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IMPLANTATION OF TESTOSTERONE COMPOUNDS IN CASES OF MALE EUNUCHOIDISM[1]

TREATMENT OF EUNUCHOIDISM

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THE EFFECTIVENESS of an endocrine preparation is measured best by its capacity to restore normal function in a characteristic endocrinopathy caused by its deficiency. Eunuchoidism, or male hypogonadism, is the clinical state in which the primary deficiency resides in the testes, and therefore it represents an ideal clinical condition for testing the effectiveness of an androgenic substance.

The synthesis of testosterone by Butenandt and Hanisch (1) and Ruzicka et al. (2) made available for the first time a male hormone which could be tested clinically. Numerous observers have found this substance and its propionic acid ester to possess striking therapeutic value. The history and bibliography of this subject have been adequately reviewed in a recent paper by Vest and Howard (3) and also in a monograph by Moore and Koch (4). These reports have described the good results following parenteral injections of testosterone in an oily vehicle, 2 to 7 times weekly. In our own experience, most eunuchoids have responded satisfactorily to doses of 25 mg. of testosterone propionate injected 3 times each week, although a few of the very severe cases have required daily treatments.

Since this is essentially 'replacement' or 'substitution' therapy, such frequent injections for an indefinite period soon become an annoyance and an expensive burden. Therefore the reports of Deanesly (5) and of Deanesly and Parkes (6) concerning the effectiveness of implanted tablets of the pure sex hormone aroused considerable interest. The possibility of administration at longer intervals and of better utilization presented obvious advantages. The successful application of this method has been confirmed by Vest and Howard (7, 8) and by Eidelsberg and Ornstein (9) who used pellets of pure crystalline testosterone in treating eunuchoids. Other workers have also reported experience with this method of treatment (10, 11).

Our own experience in 7 characteristic cases seems worthy of record because: first, crystals of methyl testosterone and testosterone propionate were used; furthermore, the method of preparation of these pellets as recently modified by one of us (G. R. B) is somewhat simpler than the procedures previously employed; and finally, the implantation of hormone crystals is still a relatively novel therapeutic strategy and recorded experiences from different groups of workers seem clearly desirable.

TECHNICAL METHODS

The mold for the preparation of the pellets is made of hardened steel and bolted to a machined flat steel block (fig. 1, 2). It contains 36 holes, each 5 mm. in depth and 1.83 mm. in diameter. The crystalline testosterone preparation,[2] in the form of powder, is packed into the holes and then compressed by a die consisting of 36 plungers which fit snugly into each hole. A pressure of 6500 lb. per square inch is applied in a hydraulic press. The pellets are forced out by removing the flat steel block and pushing the plungers completely through the mold (fig. 2A). A receptable beneath catches the pellets, each of which weighs between 8 and 11 mg., averaging 9 mg. Those used at the beginning of this study were of a smaller type, the preparation of which was described in previous publications (12, 13, 14).

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[1] Aided by a grant from the Christine Breon Fund for Medical Research.

[2] The crystalline methyl testosterone and testosterone propionate were supplied through the courtesy of Dr. E. Oppenheimer and Dr. R. C. Mautner of the Ciba Pharmaceutical Products, Inc.

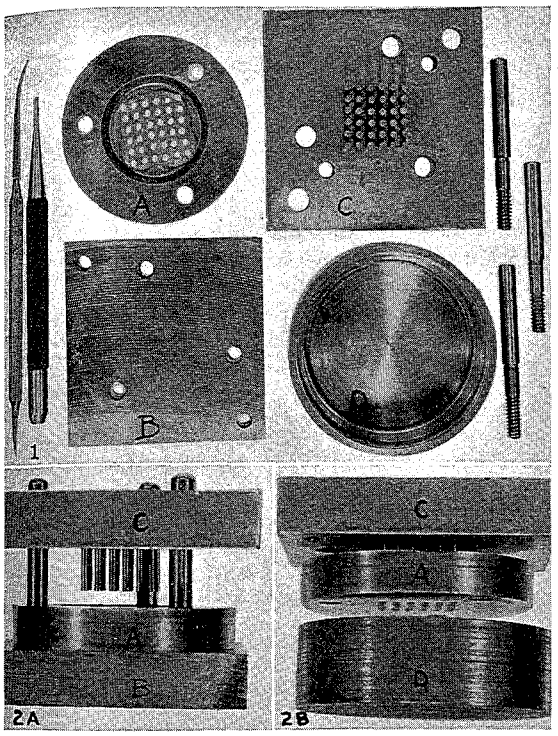

Fig. 1. COMPONENTS OF THE PELLET MACHINE. (a) mold; (b) flat steel plate with machine ground surface; (c) die with plungers corresponding to holes in mold; (d) receptacle. Fig. 2A. PELLET MACHINE ASSEMBLED AND READY FOR COMPRESSION AFTER THE POWDERED CRYSTALLINE ANDROGEN HAS BEEN PACKED IN THE HOLES. (a) mold; (b) flat steel plate; (c) die. Fig. 2B. PELLET MACHINE PARTIALLY DISASSEMBLED AFTER COMPRESSION, READY FOR EXPULSION OF THE PELLETS. (a) mold; (c) die; (d) receptacle.

After weighing, the pellets are prepared for administration by placing the required number in the lumen of a number 12 needle. The point is loosely corked and a fairly snug-fitting stylet closes the other end. The loaded needle is then placed in a test tube and sterilized in the pressure autoclave for 20 minutes at 120°C. and under a pressure of 15 lb. per square inch. The site for the implant, either on the arm or on the thigh, is prepared by sterilization of the skin followed by the infiltration of a small area with novocaine. A small incision is then made, and after removing the cork, the needle is inserted into the subcutaneous tissue for a distance of 4 or 5 cm. The pellets are left under the skin by withdrawing the needle on the stylet (fig. 3).

Discussion of technic. Sterilization in the pressure autoclave requires a compound with a high melting point so that the pellets will remain separate and will not be altered in shape. Methyl testosterone and testosterone are satisfactory in this regard, as their melting points are 163–4°C. and 154–5°C. respectively. Since testosterone propionate melts at 121–3°C., the pellets of this substance must be sterilized in an Arnold autoclave over a period of 3 days.

Studies of absorption from the pellets, made in experimental animals, indicate that the important factors are: the surface area of the pellets exposed to the tissues, the degree to which the hormone crystals have been compressed, and the physical nature of the compound. Pellets of all crystalline steroid compounds when implanted into body tissues cause a low-grade inflammatory reaction which results in the formation of a fibrous capsule around the pellets. Blood and lymphatic capillaries appear in the capsules, as well as some lymphocytes and an occasional giant cell. Absorption takes place through the capillaries at a rate probably proportional to the size of the surface area. The degree of compression in the apparatus described is practically constant; the variations due to this factor are therefore excluded. Previous observations have indicated that less compact pellets are absorbed more rapidly. The rate of absorption does not seem to be influenced by the solubility of the compound in various chemical solvents, nor by its melting point. Observations in animals in respect to pellets of methyl testosterone, in which all factors are constant except the surface area, show that absorption takes place almost equally from all surfaces, that small variations in size and weight have only a slight influence on the daily amount absorbed and that the amount absorbed daily slowly decreases.

When injected in an oily vehicle in test animals, the most effective compound of testosterone is the propionate, next in order is the methyl ether form, while the free form is the least effective (15). The clinical effectiveness of methyl testosterone, as reported below, indicates that the slow, uniform absorption from pellets may alter this relationship. Further observations on this problem are in progress.

The amount of methyl testosterone administered was at first arbitrarily set at approximately 100 mg. distributed in about 20 pellets. This amount has proved to be effective, but in later implants with larger pellets a total dose of 140 to 180 mg. was given in an attempt to prolong the effect. Experimental ob-

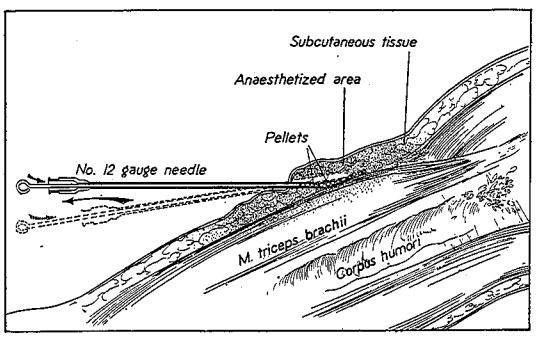

Fig. 3. DIAGRAMMATIC ILLUSTRATION OF INSERTION OF PELLETS INTO SUBCUTANEOUS TISSUES.

servations (16) have indicated that the average daily absorption from each pellet varied from 0.1 to 0.17 mg. so that the total average daily absorption varied from 2 to 3 mg. In some instances, however, the rate must have been slower, because effects from a single implant of about 100 mg. have lasted as long as 9 weeks. Waning effectiveness just before the pellets vanish completely suggests some decrease in the average daily absorption.

TABLE 1. THE IMPLANTATION OF METHYL TESTOSTERONE PELLETS

Case No.	Date	Amount implanted	No. of pellets implanted	Duration of effect
		mg.		*days*
1	10/26/39	100.3[1]	14	79
	1/11/40	83.2	18	70
	3/21/40	103.7	20	42
	5/ 2/40	149.4[2]	17	—
2	11/30/39	125.0	20	36
	1/ 4/40	98.5	20	42
	3/21/40	105.6	20	—
3	11/30/39	101.0	23	63
	3/21/40	105.6	20	48
	5/15/40	147.3[2]	17	—
4	2/ 1/40	102.7	18	50
	3/21/40	111.2	20	55
	5/15/40	148.0[2]	17	—
5	2/ 1/40	103.4	19	50
	3/21/40	100.7	20	35
	4/25/40	160.0[2]	17	32
	5/27/40	152.2[2]	17	—
6	3/21/40	109.6	20	55
	5/15/40	138.3[2]	16	—
7	4/17/40	180.1[2]	19	33
	5/27/40	147.6[2]	17	—

[1] Testosterone propionate pellets.
[2] Larger methyl testosterone pellets.

Case Histories

Case 1. W.C., (*U49328*) (fig. 4), a 31-year-old migrant was first seen in the University of California Clinic Aug. 23, 1939. Ten years previously he had sustained a severe skull fracture following which he had been unconscious for 17 hours. He then had had convulsions 2 to 12 times daily until 4 years before when a section of his skull was removed surgically. This resulted in some diminution in frequency and severity of the 'spells.' He had taken phenobarbital for 10 years. His genitalia had always been small, but he had possessed fair sexual function until the accident. After this his libido diminished gradually, nocturnal emissions ceased and he had been impotent for the preceding 5 years. He still had occasional partial erections and was shaving at approximately 2-week intervals.

At time of examination the patient weighed 147½ lb. and was tall with disproportionately long extremities. He looked younger than his age and had a high-pitched voice. Blood pressure was 105 systolic and 70 diastolic. The skin was of fine texture. The axillary hair was normal but the pubic escutcheon was typically feminine. The penis was small, measuring 5¾ cm. in length and 8½ cm. in circumference. The testes were small and soft, the right being approximately 2 by 1 cm. and the left 3 by 1½ cm. Rectal palpation indicated a small prostate. Laboratory investigations revealed a B.M.R. of −23%, and a bone age of 22 to 23 years (chronological age, 31 years). No creatin[3] was found in the urine. No urinary androgens were detectable in the urine collected for 3 consecutive days.[4]

Treatment was begun Oct. 26, 1939, with the implantation of 14 pellets of testosterone propionate, totalling 100.3 mg. The patient had 4 convulsive attacks in the next 2 days, but then they ceased for about 9 weeks. However,

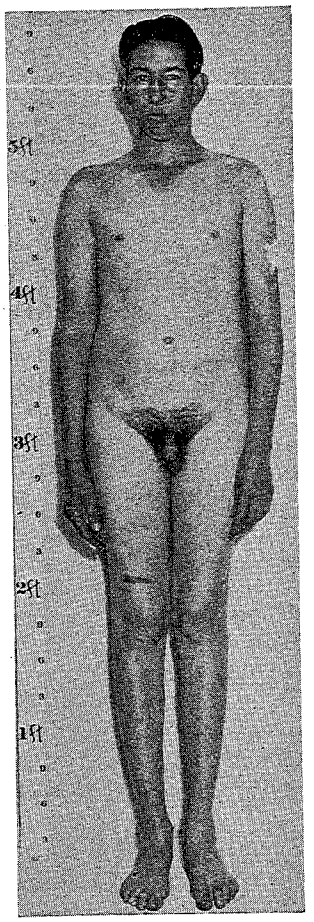

Fig. 4. *Case 1*, primary hypogonadism; age 31. Note disproportionately long extremities, small genitalia and feminine pubic escutcheon. See text for response to testosterone implants.

[3] Children of both sexes and the adult female excrete creatin in the urine. It was formerly believed that the adult male does not, but this has recently been contested. The presence of creatin in adult male urine has been considered indicative of hypogonadism.

[4] All androgen determinations were performed in the Institute of Experimental Biology, University of California, through the courtesy of Dr. Herbert M. Evans. The method of extraction described by Gallagher et al. (17) was used. Assays were made by a modification of the baby chick method as described by Burrows et al. (18) and by Frank and Klempner (19).

the site of the implant in the left upper arm became infected and began to discharge purulent material in a few days. This continued intermittently for several weeks as a result of which some of the implanted material was undoubtedly lost. This period was complicated by the unavoidable removal of 6 infected teeth and the subsequent development of purulent sinusitis. In spite of these vicissitudes there was a definite improvement in sexual status manifested by erections nearly every day and a general increase in strength and vigor. About 9 weeks after the implantation (during the sinusitis) the patient discontinued the phenobarbital for 2½ days, resulting in 10 epileptic seizures within 24 hours. At that time he began to note a definite diminution of libido and frequency of erections so that at the end of another week he had had only one erection, and three convulsive attacks had occurred. His penis at that time measured 8½ cm. in length, which represented a growth of about 3 cm.; the testes remained the same size.

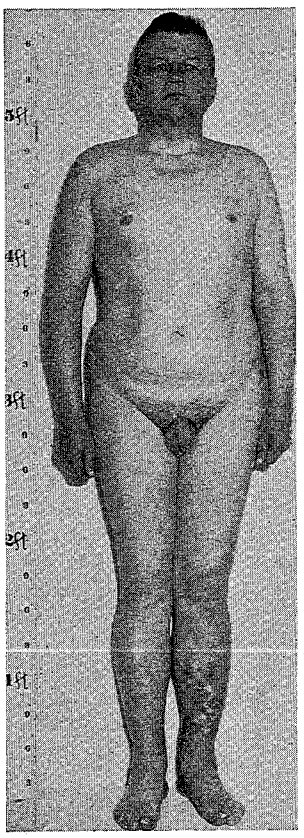

Fig. 5. *Case 2*, adult hypogonadism; age 43. Note feminized adiposity and eunuchoid fat pads in outer portion of upper eyelids. Genitalia are somewhat atrophic, pubic hair is sparse and of feminine type. See text for response to testosterone implants.

Another implant was administered on Jan. 11, 1940, 2½ months after the first, the dose being 83.2 mg. of methyl testosterone distributed in 18 pellets. The convulsive attacks then ceased and the patient's strength improved. Libido returned and erections occurred daily. Five weeks later he reported that he was shaving 2 to 3 times each week, whereas formerly shaving had been necessary only once in 2 weeks. His penis and testes were approximately the same size. The B.M.R. was −25%, the bone age showed complete epiphyseal union, urine androgens were detectable in the amount of 1 I.U. per day. He still had occasional convulsions, usually when he had neglected to take phenobarbital.

A third implant was given on March 21, 1940, consisting of 103.7 mg. of methyl testosterone in 20 pellets. Just prior to this, erections had occurred less frequently. This implant resulted in an increased number of erections but the epileptiform seizures continued. There was a noticeable diminution of effect after about 5 weeks.

A fourth implant was given on May 2, 1940, consisting of 149.4 mg. of methyl testosterone in 17 pellets. At his last visit 11 days later, the patient again reported an increased number of erections and one nocturnal emission. At this time the penis measured 8¼ cm. in length and 9 cm. in circumference, and the testes were 2½ by 1½ and 3½ by 2 cm. on the right and the left respectively. These measurements represented some growth of both the penis and the testes.

Case 2. V.N., (U31605) (fig. 5), a 42-year-old white Russian masseur, was first seen in the University of California Clinic in May, 1938. The family history revealed that two siblings had had toxic goiters. In the preceding 7 months the patient had lost 32 lb. and had had weakness and vertigo. Libido had waned and he had become impotent. During this time he had lost hair from the chest and the pubic region.

Examination showed an enlarged thyroid and some atrophy of the penis and testes. His B.M.R. was +38% and later +30%; the plasma cholesterol was 183 mg.%. In July 1938 a subtotal thyroidectomy was performed because of a hyperplastic thyroid gland. Two months later he had regained 18 lb., but complained of weakness, stiffness of the joints, loss of head hair, and of feeling cold continuously. His B.M.R. was −22% and plasma cholesterol was 303 mg.%. After another 2 months' period he had further gained 11 lb. and, because of postoperative hypothyroidism was given desiccated thyroid. This caused headaches and swelling of the face; so thyroxyl was substituted. Later he was able to tolerate desiccated thyroid made by a different firm, which was much cheaper than thyroxyl. On this preparation he felt better generally, but there was no return of libido or potentia. He had occasional hot flashes and nocturnal emissions occurred about every 2 months. At this time (April, 1939), in spite of previously having been "strong sexually," he had been unable to have intercourse for 1½ years. His skin had become fine in texture and the loss of hair had continued.

Examination showed him to look older than his years and his skin was finely wrinkled. There were fat pads in the outer portions of the upper eyelids, a characteristic of hypogonadism. The hair on the head was gray and of fine texture. There was no hair on the trunk or the extremities and the pubic hair had a feminine distribution. The penis and scrotum were somewhat small, the former measuring 8 cm. in length and 9¼ cm. in circumference. The right testicle measured 3½ by 2½ cm. and the left 3 by 2½ cm. The B.M.R. was then −4%, the glucose toler-

ance curve was flat and the sella turcica appeared normal in an x-ray of the head. Androgens were estimated in a 3-day urine sample and 20 I.U. per day were found (normal range, 25 to 50). The patient's weight varied from 210 to 215 lb. and his blood pressure was 120 systolic and 70 diastolic.

On November 30, 1939, 125 mg. of methyl testosterone in 20 pellets were implanted. Soon thereafter the patient felt stronger, had occasional erections, and in 5 weeks had had 2 nocturnal emissions. However, he was still unable to have intercourse, so on January 4, 1940 (5 weeks later), he was given another implant of 98.5 mg. in 20 pellets in the opposite arm. After this the erections became more frequent, occurring once or twice daily, and the patient had successful intercourse twice in the following 3 weeks. Five weeks after the second implant he felt stronger and his beard was heavier. At this time he became somewhat more nervous, had some palpitation and lost some weight, so that the dose of thyroid had to be reduced. There had been a slight increase in axillary hair. The penis now measured 8½ cm. with a circumference of 9 cm. and the testes measured 4 by 3 and 4 by 2½ cm. on the right and left respectively. A rectal examination indicated a prostate less than one-fourth normal size.

One week later (6 weeks after the implant) the patient reported a definite drop in libido and no more erections. The urine androgens were tested again and none were detected in a 3-day sample. His weight was 212 lb. and his blood pressure 120 systolic and 70 diastolic. His general strength remained good until the material was available for the next implant on March 25, 1940, when 20 pellets of methyl testosterone were administered, representing 105.6 mg.

At his last visit 2 months later the patient reported that he had had a marked effect from the implant for 1 month, with erections every day and nocturnal emissions about every 2 weeks. During the second month there had been some gradual diminution but he had had satisfactory intercourse 3 weeks before. A definite drop in libido had been apparent in the preceding few days. Beard and chest hair were much heavier so that daily shaving was necessary. His general strength was improved with the result that he had secured a much better position. His weight was now 217¼ lb. The penis measured 9 cm. in length (formerly 8 cm.) and 9¼ cm. in circumference and the testes measured 4½ by 3 cm. bilaterally (representing some increase in size). At this time (May 24, 1940) another implant of methyl testosterone was administered, totalling 153.8 mg. in 16 pellets.

Case 3. L.K. (*U20634*) (fig. 6, 6A, 6B), a 24-year-old butcher was seen in September, 1937. He had had occasional erections and sexual dreams since he was 10 years of age and had tried masturbation, but he had never achieved an emission. An operation for bilateral undescended testicles had been attempted when he was 16 years old and at that time the left testicle was found to be almost completely atrophic. He had never shaved and had grown 1 inch in the preceding year.

The patient was 71¾ inches tall with disproportionately long arms and legs. He weighed 146 lb. and his blood pressure was 110 systolic and 80 diastolic. His

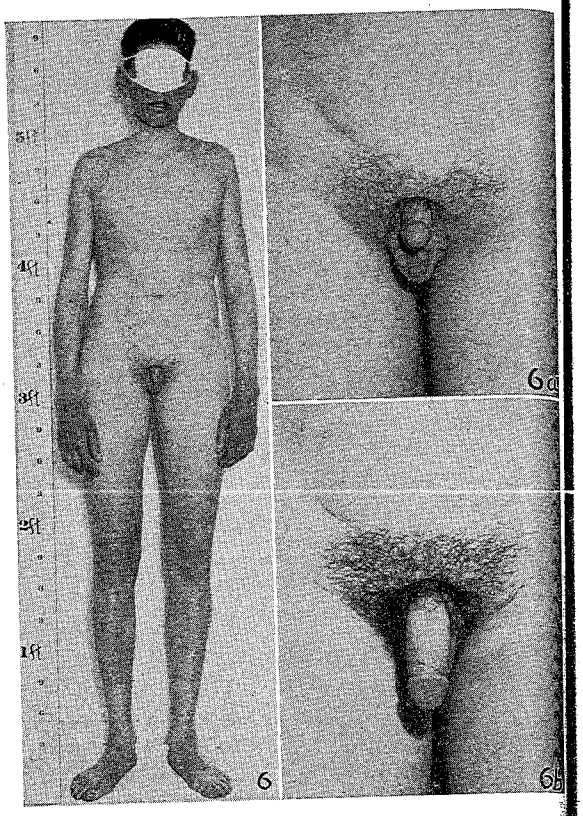

Fig. 6. *Case 3*, typical pre-adolescent eunuchoid (primary hypogonadism); age 25. Before treatment. Note disproportionately long extremities, broad pelvis, childish genitalia and sparse pubic hair. Has never shaved. Voice still high pitched. Fig. 6A. *Case 3*, before treatment; age 25. Note scars from operation at the age of 16 for cryptorchidism. No definite testicular tissue palpated. Fig. 6B. *Case 3*; age 27. After 21½ months' treatment with testosterone injections and implants. Note striking growth of penis and increased amount of pubic hair.

voice was high pitched and he looked younger than his age. A few axillary hairs were present and the pubic hair was sparse. The penis was small, measuring 4¾ cm. in length and the only scrotal content was some questionable tissue on the left. There was possibly some testicular tissue in the inguinal canals. Laboratory examination revealed a B.M.R. of −4%, a rather flat glucose tolerance curve, urinary creatin of 430 mg.%, and a bone age of 15 years (as compared to the chronological age of 24).

Treatment was begun with the equine gonadotropic hormone[5] in doses of ½ to 4 cc. 3 times weekly for 3 months. The patient reported a slightly increased number of erections, but the genitalia were unchanged in appearance and there were no other effects. At this time a small amount of prostatic tissue could be felt.

The patient was then given testosterone propionate hypodermically in doses of 10 mg. 3 times weekly. After 4 months of somewhat irregular administration, he reported that he felt much improved. On the night of the

[5] Gonadin, kindly furnished by the Cutter Laboratories, Berkeley.

[6] Perandren, kindly furnished by the Ciba Pharmaceutical Products, Inc.

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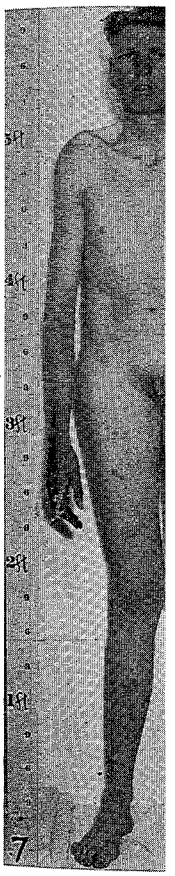

Fig. 7. *Case 4*, t
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first injection he had had a spontaneous orgasm without emission and later he had had a nocturnal emission. He shaved each week and the penis was larger, measuring 5½ cm. in length. The dose was then increased to 25 mg. 3 times weekly. This was administered fairly regularly for 11 months and resulted in more frequent erections, occasional nocturnal emissions and occasional masturbation. His voice was deeper, he had gained 20 lb., and his general strength and feeling of well-being improved. His height had increased ¾ of an inch to 72½ inches. The blood pressure was unchanged, being 110 systolic and 60 diastolic. The breasts were somewhat fuller and hair growth had increased so that there now was a normal amount of axillary hair and a moderate pubic escutcheon. The penis measured 8 cm. in length, a growth of over 3 cm., and was 10 cm. in circumference. The testes now were palpable—bean-sized on the right and the size of a small olive on the left. The bone age was 19 years (an increase of 4 years in 2 years' elapsed time); the urinary creatin was 864 mg.

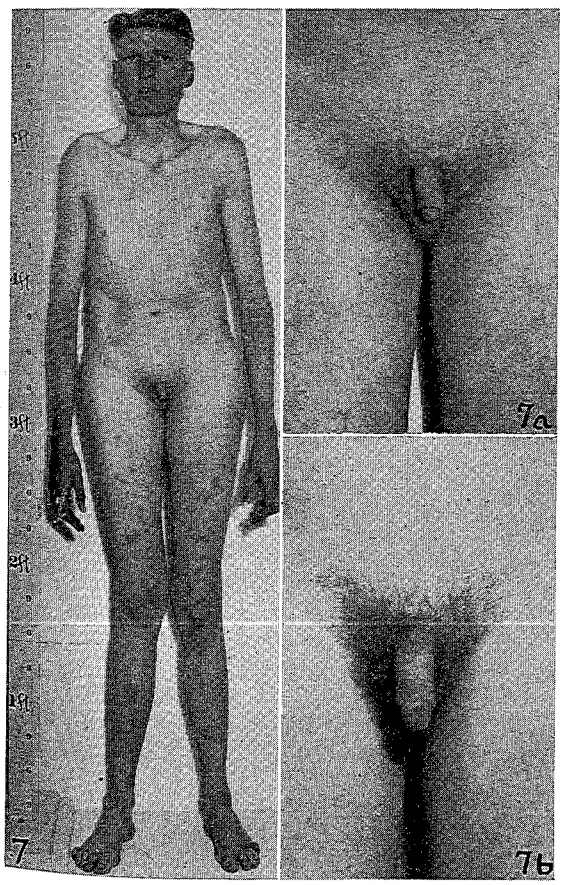

Fig. 7. *Case 4*, typical primary hypogonadism; age 31; before treatment. Note characteristic eunuchoid proportions with long arms and legs and broad pelvis; tiny genitalia, very sparse pubic hair. Had never shaved; voice high pitched. Fig. 7A. *Case 4*. Before treatment; age 31; testes size of pine-nuts, prostate not palpable. Note feminine contour of thighs. Fig. 7B. *Case 4*, age 33; after 17 months of treatment with testosterone injections and implants. Note marked growth of penis and increased amount of pubic hair.

On Nov. 30, 1939, the injections were stopped and 23 pellets of methyl testosterone, totalling 101 mg., were implanted subcutaneously. Seven weeks later the patient reported continued improvement with maintenance of the former sexual status. He was still having erections each day and occasional nocturnal emissions. His penis was larger, being 8½ cm. long and 9 cm. in circumference. Eleven weeks after the implant the patient reported that he had had a urinary infection, probably a pyelitis, requiring treatment with sulfanilamide, and for 2 weeks had noticed diminished libido and infrequent erections. A 3-day urine sample at this time showed only 1 I.U. of androgen excreted daily. Five weeks later the urinary infection had cleared, but there had been no return of libido. His general strength remained good. He weighed 165½ lb., and the blood pressure was 120 systolic and 70 diastolic. The penis was unchanged, but the testes were somewhat larger. Both were at the upper poles of the scrotum. The prostate was about one-fourth normal size.

At this time (March 21, 1940) another implant was given consisting of 105.6 mg. of methyl testosterone compressed into 20 pellets. This caused a return of libido and erections, reaching a peak at 16 to 19 days. Definite diminution of effect was noted 7 weeks after the implant. On May 15, 1940 (after an 8-week interval), the patient measured 72 7/8 inches, a further increase of 3/8 of an inch in height within 6 months; his weight was 170 lb., a gain of 4 lb. in the same length of time. His penis now measured 9 cm. in length (a growth of 1 cm. since the start of implantation therapy) and the circumference was 9¼ cm. The testes were slightly larger. At this time another implant was given, totalling 147.3 mg. of methyl testosterone in 17 pellets.

Case 4. J.J. (U36521) (fig. 7, 7A, 7B), A 31-year-old railway freight handler came to the University of California Clinic in May, 1938. His family history revealed that his mother and one sister had been confined in mental hospitals and that one brother was subject to spells of epilepsy. The patient had done poorly in school and had had epileptiform seizures from the age of 16. These had gradually diminished in frequency since the age of 25 and had been completely absent for 2 years.

The patient had never developed sexually, but had had some libido and had tried masturbation frequently without ever having an orgasm. Intercourse had been attempted unsuccessfully 8 to 10 times since the age of 21, and at the last attempt, 1 year previously, he had contracted gonorrhea. During the preceding 2 years he had developed a small amount of axillary and pubic hair, but his beard was only a fuzz which was clipped every 2 or 3 weeks.

On examination he looked decidedly younger than his age and exhibited the typical eunuchoid disproportionately long extremities. His height was 71 inches and his weight 133 lb. His voice was high pitched and the skin smooth and slightly wrinkled. The blood pressure was 120 systolic and 75 diastolic. Two to six axillary hairs were present on each side and there was a fair amount of pubic hair. The penis was small, measuring 4½ cm. in length (about normal for a 5-year-old boy),

and the testes in a small scrotum were very small. No prostatic tissue could be felt by rectum. B.M.R. was −7% and the plasma cholesterol 190 mg.%; the bone age was 18 years (compared to a chronological age of 31); no androgens were detected in complete urine specimens for 3 consecutive days; no urinary creatin was present.

In October, 1938, the patient was started on equine gonadotropic hormone[7] and received this in doses of ½ to 2 cc. (100 to 400 U) thrice weekly for 3 months. As a result of this, erections occurred with slightly increased frequency, but masturbation remained unsuccessful. His penis was unchanged, but the scrotum and testes became somewhat larger. At the end of 3 months, the right testicle measured 3 by 1½ cm. and the left 2 by 1 cm. (a definite increase in size). Again no prostatic tissue could be felt. Urinary androgens were re-tested in a 3-day specimen and 21 I.U. per day were present (normal 25–50). He now weighed 137½ lb., a gain of 4½ lb.

The patient was then started on testosterone propionate. At first 10 mg. was given and the dose was increased shortly to 25 mg. 3 times weekly at which level it was continued for 1 year. He had immediate prolonged erections, and after 1 month commenced to have emissions. After 3 months, he performed sexual intercourse successfully for the first time. At the end of 1 year he was having 2 to 5 erections daily and was masturbating twice weekly. In addition he was able to have intercourse about every 2 weeks. His general strength and appearance had improved and there was a definite increase of axillary and pubic hair. The beard was reported to be growing somewhat faster, but still only required "cutting" every 2 or 3 weeks. The epileptic seizures had returned about the middle of the year while the patient was away on a trip. He continued to have these about once each month.

Examination at the end of the year showed him to be 71¼ inches in height and to weigh 152 lb., a further gain of 14½ lb. The blood pressure had not changed, being 120 systolic and 80 diastolic. His penis now measured 8 cm. in length (formerly 4½ cm.) and the testes were somewhat smaller (right 2 by 1 cm., and left 1½ by 1 cm.). The prostate could now be felt and was approximately half the normal size. The secretion was examined and was normal, but no spermatozoa were seen. His bone age at this time was 19 years (an increase of 1 year in 1 year), and urinary androgens were now 5 I.U. per day.

On Feb. 1, 1940, the hypodermic injections were discontinued and 18 pellets of methyl testosterone, totalling 102.7 mg., were implanted subcutaneously. Five weeks later the patient stated that his libido had increased and 7 weeks after the implant he reported that his beard was heavier and that no further "seizures" had occurred. At this time (March 21, 1940) a second implant was given, with a total dose of 111.2 mg. of methyl testosterone distributed in 20 pellets. Eight weeks later he reported continued sexual stimulation with some moderate decrease in the preceding week. At this time his height was 71⅜ inches (an increase of ⅜ of an inch in 17 months) and he weighed 151 lb. (a gain of 18 lb. in the same interval). His penis now measured 9 cm. in length and 8 cm. in circumference, having enlarged somewhat under implantation therapy. The testes were also slightly larger, measuring 2½ by 1½ on the right and 2 by 1 cm. on the left. At this time another implant was given, totalling 148 mg. of methyl testosterone in 17 pellets.

Case 5. A.H., (U39262) (fig. 8, 8A), a 26-year-old graduate student was first seen in the University of California Clinic in May, 1934, his chief complaint being "lack of development." The family history revealed that 1 sister was underdeveloped and that a brother had not grown pubic hair until the age of 17. The patient's genitalia had always been small and his testes had been migratory, being found in the scrotum and inguinal canals at different times. He had never experienced any libido, but had had occasional erections. His beard required shaving only at 2-week intervals.

Examination showed the patient to be a typical pre-adolescent eunuchoid 70½ inches in height with characteristic disproportionately long extremities. He weighed 118 lb. and the blood pressure was 130 systolic and 80 diastolic. Axillary hair was scant but there was a moderate amount of pubic hair. The penis and scrotum were small

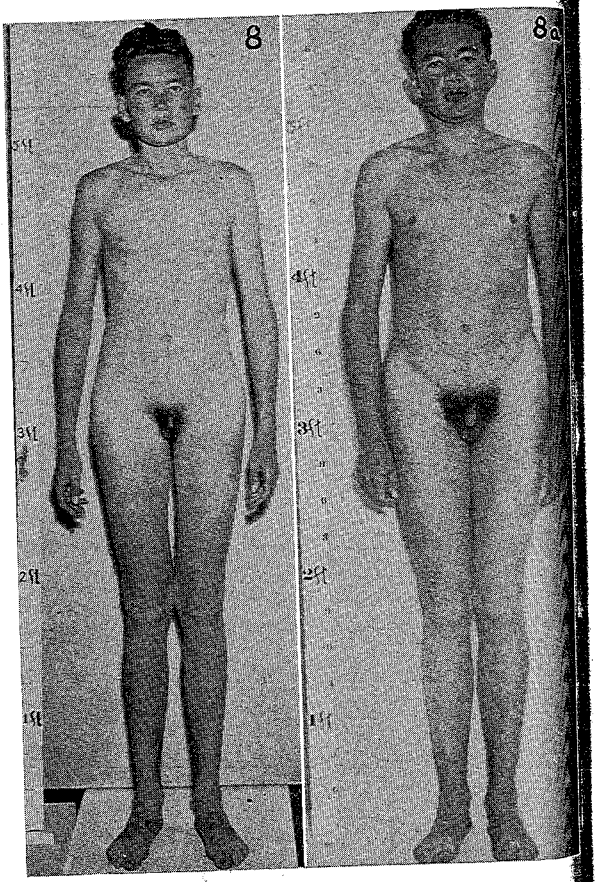

Fig. 8. *Case 5*, typical primary hypogonadism; age 26, look much younger. Note disproportionately long extremities, rel tively broad pelvis with feminine contour of thighs, minu genitalia and sparse pubic hair. Fig. 8A. *Case 5*, age 30; after months of testosterone injections and implantations. Had gain 17 lb; more masculine build; rather heavy growth of pubic ha becoming masculine in distribution.

[7] Gonadin, kindly supplied by the Cutter Laboratories.

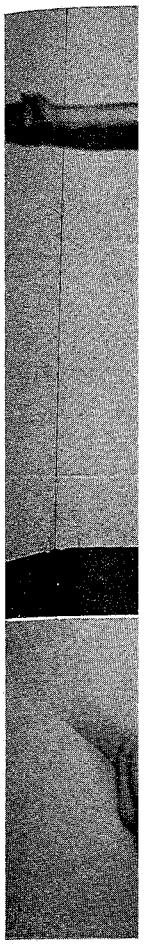

Fig. 9. *Case* Genitalia infanti no beard. Fig. 9. ary 1937) after pionate (5 mg. a decided chang ment with test adult size.

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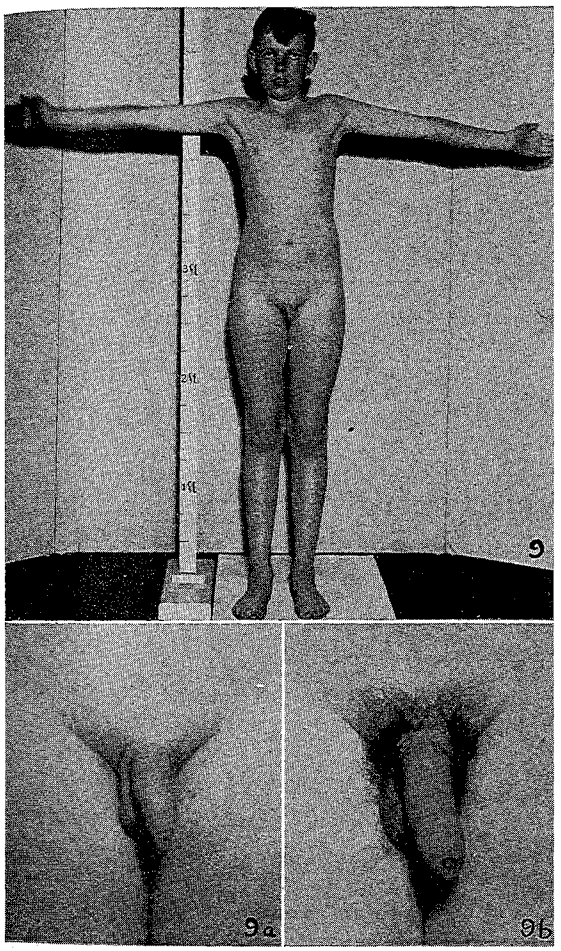

Fig. 9. *Case 6*, primary hypogonadism; age 17, looks younger. Genitalia infantile; no pubic or axillary hair; voice high pitched; no beard. Fig. 9A. *Case 6*, age 21. Appearance of genitalia (January 1937) after 3 months of very small doses of testosterone propionate (5 mg. 3 times weekly). Even this amount had produced a decided change. Fig. 9B. *Case 6*, age 24; after 3½ years' treatment with testosterone injections and implants. Genitalia now adult size.

the former being only 2½ cm. in length with an approximate circumference of a lead pencil, while the testes were the size of date seeds. No prostatic tissue could be felt. Laboratory examinations revealed a B.M.R. of −18% and a bone age of 14 years (chronological age, 26 years).

Previous treatment had been without effect and no endocrine therapy was prescribed, the male hormone not having been discovered at that time. However, the patient was seen again at the age of 30. He then weighed 133 lb. His sexual status was unchanged. Periodic migraine attacks were an additional complaint. At this time no urinary androgens could be detected in a urine sample collected over 3 consecutive days.

Treatment was begun 3 months later, in March, 1939, with testosterone propionate,[8] in a dose of 25 mg. 3 times weekly. After 4 months of treatment (50 doses) the patient showed marked improvement. He reported continuous priapism during the first week of treatment and frequent erections thereafter. The migraine attacks had disappeared; he had gained 15 lb., felt stronger and was shaving twice weekly. His voice had become considerably lower pitched and he noted also that his nipples were slightly sensitive. The penis now measured 3¾ cm. in length (formerly 2½ cm.) and 5¼ cm. in circumference. The testes were larger, each one being the size of a small olive. The B.M.R. was then −17% and the plasma cholesterol 303 mg.%.

Dosage was then increased by having the patient continue the injections of 25 mg. 3 times weekly with the addition of inunctions of testosterone propionate ointment,[9] 4 mg. nightly. After 2 months he reported no essential change subjectively, but the penis was larger measuring 4½ cm. in length and 7 cm. in circumference.

The testosterone propionate injections of 25 mg. 3 times weekly were taken more or less continuously for 11 months until February, 1940. At this time the patient was having 2 or 3 erections daily and occasional nocturnal emissions. His voice was deeper and there was a heavier growth of beard and body hair. The penis was 6 cm. in length and 6¾ cm. in circumference, and the testes each measured 2½ by 1½ cm. Semen had been obtained twice by masturbation and the second sample showed an increase in amount (1.2 cc.) and cellular content but no spermatozoa were seen. A recent B.M.R. had been −2% and plasma cholesterol 222 mg.%.

The patient then weighed 151½ lb., a gain of 18 lb., and his blood pressure was 115 systolic and 70 diastolic. As the genitalia were still quite small, it was decided to raise the dose still further. He was advised to continue injections of testosterone propionate in doses of 25 mg. 3 times weekly, and in addition 19 pellets of methyl testosterone, totalling 103.4 mg., were implanted subcutaneously. A definite increase in libido and in the number of erections resulted with the maximum effect about 10 days after the implant. Two and one-half days after the implant another 3-day urine sample was examined for androgens, and excretion of 18 I.U. per day was found (normal 25 to 50).

Four weeks after the implant the patient had to stop his hypodermic injections for 10 days and there was a definite diminution of libido which returned to some degree on resumption of injections. After 7 weeks the patient weighed 149 lb. and his blood pressure was 110 systolic and 70 diastolic. He was having 1 to 2 erections daily and the secretion from masturbation measured 1.8 cc. (the most observed). The prostate now was 1/3 normal size and the secretion appeared normal but without spermatozoa.

At this time (March 21, 1940) another implant was given with a total dose of 100.7 mg. of methyl testosterone distributed in 20 pellets. Following this the erections increased to 4 daily, but after 2 weeks the patient was forced to stop his injections of testosterone propionate for the following 3 weeks. This resulted in a markedly decreased number of erections. Another implant was given after a 5-week interval on April 25, 1940, the total dose being 160.5 mg. in 17 pellets. At the same time the

[8] Supplied as neo-Hombreol by the Roche Organon Company.

[9] Supplied as oreton ointment by the Schering Company.

patient resumed his injections of testosterone propionate, 25 mg. 3 times weekly. Four and a half weeks after the implant he reported a marked sexual stimulation and had masturbated once producing 2½ cc. of secretion. His height and weight had remained stationary. The penis at this time measured 6¼ cm. in length and 8½ cm. in circumference; and the testes were 3 by 1¾ cm. bilaterally. The penis therefore had increased in circumference but only slightly in length since the addition of the implants. A bone age determination at this time was 18 to 19 (chronological age, 32), or an increase of 4 years in 6 years' elapsed time.

Case 6. B.C., (*U4545*) (fig. 9, 9A, 9B), a 17-year-old student was seen at the University of California Clinic in March, 1933. Examination showed him to be 63¾ inches in height with disproportionately long extremities. The genitalia were underdeveloped (length of penis 7 cm., testes the size of small olives and prostate barely palpable). His voice was high pitched, he had no beard and axillary and pubic hair were completely lacking. His weight was 114 lb. and the blood pressure was 95 systolic and 65 diastolic. The B.M.R. was −24%, glucose tolerance curve was a low normal and the sella turcica appeared slightly small. The bone age was 15 to 17 years.

For the first 6 months the patient was given daily injections of gonadotropin.[10] His sexual status as well as his height remained unchanged, but his weight increased to 123 lb. and the B.M.R. to −16%. He was then given 1 grain of desiccated thyroid daily for 13 months, during which time he grew to a height of 66½ inches and a few pubic hairs appeared. However, the sexual status remained otherwise unchanged.

After 5 months without therapy (at the age of 19½ years) he was started on androstine,[11] 6 tablets by mouth and 1 ampule by injection daily. After 10 months of this treatment, he was having erections twice a week and emissions about twice a month, but the genitalia were unchanged in size. At this time his height was 67¾ inches, his weight 132 lb., the length of the penis 7 cm., the testes the size of medium olives and a few wisps of pubic hair were present.

After a brief lapse in therapy, on Nov. 6, 1936, when the patient was almost 21 years old, he was started on testosterone propionate[12] 5 mg. hypodermically 3 times weekly. A definite response occurred and after 5 months the dose was increased to 25 mg. 3 times each week. In May, 1938, the bone age was still 16 to 17 years. In February, 1939, after 2¼ years of this therapy, the patient was having erections each day and emissions about 3 times weekly; so the frequency of the injections was cut to twice weekly. This was continued until November, 1939, when the penis was considered of adult size (length 11½ cm.), and the testes and the prostate were about half normal size. Prostatic secretions were normal but no spermatozoa were seen. The patient was having 0 to 5 erections daily and emissions about twice weekly. His voice was deeper and he was shaving every 2 weeks. The pubic hair had increased and there was moderate growth of axillary hair. His weight was 168 lb. (a gain of 36 lb.

Treatment was then discontinued. A condom spec men after 2 months showed no spermatozoa and at th time the libido diminished and then disappeared. Aft 4 months without treatment, the patient still was havin erections nearly every day, but emissions occurred onl every 3 weeks. He had lost 14 lb. (to 154½ lb.). He wa more nervous and required more sleep. His beard wa growing less vigorously so that he shaved only every or 4 weeks. The penis was smaller, measuring 9½ cm in length and 9¼ cm. in circumference. Each testis mea ured 4 by 2 cm. The prostate could barely be felt. Heig was now 70½ inches and the blood pressure was 1 systolic and 60 diastolic. The B.M.R. was −13% an the bone age had increased to 18 to 20 years (chronologi age 24). Urinary androgens were tested in a 3-day samp and the excretion was 5 I.U. per day (normal 25 to 50).

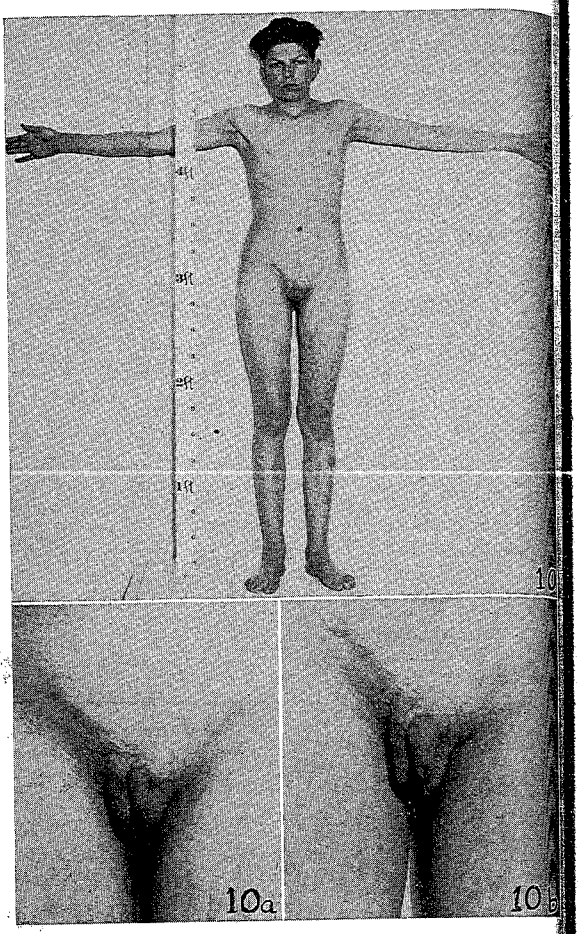

Fig. 10. *Case 7*, primary hypogonadism; age 24, looks young Note disproportionately long extremities, feminine contour thighs, tiny genitalia, sparse pubic and axillary hair. Voice hig pitched; upper eyelids show puffy appearance characteristic eunuchoidism. Fig. 10A. *Case 7*, age 24; before treatment. Ope ative scar dates back to hernia repair in early childhood. No tiny penis. Left testicle in lower end of inguinal canal. Fig. 10 *Case 7*, appearance 1 month after implant of 180.1 mg. of meth testosterone. Had priapism for 1 week starting 2 days after th implant.

[10] Antuitrin-S, Parke, Davis & Co.
[11] Kindly furnished by Ciba Pharmaceutical Products, Inc.
[12] Perandren, kindly furnished by Ciba Pharmaceutical Products, Inc.

At this time (March 21, 1940) an implant of methyl testosterone was given totalling 109.6 mg. distributed in 20 pellets. A definite effect was apparent 1 week later when erections had increased to 3 to 5 daily and the patient began to have fairly frequent nocturnal emissions. After 8 weeks he was still having 2 erections daily and emissions every second night. His penis now measured 11½ cm. in length (a gain of 2 cm.) with a circumference of 10½ cm. The testes were unchanged. Another implant was then given totalling 138.3 mg. of methyl testosterone distributed in 16 pellets.

Case 7. R.C., (*U57397*) (fig. 10, 10A, 10B), a 24-year-old student was first seen in the University of California Clinic on April 12, 1940, his chief complaint being "lack of development." An identical twin brother had matured physically but was mentally retarded. The patient's development had paralleled that of his brother until the age of 12, but had progressed no further. The left testis was undescended but had come down once previously during some treatment with an anterior pituitary preparation which had also caused the patient to shave infrequently for a limited time. He was always cold and his general strength was below the average. His height was still increasing by about ½ inch a year. He had never had any libido, though occasional erections had occurred as well as a few nocturnal orgasms without secretion. In the preceding 5 months he had had several nocturnal syncopal attacks with sweating and pallor followed by nausea and vomiting. The patient had finished high school but had been unable to obtain employment because of his youthful appearance and high pitched voice. At this time he was attending a trade school and doing housework to support himself.

On examination he was found to be slender and to look younger than his age. His height was 66¾ inches and his weight 129 lb., with disproportionately long extremities. His eyelids were puffy and the skin was dry, wrinkled and of a mottled, fawn color. There was a moderate amount of axillary hair but the pubic hair was scant. The penis was small, measuring 5 cm. in length and 5½ cm. in circumference. The left testis was undescended, both were the size of small olive pits. Prostatic tissue was barely palpable. Laboratory studies showed: B.M.R., −5%; plasma cholesterol, 175 mg.%; glucose tolerance curve, normal; no urinary creatin; bone age, 16 to 17 years (chronological age, 24); urinary androgens in a 3-day specimen, 5 I.U. (normal 25 to 50).

On April 17, 1940, the patient was implanted with 19 pellets of methyl testosterone totalling 180.1 mg. Two days later he developed priapism which lasted for 1 week. He then had 5 to 6 erections daily, until about 1 week before his last visit 5½ weeks after the implant. Nocturnal emissions had occurred 2 to 3 times a week. The patient stated he felt stronger. His weight and height were unchanged, but the penis was larger, measuring 7 cm. in length and 8 cm. in circumference. The testes were slightly larger.

DISCUSSION

In the above cases an implant of testosterone propionate was used only once, namely in *case 1*. Because of the infection that occurred, methyl testosterone was chosen for all subsequent implants. However, in spite of the infection and probable loss of some of the pellets, the testosterone propionate caused a decided clinical response. The subsequent doses of methyl testosterone in the same patient caused continued improvement and the duration of effect was approximately the same, but the results were not quite as dramatic.

Case 2 was not that of a primary eunuchoid but of one who developed hypogonadism coincidentally with hyperthyroidism. The latter was changed to hypothyroidism by a subtotal thyroidectomy, and this was in turn corrected by treatment with desiccated thyroid. All this fluctuation in thyroid function had no effect whatsoever on the patient's hypogonadism. The initial dose of 125 mg. of methyl testosterone caused some improvement but was not sufficient to restore potency. However, the second dose of 98.5 mg. given 5 weeks later had the desired effect. It was also interesting to note that as the patient's sexual function improved he needed less thyroid to control his hypothyroidism.

In cases 3 and 4 implants were used as continuation therapy after prolonged treatment with testosterone propionate injections. In these instances improvement was maintained. *Case 3* went 9 weeks without definite diminution of libido, but then noticed a change coincident with a pyelitis. *Case 4* noted an increased level of libido and sexual function after the implant and did not experience a diminution, until after 7- and 8-week intervals.

Case 5 had also had injections of testosterone propionate for a long period of time. His genitalia were the smallest of any in our group. As his condition seemed to be stationary as regards further growth of genitalia, the implants were given in addition to the usual testosterone injections. A definite increase in the size of the penis resulted.

Case 6 had had prolonged therapy with testosterone propionate so that his genitalia had attained adult status. However, treatment had been discontinued for 4 months, and after 2 months definite diminution in genital function and size had occurred. After the implant there was a restoration of function and increase in size.

Case 7 presented a striking deficiency and had not had previous testosterone therapy. The preparation of the larger pellets made possible a greater initial dosage in his case (180.1 mg.). The result of priapism for 1 week would seem to indicate that the dosage was too large in this instance. Cases with marked deficiency and without previous testosterone therapy seem to show a more intense initial response to implantation.

The obvious effects of treatment by implant are similar to those following injections of male hormone.

Increase in size of genitalia and increase in sexual function have resulted. A definite increase in size of the prostate occurred under therapy with both injections and implants (*case 1*, 3, 4 and 5). *Case 2* in whom the eunuchoidism developed at the age of 42, had a very small prostate, apparently due to lack of male sex hormone. This finding is difficult to reconcile with the testosterone treatment of prostatic hypertrophy.

Gain in weight was a frequent result of therapy, being marked in cases 2, 3, 4, 5 and 6. An increase in general strength was universal. The beard growth became somewhat heavier as a result of treatment, but never approached normal except in *case 2*. There was never any definite effect on blood pressure, all of the patients having low normal levels.

Cases 1 and 5 had fairly low basal metabolic rates, but only one of these (*case 5*) was raised to normal by treatment. Retarded bone age is a characteristic finding in the pre-adolescent eunuchoids and this showed advancement under therapy in all the cases tested (1, 3, 4, 5 and 6).

A study of androgen excretion was not helpful. The amount was always diminished or absent before treatment and there was occasionally some increase after therapy, but in *case 2* the opposite effect was noted. The most marked increase was in *case 4* after therapy with the equine gonadotropic hormone (0 to 21 U daily), but the excretion diminished to 5 U daily following later treatment with testosterone. From our observations it would seem that androgen determinations are of little value in checking the improvement from testosterone therapy, nor are they necessary even for diagnostic purposes. In view of this limited clinical usefulness and the elaborate time-consuming and expensive laboratory procedure necessary for accurate determination, quantitative androgen assays are not recommended in clinical practice.

In cases 3, 4 and 6 it was possible to compare the effects of the implantation of methyl testosterone pellets with the injection of testosterone propionate in oil. Satisfactory results had been obtained with 25 mg. of the testosterone propionate injected 3 times weekly. In these instances the patients showed no subjective or objective diminution of effect on the pellet regime. In *case 3* the first implant was effective for 9 weeks and the second for 8 weeks. Thus, over a period of 17 weeks, 206 mg. of methyl testosterone in pellet form was adequate substitution for 1275 mg. of testosterone propionate in oil, which would have been administered hypodermically in the same period of time. In *case 4* the first implant was effective for 7 weeks, the second for 8 weeks. In this period of 15 weeks, 213 mg. of methyl testosterone pellets proved as effective as 1125 mg. of testosterone propionate in oil which would otherwise have been used. Similarly, in *case 6* the first implant of 109.6 mg. was effective for 8 weeks, and thus replaced 600 mg. of testosterone propionate in oil. Thus, in these 3 cases 528 mg. implanted equalled 3000 mg. parenterally in oil.

The duration of effectiveness with a total dose of approximately 100 mg. of methyl testosterone varied from 35 to 70 days, with an average of 49 days, or 7 weeks. The only figures available at this time on the duration of effect following the larger doses of 140 to 180 mg. are two instances in cases 5 and 7. It was anticipated that the effective period would be prolonged, but it was not the case in these instances. When an implant has been 'used up,' no pellets can be felt at the site and there have been no indurations or other unpleasant local symptoms.

SUMMARY

Seven typical cases of eunuchoidism are presented —6 of the preadolescent type and 1 in which the onset seemed related to hyperthyroidism. Treatment was by implanting pellets of crystalline methyl testosterone and/or crystalline testosterone propionate. Total dosage of each implant early in the work varied between 83 and 125 mg. compressed into pellets averaging 5 to 6 mg. each. Later larger pellets were prepared so that doses of 140 to 180 mg. could be given. This was the only type of treatment in three of the cases but in three of the remainder it was used as continuation therapy after injections in oil, in order to compare the effectiveness of the two methods of treatment in the same individual. In the remaining case, pellets were given in addition to continued injections in oil to determine the effect of additional dosage. The duration of effectiveness with the smaller dosage averaged 7 weeks. Testosterone propionate pellets seemed somewhat more potent clinically, but methyl testosterone was easier to prepare and safer to administer. The absorption from each pellet of methyl testosterone was approximately 0.1 mg. to 0.17 mg. per day and the effective clinical dosage was found to vary between 2 and 3 mg. per day.

The method of preparing these pellets is described in detail and the technical difficulties are discussed. The high melting point of methyl testosterone pellets permits sterilization in the pressure autoclave, thus materially reducing the possibility of contamination.

This experience indicates that the uniform continuous absorption from such pellets is more efficient than injections of the hormone in oil so that approximately one-fifth of the dosage is required to obtain similar results. The eventual cost of continuous treatment should therefore be less and the interval of about 7 weeks between implantations is a decided improvement over injections 2 to 7 times weekly.

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