers of urinary hormones were in the range typical of castrates (Table I).

In these eunuchs the low values for urinary androgens and estrogens and the supranormal quantities of urinary gonadotropins are evidence that the state of testicular insufficiency

¹⁶ Kenyon, A., Gallagher, T., Peterson, D., Dorfman, R., and Koeh, F., *J. Clin. Invest.*, 1937, **16**, 705.

¹⁷ Werner, S. C., *J. Clin. Invest.*, 1943, **22**, 395.

¹⁸ Hamilton, J. B., *J. A. M. A.*, 1941, **116**, 1903.

has not been compensated for in a material fashion by androgens derived from extragonadal sources. That the titers of these urinary hormones would reflect such androgenic stimulation as was present, was indicated when at a later date these men received daily intramuscular injections of 20 mg of testosterone propionate in one cc of peanut oil. With this treatment, which appears to provide only a minimal degree of replacement therapy (Hamilton;¹⁸ Catchpole, Hamilton, and Hubert¹¹), the quantities of urinary androgens and estrogens were increased to lie within the range found in normal men (Hamilton, Dorfman, and Hubert⁷) and the amounts of urinary gonadotropins were reduced to normal or subnormal limits (Catchpole, Hamilton, and Hubert¹¹).

Comment. Two men who had been completely castrate for 13 and 18 years, respectively, had a marked capacity for penile erection, as observed during physical examina-

tions and as tabulated in records kept daily for a year. Statements as to the interest and ability in intercourse exhibited by one of these men who was married were corroborated by his wife. Low titers of urinary androgens and clinical and laboratory evidence of testicular insufficiency, including supranormal values for urinary gonadotropins, provide assurance that there was no considerable androgenic secretion derived from extragonadal sources.

It would appear, then, that a marked capacity for penile erection may continue for many years subsequent to castration and that this phenomenon is not the result of stimulation by androgens derived from extragonadal sources because it may occur in individuals with definitely subnormal titers of androgens in the bodily tissues and fluids. It is not suggested that this phenomenon is typical of the majority of castrate men.

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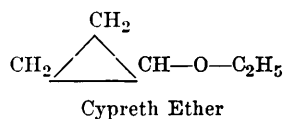
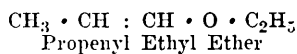
Anesthesia: XI. The Anesthetic Action of Propenyl Ethyl Ether.*

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In former studies¹ the authors showed that cyclopropyl ethyl ether (cypreth ether) was an anesthetic agent in many species of animals. Attempts to induce surgical anesthesia in man with this agent were not satisfactory.² In man, the concentration of the vapors of cypreth ether required to induce anesthesia were irrespirable. It occurred to us to prepare

an isomer of this true hybrid molecule between cyclopropane and ethyl ether.



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¹ Krantz, J. C., Jr., Carr, C. J., Forman, S. E., Evans, W. E., Jr., and Wollenweber, H. L., *J. Pharm. and Exp. Therap.*, 1941, **72**, 233.

² Kilborn, M. G., Forman, S. E., Evans, W. E., Jr., and Krantz, J. C., Jr., *Anesthesiology*, 1942, **3**, 414.

Propenyl ethyl ether is a volatile, colorless liquid, with a characteristic ethereal odor; it boils at 69°C and has a specific gravity of 0.774 at 20°C. At 25°C, 0.5 cc of this ether dissolves in 100 cc of water and the compound is not hydrolyzed at pH 7.4 in a phosphate buffer. Concentrations of the vapors of propenyl ethyl ether sufficient to produce