# A Singularly Long-Acting Ether of Testosterone. (31472)

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Recently Brown* synthesized a trimethylsilyl ether of testosterone, the 17-hydroxyl being replaced by O-Si$(CH_3)_3$. When this compound was administered intramuscularly to castrated male rats over a period of 7 days, according to the method of Eisenberg and Gordan(1), it showed only 10% the androgenic and myotrophic potency of testosterone propionate.† It was considered that this apparently low activity might indicate slow absorption or slow destruction of the steroid and thus a long duration of effect might be achieved.

In an earlier paper we reported on changes in the weights of the seminal vesicles, ventral prostate glands and levator ani muscles of castrated male rats at various times after a single injection of testosterone propionate and several other androgenic-myotrophic steroids (2). The maximal response to a single subcutaneous injection of testosterone propionate was noted after 7 to 10 days. A similar study was set up to compare the effects of testosterone propionate and the 17-trimethylsilyl ether (SC-16148).

Immature male rats were castrated at 25 days of age and 21 days after the operation they were weighed and treated with a single subcutaneous injection of 10 mg of the steroid suspended in 0.2 ml of corn oil. The rats were sacrificed at varying periods from 2 to 50 days after the injection. The seminal vesicles, ventral prostate glands and levator ani muscles were dissected out and weighed. There were 8 or 9 rats in each group. The results are shown in Fig. 1. As in the earlier study, the maximal androgenic response to a single injection of testosterone propionate, as measured by seminal vesicle and ventral prostate weights, was observed after 7 to 10 days. With SC-16148 the peak androgenic response was observed at 20 to 30 days. Not only did

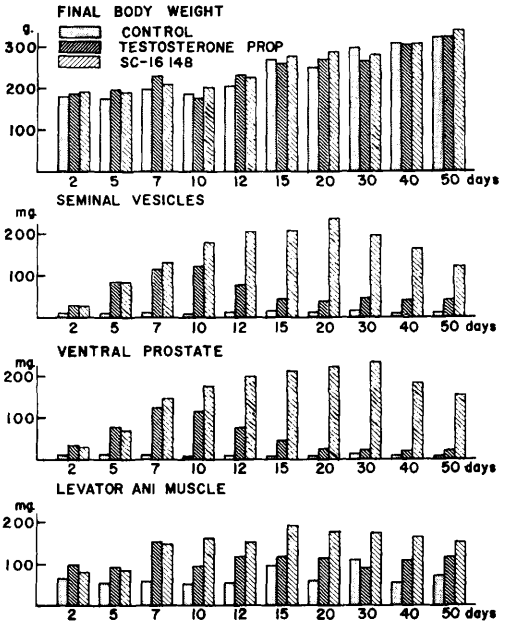


FIG. 1. Terminal body, seminal vesicle, ventral prostrate gland and levator ani muscle weights in castrated rats at various times following a single subcutaneous injection of testosterone propionate or the trimethylsilyl ether of testosterone (SC-16148). Each bar is an average value for 8 or 9 rats.

SC-16148 demonstrate a much longer period of effectiveness but also the weights of the accessory organs reached much higher levels.

The myotrophic effect of SC-16148 was also prolonged but the stimulatory effect on the levator ani muscle was less dramatic than the effect on the seminal vesicles and ventral prostate gland. The gains in body weight were not apparently altered by either compound.

While the trimethylsilyl ether of testosterone was much less effective than testosterone propionate in a short term assay in which the compounds were injected daily over a 7-day period,† the continued growth of the seminal vesicles and ventral prostate glands for a period of 20 to 30 days following a single injection of the compound demonstrates that this trimethylsilyl ether has a singularly prolonged duration of action. Although relative potencies of the two com-

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pounds cannot be assigned from this study, nevertheless it is evident that the trimethylsilyl ether is much more effective than a similar dose of testosterone propionate by 7 days after a single injection.

In an earlier study(2) I reported the prolonged effects of a single injection of 4-estrene-3$\beta$,17$\beta$-diol 3,17-dipropionate in castrated rats. The maximal response to this dipropionate was achieved by the tenth day as indicated by seminal vesicle weights of 134 mg and ventral prostate weights of 113 mg. With the trimethylsilyl ether, the maximal seminal vesicle weights, 237 mg, were observed 20 days, and the maximal ventral prostate gland weights, 232 mg, 30 days after the single injection.

In somewhat similar tests the peak ventral prostate response to testosterone-17-cyclopentylpropionate was observed at 14 days (Sala and Baldratti(3)). The 3-cyclopentyl enol ether of methyltestosterone produced its maximal effect only a few days later than did methyltestosterone (Meli(4)). Diczfalusy(5) reported peak effects after a single injection of testosterone-17-enanthate at 16 to 28 days, testosterone-17-cyclopentylpropionate at 16 to 28 days while the p-hexophenyl propionic acid ester of testosterone produced its peak response at 42 days. In a review of steroid esters, Junkmann and Witzel(6) indicated a maximal response to the 17-enanthate (14 days) and the cyclopentylpropionate (12 days) only slightly delayed compared to the propionate (11 days).

Interest in the trimethylsilyl ether of testosterone arises from its long duration of action, the magnitude of the ultimate response in the male accessory organs and its unique chemical composition.

*Summary.* Substitution of a trimethylsilyl ether for the propionic acid moiety in testosterone propionate resulted in a peculiarly long-acting androgenic compound. The maximal response to a single subcutaneous injection in castrated rats was obtained 20 to 30 days after treatment. Not only was the duration of effectiveness of the trimethylsilyl ether much greater than that of the same dose of testosterone propionate, but the ultimate magnitude of the response was also increased.

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## Absence of an Exaggerated Renal Response to Acute Salt Loading In Salt-Hypertensive Rats.* (31473)

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Hypertensive individuals generally respond to expansion of their body fluids by a greater natriuresis and diuresis than normotensive subjects. The mechanism for this phenomenon remains unexplained. It was suggested that the enhanced natriuresis was due to the high pressure *per se,* and was consequently a result of the hypertensive state(3,14,16). Other workers have attributed the phenomenon to an abnormal sensitivity of a volume regulating mechanism associated with hypertension(24,26), and possibly preceding the advent of high blood pressure(25).

In man, a basic difficulty in determining whether the exaggerated response to acute salt

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