PERORAL USE OF METHYL TESTOSTERONE IN TESTICULAR DEFICIENCY

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The effects of androgenic hormone therapy have been studied rather completely within the past few years, not only in testicular deficiency but also in such conditions in women as menorrhagia, the climacteric, and for the inhibition of lactation.

In eunuchoidism or eunuchism the typical effects of androgens include increase in libido sexualis, in potence, energy, growth of the external and internal genitalia, stimulation of growth of secondary sexual characteristics, and if the dose is sufficient, the rate of epiphyseal closure increases. Where sperms are present, continued large doses of testosterone propionate tend to suppress their production. In addition, there are certain metabolic effects which include retention of sodium, chloride, nitrogen, and water, with an accompanying gain in body weight[1]. There is evidence also that some elevation of the basal metabolic rate exists, although to date this is less definite.

Most striking clinical effects have been produced by the intramuscular use of testosterone propionate in oil in doses approximating 10 to 50 mg. a day or on alternate days. Apart from depression of sperm production[2] and the possibility of too rapid epiphyseal closure, no harmful effects of consequence have been reported. In women, production of masculinization is an obstacle to its free use.

The evidence that good clinical results can be obtained by percutaneous administration of androgens is not impressive. Vest[3] has shown clearly in cases of eunuchoidism that excellent results can be obtained by the subcutaneous implantation of pellets of testosterone. Foss[4] reported the successful clinical use of peroral methyl testosterone. The results were comparable to those reported by us[5] and others in cases of testicular deficiency treated with injections of testosterone propionate.

Since January, 1940, we have observed some clinical effects of methyl testosterone given orally in nineteen cases of various types of testicular failure and impotence and in a few cases of women. It is not advisable at this time to make a complete comparison of these results with those of cases treated with testosterone propionate. It is evident, however, that the drug is very effective and that its effects appear to differ in some ways from those of testosterone propionate.

Methyl testosterone has been given to our cases in tablets containing 25 mg. each. In most instances a dose of 25 to 75 mg. per day has been employed and in a few cases as much as 150 mg. a day has been given. Such treatment has been well tolerated in all cases, and there have been no gastro-intestinal disturbances.

In cases of testicular deficiency, either with obvious clinical signs or in those few in which the diagnosis was accepted on the basis of symptoms and low androgen assays, the response to this treatment was approximately the same as that seen following injections of testosterone propionate. Within a few days there occurred a striking increase in the number and power of penile erections, and a sense of energy and well being was noted. These symptoms usually disappeared within a week after discontinuing the drug. After several weeks of treatment there was a measurable increase in the size of the penis, and an increase in the amount of pubic and axillary hair. In one case lowering in the pitch of the voice was noted after two months of therapy. In another, a distinct increase in the size of the prostate could be detected after four months of treatment.

In patients who previously had had injections of testosterone propionate over many months, it was judged that the symptomatic effect of a certain amount of testosterone propionate could be reduplicated by approximately three to four times the amount of methyl testosterone by mouth. In several cases it was noted that the striking sexual stimulation which occurred within a few days tended to diminish after several weeks, while the same dosage continued to be used. A similar diminution of effect has been noted from continued doses of diethyl stilbestrol in women (Schorr and Papanicolaou). Whether this may be connected with an increasing power on the part of the liver to metabolize the drug, as has been suggested for diethyl stilbestrol, is unknown. On ingestion of methyl testosterone, gain in body weight has been a prompt and rather striking feature in some cases. On doses of 75 mg. a day, weight gains on the order of ten pounds in two weeks have been seen. One man voluntarily discontinued taking the drug because of an uncomfortable sense of bloating, associated with a gain of thirteen pounds in weight in twenty-three days. In another case, a similar gain in weight was associated with severe headache. In this instance treatment was being given for hypogonadism incident to a pituitary tumor which had been operated upon within the preceding month, and it was suspected that the headache was caused by an increase in intracranial edema. Such increases in body weight suggest that the effect of methyl testosterone on sodium, chloride, and water retention is similar to that seen following the use of testosterone propinate and other related steroids.

Studies of excreted androgens following the oral administration of methyl testosterone indicate that in the body the metabolism of this material differs materially from that of injected testosterone propionate. In the case of the latter drug, it has been shown that the symptomatic response in hypogonadal males is associated with a rise of urinary androgens to approximately the range of normal. Single injections of 10 mg. of testosterone propionate into eunuchoid men cause an increase

in excreted androgens varying from 10 to 20 international units in twenty-four hours. Following injection of 50 mg., 60 to 100 units is excreted in twenty-four hours[6]. This sequence does not appear to take place with methyl testosterone. Following administration of amounts of methyl testosterone sufficient to give a decided symptomatic response, little or no rise in urinary androgens can be detected by the capon assay method of McCullagh and McLin[7].

In cases observed to date, methyl testosterone seems to have a definite effect in causing an elevation of the basal metabolic rate. This is illustrated in the case reported below. Each basal metabolic rate listed is an average of two runs. The Sanborn graphic apparatus was used and the Aub-Dubois standards were employed.

Report of Case

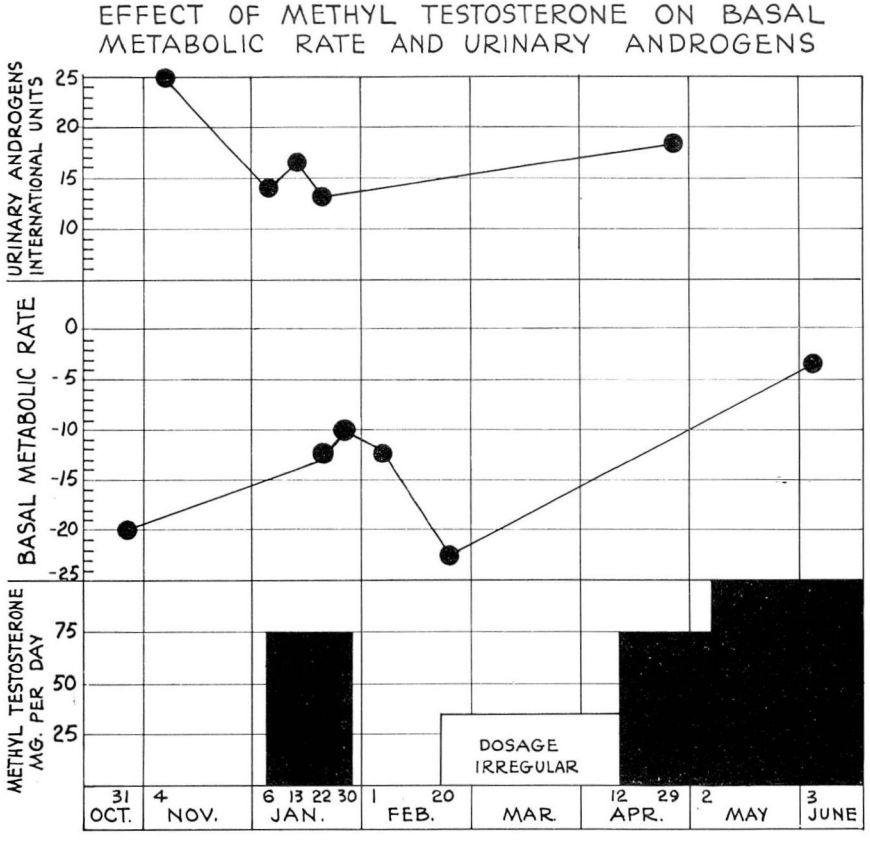
A man, twenty-eight years of age, was examined in September, 1939. At the age of fourteen years, severe trauma to both testes had been followed by marked swelling. Repeated trauma to both glands occurred six months later and this was followed by complete disappearance of the testes, so far as the patient could determine. The voice had changed somewhat prior to that time. Following the second injury, there was little or no further development of pubic and axillary hair or genital growth. Secondary sex characteristics, such as the beard, did not appear. He married when twenty-five years of age. He had little or no sexual desire and coitus was possible, occasionally with orgasm but without ejaculation. There were no signs suggestive of pituitary disease or hypothalamic injury. He had no cold intolerance, no dryness of the skin, hair, or nails, and no edema or paresthesiae. He was 70¾ inches tall, with a span of seventy-two inches and he weighed 188 pounds. The facial appearance was boyish. The skin was very fine in texture, and there was no beard. The pubic and axillary hair was sparse and there was virtually no hair on the trunk or extremities. The penis measured 10 cm. in length from the pubic bone to the tip. The scrotum was very small and no testes were palpable. The prostate gland was minute, its borders being defined with difficulty by rectal palpation.

Wassermann tests of the blood gave negative reactions. Other laboratory tests were not significant, except those listed below. Blood cholesterol determinations done in October, 1939, and in February, 1940, were 222, 208, and 194 mg. per 100 cc. A roentgenogram of the skull indicated no enlargement of the sella turcica, and all the epiphyseal lines were closed. A modified Friedman test showed no measurable gonadotropic substances.

A diagnosis of eunuchoidism of moderately severe degree following testicular trauma was made.

The treatment was as follows: For twenty-three days he received 25 mg. of methyl testosterone given orally in tablet form three times a day. Within a day or two, erections, which had occurred once a week or less, were occurring daily. After two weeks erections were occurring almost constantly. The patient noted considerable fullness of the tissues of the body and a sense of bloating. In twenty-three days his weight had increased to 213¾ pounds, a gain of 13¾ pounds. Treatment was discontinued and no methyl testosterone was taken from January twenty-ninth to April twelfth. Following the discontinuance of treatment, sexual stimulation disappeared in about a week and the patient noted that he had less energy. Twenty days after discontinuing treatment, his weight had

fallen to 209 pounds. From April twelfth to May twenty-second methyl testosterone was given in doses of 25 mg. three times a day. Again there was a marked increase in sexual power within four days after beginning treatment. After this had been continued for several weeks, a gradual diminution in the sexual stimulation occurred, and thirty-nine days after beginning treatment (May 21), erections were occurring about normally but there was no excessive stimulation. His weight had fallen to as low as 201 pounds on the second of May and rose again to 209 on May twenty-first. By the twenty-first of May certain anatomical changes had taken place. There was some growth of the penis. On June fifth the penis was 15 cm. in length and much increased in diameter. The prostate was distinctly larger than on the original examination, having increased from perhaps one quarter to three quarters of normal size. The patient still noted an increase in the sense of energy as compared to the period prior to the treatment. On June fifth he weighed 214 pounds.



Repeated estimations of the basal metabolism indicate that methyl testosterone has a distinct effect upon the basal metabolic rate. On October 31, 1939, the basal metabolic rates averaged minus 20 per cent. After having had treatment as listed above for twenty-four days, the basal metabolism was minus 12 per cent. The following day it was minus 10 per cent. On February first it was minus 12 per cent. After having had no treatment for twenty-two days, the basal metab-

olism was minus 23 per cent. No thyroid therapy had been used throughout. The drug was then used in the doses indicated on the chart. The basal metabolism was minus 4 per cent on June third, following doses of 100 mg. per day.

Assays for urinary androgens were equally interesting. Before any treatment was given, bio-assay by the method of McCullagh and McLin[7] showed 25 international units on November fourth. An assay of this height has been seen occasionally in hypogonadal individuals, and, although it is not the rule, it undoubtedly represents definite quantities of androgens. These almost certainly arise from the adrenal cortex and do not represent testicular hormones. On January sixth, prior to the beginning of treatment, repetition of the bio-assay showed 14 international units. Assays in normal individuals by this method show between 18 and 80 international units of androgens. Treatment was begun on January sixth and one week later, when striking clinical effects were obvious, bio-assay revealed 16 international units of androgens, and one week subsequently, when sexual stimulation was excessive, bio-assay had still shown no rise whatever, showing 13 international units. On April twenty-ninth, following consistent use of 75 mg. of the drug daily, bio-assay revealed only 19 international units of androgens. As mentioned above, such a complete lack of response, so far as can be determined by the measure of excreted androgens, is entirely different from that which we have seen following the use of testosterone propionate, and indicates clearly that the metabolism of this substance in the body differs from that of testosterone propionate.

Summary

Oral methyl testosterone is effective therapy in eunuchoidism. In terms of clinical symptoms its effectiveness as compared to testosterone propionate injections approximates 3 or 4 to 1.

The metabolism of methyl testosterone differs from that of testosterone propionate in that clinically effective doses of the propionate are followed by a rather marked increase in urinary androgens. With methyl testosterone, this sequence does not occur to the same extent.

Methyl testosterone has the power to raise the basal metabolic rate.

An illustrative case is reported.

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