TREATMENT OF SEXUAL UNDERDEVELOPMENT WITH SYNTHETIC MALE HORMONE SUBSTANCE[1]

JAMES B. HAMILTON[2]
From the Departments of Anatomy and Physiology, Albany Medical College, and Albany Hospital
ALBANY, NEW YORK

This report of a single case is deemed worthwhile because of *1)* the lack of reports of similarly treated cases, *2)* the very limited amount of synthetic male hormone that was available for this investigation, *3)* the extensive study made of this individual before and after treatment, and *4)* the wide bearing of these findings upon endocrine treatment of hypogenitalism, cryptorchidism, impotence, migraine, acne and menopausal symptoms.

History and Examination. The patient was a 27-year-old white male medical student whose chief complaints were headache in right frontal and temporal regions, attacks of malaise, hot flushes, proneness to fatigue and social stigmata due to feminine aspect and high voice. In 1933 the patient received 3 injections of 1 cc. antuitrin-S weekly for a 3-week period, followed by 2 weeks of rest; this was continued for 3 months with but slight alleviation of symptoms. Save for similar menopausal symptoms of flushes and headaches in the mother, the family history was irrelevant. The patient had had measles, influenza complicated by pneumonia, chicken pox and scarlet fever before the age of 15. The organ systems except the endocrine, reproductive, osseous and integumentary were essentially normal.

The general body picture was that of a pre-puberal castrate with a feminine emphasis in the wide hips, genu valgum, girdle distribution of fat, protruding mammae, and retarded development of larynx, genitalia and hair (fig. 1, *A*). The long limb bones were proportionally longer than the other bones. The epiphyseal union was not complete in the ulna or radius. The jaw, facial eminences and digits might be considered to be of a hypopituitary type and in contrast to the condition encountered in acromegaly. Figure 1, *A,* shows the receding jaw, non-prominence of facial eminences, and the long, tapering digits. The proximal metacarpals of the index and second fingers were of a greater length and diameter than those of the other two fingers. Hair was sparsely distributed in the axilla and in a feminine manner on the pubis. There was no hair on the abdomen, chest or face, save on the upper lip which was shaved more from desire than necessity about once every 10 weeks. Large dark circles were seen beneath the eyes. The genitalia (fig. 1, *B*) were somewhat smaller in size and degree of development than those of a small boy of 3 or 4 years of age. The penis was 2.5 cm. long and 1.2 cm. in diameter, with a prepuce not clearly differentiated from the glans. The urethal orifice was exceptionally small. The scrotum was a flat band-like structure without rugae or pen-

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dulousness, its wall thin and not deeply pigmented. The testes and epididymides were not identified with certainty. The patient stated that infrequent erections but not ejaculations had occurred. A prostate could not be identified by rectal palpation save that 2 small pea-sized lumps could be felt beneath a pad of edematous tissue. The mammae were large with light pink nipples and areolae. Only adipose tissue could be palpated.

Roentgenograms of the pituitary disclosed a sella turcica within low normal limits (12 mm.). Repeated assays of the urine for gonadotropic substance gave negative results in the rabbit pregnancy test.

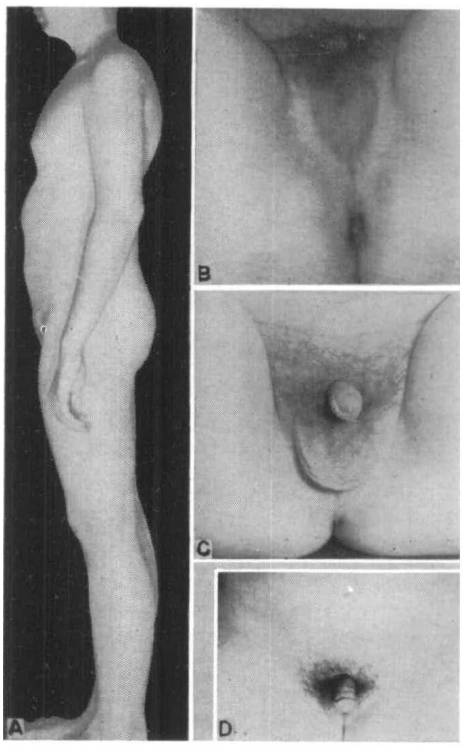

Fig. 1. *A* and *B*, Patient before treatment. Note sexual and laryngeal underdevelopment, gynecomastia. *C* and *D*, Same patient after 3 weeks treatment with male hormone substance, testosterone acetate.

The larynx was shown to be small on laryngoscopic and x-ray examination, indistinguishable in external profile, and lacking in the growth changes produced in the male larynx at puberty. The voice was very high-pitched and of small volume. The nasal mucosa exhibited no congestion, swelling, or secretion in areas which have been shown in monkeys and in humans to be controlled by male hormone substance (1).

The patient was intelligent, industrious, trustworthy, prone to anxiety, emotionally unstable, concerned about and feeling somewhat inferior because of his condition. No feminine traits were discernible. He was engaged to be married.

The basal metabolic rate was —17 and —19. Blood and urine constituents were present in essentially normal amounts. Perhaps noteworthy was the absence of creatinuria. Ten tests made over a period of 3 years gave an average daily level of 1.1 mg.

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Treatment. The patient was given a total of 550 mg. of testosterone acetate[3] in 14 injections, 3 injections per week, for a period of 1 month. Peanut oil was selected as the vehicle, since the type and amount of oil is significant (2).

Injections were subcutaneous and intramuscular, in arm or in buttock. At the end of these injections the patient received oil which, unknown to him, did not contain the potent male hormone substance he had been receiving. When he became thoroughly aware of the absence of response, all injections were stopped for 1.5 months. Injections were begun again 2 times a week, with a smaller dosage of 5 mg. of testosterone propionate in peanut oil, since the propionate compound has been shown to be absorbed more slowly than the acetate (2). After 10 injections of 5 mg. each, the dosage was increased to 20 mg. of testosterone propionate given twice weekly.

RESULTS

First Period of Treatment. The effect of the hormone administration was seen within 60 hours after the first injection, when the patient experienced pronounced penile erections. After 6 days erections occurred repeatedly and continued throughout the month, at times reaching a state of priapism. Despite the small size of the penis the patient felt conspicuous because of the erectile condition. The left side of the scrotum contained a mass in which testis and epididymis were not distinguished. The scrotum appeared to be somewhat thicker and of a darker color, the glans penis more pink.

Within 2 weeks the scrotum became much larger, rugose, pendulous, and more pigmented. The mass in the left side of the scrotum enlarged until a well-formed epididymis could be differentiated from a tiny atrophic testis. The penis increased in both length and diameter. The larynx was congested; the thyroid was felt to be larger.

After 3 weeks the areolar tissue became more darkly pigmented, somewhat rugose and tender to deep pressure. The nipple was more prominent and beneath it appeared a rather firm area. On rectal examination the prostate was felt to be heart-shaped and of moderate thickness. Both testes and epididymides were palpable in the scrotum. Figures 1, *C* and *D* show the increased length and diameter of the penis, and the pendulousness of the scrotum. The urethral opening was also enlarged.

The hot flushes disappeared entirely throughout the period of treatment. One moderately severe migraine attack occurred. The patient was more energetic than usual, self-assured and in higher spirits. There was some question as to a lowering of the pitch of the voice. Small hairs appeared on the chest and in a masculine distribution above the pubis. Periods between shaving of the upper lip were shortened to 2 weeks. The dark circles beneath the eyes became lighter in color.

Period of Withdrawal. Five days following the last injection a series of 4 hot flushes were experienced and the erections became infrequent. By 11 days there was a moderately severe attack of migraine, repeated hot flushes, lassitude, some loss of self-assurance, and some huskiness of the voice. By 16 days an acneform eruption was seen on back and chest, which progressed to include

[3] Testosterone acetate and testosterone propionate (Perandren) were furnished through the courtesy of the Ciba Company.

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the face and neck. Hot flushes and migraine occurred as before treatment. There was some decrease in prostatic, epididymal and scrotal size, but less regression of penile growth. Mammary tenderness persisted and a specimen which was taken for biopsy seemed to resemble female mammary structure in gross characteristics, but in histological examination was seen to contain lacteriferous ducts without alveolar tissue.

The acne gradually disappeared as the period of hormone withdrawal lengthened to 1½ months. The dark circles returned beneath the eyes.

Second Period of Treatment. A smaller dosage of 5 mg. of testosterone propionate was employed twice weekly. The phenomena observed in the first period of treatment were again encountered but in lesser degree. Erections reappeared, hot flushes disappeared; migraine attacks became less severe. Genital growth was resumed. The acne returned at the onset of the injections, but disappeared as the treatment continued. After 10 injections, the dosage was increased to 20 mg. administered twice weekly. Growth became more rapid. The patient reported more energy and self-assurance.

DISCUSSION

The course of this study has permitted *1)* recognition of the effects of synthetic male hormone therapy in man; this patient represented a biologically-controlled subject due to an extreme hypogonadal condition: *2)* differentiation of results due to injected male hormone from those due to bodily-produced male hormone, since *a)* the patient was physiologically castrate, and *b)* the growth changes followed injections, regressed upon cessation of injections and reappeared after resumption of injections: *3)* distinguishing of effects of the injected hormone from mentally-induced reactions, *a)* since when the patient received impotent substance, which he thought was potent, a lack of response appeared and was recognized by the patient, and *b)* by virtue of intelligence and medical training, the patient carefully analyzed and separated these effects as much as possible.

The data concerning the response of this patient is relevant to several clinical conditions which, theoretically at least, can be treated either by anterior pituitary-like substances (gonadotropic material extracted from pregnancy urine, such as antuitrin-S or follutein), or by gonadal substances, which in the male can be testicular extracts or synthetic material. Without a lengthy discussion of the relative merits of gonadotropic and gonadal substances (3), this patient will serve as an example of the results being obtained with synthetic male hormone (gonadal) substances in several of the following conditions, until our cases under study at present can be compared with those treated by pregnancy urine extracts.

Male Hypogonadism. Pregnancy urine extracts and male hormone substances develop secondary sex characteristics, but in regard to spermatogenesis can be expected to do no more than maintain an already existing spermatogenesis. Even such maintenance has been proven only in animals (4, 5, 6). For the induction of sperm production it seems likely that a gametokinetic substance, such as might be obtained from menopausal or castrate urine, would be necessary.

Since presumably the effect of gonadotropic substances on the genitalia (7) is

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only by stimulation of the gonads to produce gonadal material and must, therefore, depend upon a responsive testis, it is interesting to note that the patient reported here had responded but slightly to over 30 injections of 1 cc. antuitrin-S.

Cryptorchidism. Descent of the testes with pregnancy urine extracts has been obtained by many workers, an effect believed by the author (3) to be due to the male hormone produced upon stimulation of the testis by gonadotropic material. The use of anterior pituitary-like substances is subject to the criticism that they depend upon a responsive testis, are but extracts, and may have a wide variety of effects besides that desired. An evaluation of the benefits and limitations of male hormone substances as determined by studies in monkeys and humans has been written (8), along with a partial analysis of the processes incited by male hormone in producing descent of the testis.

Impotence. It is difficult to separate the mental from the physical aspects in incapacities to obtain penile erection. This renders all the more significant the finding in immature animals and in children as young as 18 months that erections have been induced and in some instances approach a condition of priapism following injections of the male hormone substances, testosterone acetate and testosterone propionate (9). Striking, too, are the erections in the present case and the finding (9) that a man, impotent for 8 years, can carry on intercourse after he received injections of male hormone substance, but not after he received injections of the oil vehicle alone—even though he believed the mock injections to be potent. Induction of erections has been reported in 2 hypogonadal cases receiving male hormone extracts (10), and in cryptorchid children receiving pregnancy urine extracts (11) (which presumably stimulate the testis to produce made hormone).

Acne. Some degree of success has been reported in the treatment of acne with gonadotropic (12) and estrogenic (13) material. It is interesting to note that this patient, who had never shown evidence of the presence of male hormone or of acne, did not develop the condition when large amounts were injected in the first period of treatment, but acquired acne in the period following cessation of treatment, when assumedly the male hormone content fell to a fairly low level (hot flushes had appeared). Toward the end of the withdrawal period the acne tended to disappear, but returned when small amounts of male hormone were administered and then disappeared when a higher level of male hormone substance was attained. On this suggestive evidence a small group of boys complaining of severe acne during puberty has been treated with testosterone propionate with disappearance of the acne. A long post-treatment study and more cases are necessary, however, before the value and contraindications of this treatment can be ascertained.

Hot Flushes and Migraine. The prompt disappearance of hot flushes when the patient was under treatment and the equally rapid reappearance upon cessation of treatment may suggest a study of male hormone treatment of menopausal conditions. Extreme caution is urged, however, for male hormone substances have a pronounced masculinizing effect in the female (14), and will inhibit pituitary activity (15) in rodents and menstruation in both monkey and human (8). The results obtained with gonadotropic (16) and estrogenic (17) substances in certain types of migraine plus the alleviation seen in the patient during treatment may suggest male hormone treatment of this condition. In the female, at least, much too little is known about the influence of male substances to risk haphazard use.

Voice. The possibility of lowering of the pitch of the voice is intriguing and in this patient is a vital point, since he feels that fairly authoritative vocal expression would aid him considerably in the contacts incident to the practice of medicine.

Miscellaneous. The changes in the color of the region below the eye are incom-

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plete evidence of control exerted over this region by gonadal hormones and is in agreement with the changes noticeable in some women during various parts of the menstrual cycle. It recalls the facial sexual skin in monkeys.

The mastitis brought to mind the transient mastitis often encountered in boys at the time of puberty.

Mental Changes. Definite relationship of male hormone level to mental attitude is difficult because the patient realized that an attempt was being made to help him, and more important, he realized the progress he was making physically. This knowledge plus the number of other accessory influences make definite correlation precarious. The subject attempted, however, with admirable aloofness and clarity to study the changes in himself and was convinced that he was more energetic, virile and self-assured when under treatment. The increase in these qualities was vouchsafed by associates. The subject complained during cessation of treatment that his attempts to combat recession were futile and he believed that his buoyancy of spirits was not confined to physical betterment. It will be worthwhile to note the results of psychologists and psychiatrists in the use of this material in adolescence and in such patients as male perverts.

Finally, it should be noted that no deleterious effects were observed on the blood or urine constituents of the patient, a fact confirmed by similar tests in other patients receiving testosterone acetate and propionate (8). Nevertheless, the period of treatment in this patient has been short. Further observation and many additional cases must be investigated before generalizations can be made.

SUMMARY

Synthetic male hormone substances were administered to a 27-year old hypogonadal male, 'physiologically castrate' from birth, who provided an excellent subject for evaluation of the effect of these materials. The hypogonadism, cryptorchidism, impotence, hot flushes, migraine, and mental attitude were treated with some degree of success. Brief discussion is given of the relation of these results in this clear-cut case to the subject of male hormone treatment, with especial reference to cryptorchidism, hypogonadism, impotence, menopausal symptoms, migraine and acne. The possible influence of made hormone upon the pitch of the voice, the area of pigmented skin under the eye and the mental attitude is mentioned.

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