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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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[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.

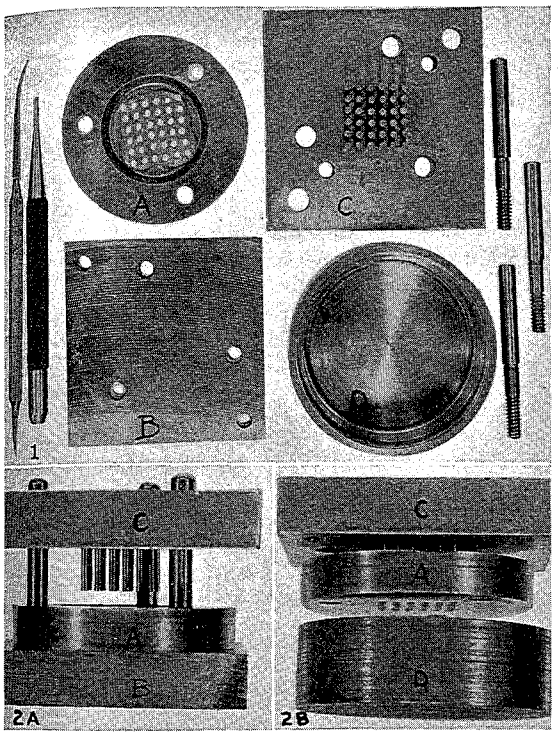

Fig. 1. COMPONENTS OF THE PELLET MACHINE. (a) mold; (b) flat steel plate with machine ground surface; (c) die with plungers corresponding to holes in mold; (d) receptacle. Fig. 2A. PELLET MACHINE ASSEMBLED AND READY FOR COMPRESSION AFTER THE POWDERED CRYSTALLINE ANDROGEN HAS BEEN PACKED IN THE HOLES.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

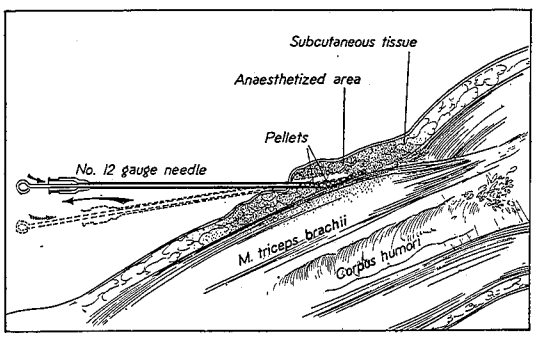

Fig. 3. DIAGRAMMATIC ILLUSTRATION OF INSERTION OF PELLETS INTO SUBCUTANEOUS TISSUES.

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,

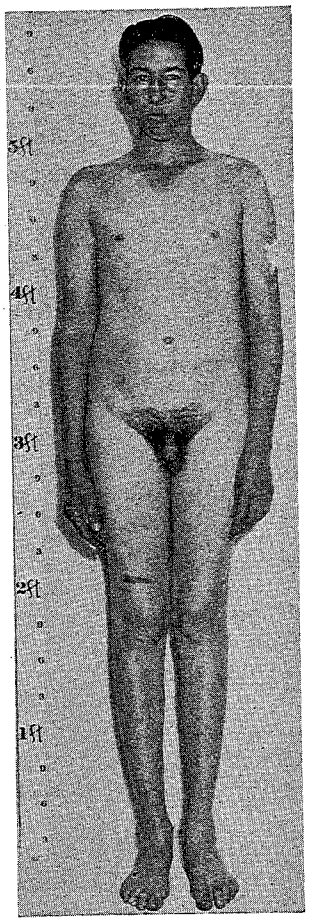

Fig. 4. *Case 1*, primary hypogonadism; age 31. Note disproportionately long extremities, small genitalia and feminine pubic escutcheon. See text for response to testosterone implants.

[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).