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Comparative Study of Effects of Testosterone Propionate Administered Intraperitoneally and Subcutaneously.

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It is now generally recognized that the potency of hormones may vary in accordance with their mode of administration. Working with the female rat, Israel, Meranze, and Johnson,[1] for example, have observed that the liver counteracted the effect of estrogens, a fact which they have used to explain the lessened potency of this hormone when administered intraperitoneally.

Working with the androgens, Deanesly and Parkes[2] also concluded that intraperitoneal injection resulted in minimal effectiveness. They, however, felt that this was due to the rapid absorption which the peritoneal lining favors.

In a previous communication[3] observations concerning the efficacy of intraperitoneally administered testosterone propionate were reported.

The following study offers added evidence that the potency of testosterone propionate is not necessarily diminished when administered intraperitoneally, but under certain conditions may even be enhanced.

For this study 45 male albino rats *(Mus norvegicus var. albus)* of Wistar Institute Strain and of approximately similar body weights were divided into 3 groups, each containing 15 respective litter mate brothers. Each animal in Groups 1 and 2 received 50 γ testosterone propionate (Perandren) dissolved in 0.1 cc sesame oil daily for 10 days. In Group 1, this was given intraperitoneally; in Group 2, subcutaneously. Animals in Group 3 served as litter mate controls. The first injection was given at 22 days of age; the last at 31 days, 24 hr after which all animals were weighed and sacrificed. Seminal vesicles (empty) and testes (without epididymides) were dissected and weighed.

The data were statistically analyzed and observed differences were considered to be "probably significant" only if the significance ratios were 3 or more.[4]

Results. From Table 1 it may be seen that body weights before and after treatment were statistically within the limits of random sampling for all groups.

The seminal vesicles became significantly larger by 274% for those intraperitoneally treated, and by 185% for those subcutaneously treated.

The testes of both treated groups were significantly smaller than those of the controls. For the animals treated intraperitoneally this was —41.9%, while for the subcutaneously injected animals it was —52.8%.

Discussion. Although when statistically considered, differences in body weights between the groups remained within the limits of random sampling, it is interesting that the group treated intraperitoneally did show a final body weight which was 7.53% less than that of the controls. This decrease at the end of treatment when added to the 3.86% by which the same group was heavier (than their controls) prior to treatment shows a total weight change of 11%. When this total weight change (*i.e.* gain in weight) is submitted to statistical methods it discloses a significance ratio of 2.56. While this, too, fails to reach the criterion set for "probable significance," its magnitude certainly indicates a trend: namely, that of inhibition of body growth (*i.e.* weight) by testosterone propionate. Since it has been shown by more protracted experiments that

[1] Israel, S. L., Meranze, D. R., and Johnson, C. G., *Am. J. Med. Sci.*, 1937, **194**, 835.

[2] Deanesly, R., and Parkes, A. S., *Proc. Roy. Soc.*, 1937-38, **124**, 279.

[3] Rubinstein, H. S., and Kurland, A. A., *Endocrinology*, 1941, **28**, 495.

[4] Pearl, R., *Medical Biometry and Statistics*, 2nd edition, Saunders, Philadelphia, 1930.

TABLE I.
Effects of Androgen Administration to Rats.*

		Difference from control		
		Wt	%	S.R.
Initial Body Wt (g)				
Control	31.1 ± 0.4			
Intraperitoneal test	32.3 ± 0.7	+1.2 ± 0.81	+3.86	1.48
Subcutaneous test	32.1 ± 0.6	+1.0 ± 0.72	+3.24	1.39
Final Body Wt (g)				
Control	63.8 ± 1.6			
Intraperitoneal test	59.0 ± 1.5	—4.8 ± 2.19	—7.53	2.19
Subcutaneous test	64.8 ± 1.9	+1.0 ± 2.50	+1.57	0.40
Seminal Vesicular Wt (mg)				
Control	16.6 ± 1.0			
Intraperitoneal test	62.1 ± 3.9	+45.5 ± 4.1	+274	11.10
Subcutaneous test	47.3 ± 3.2	+30.7 ± 3.3	+185	9.31
Testicular Wt (mg)				
Control	556.2 ± 21.7			
Intraperitoneal test	323.6 ± 18.9	—232.6 ± 28.8	—41.9	8.10
Subcutaneous test	262.1 ± 16.3	—294.1 ± 25.0	—52.8	11.75

*A comparison of body weights, seminal vesicular and testicular weights of animals injected with 50 γ testosterone propionate daily for 10 days (from 21 to 31 days of age) either intraperitoneally or subcutaneously with their litter brother controls. S.R. indicates "significance ratio."

suitably small doses stimulate[5,6] and large doses inhibit body growth,[7] it must be inferred that in all probability the 50 γ dosage was more potent (for this sized animal) by intraperitoneal injections than by subcutaneous administration.

This difference in potency is also reflected in the effect on the seminal vesicles, a comparison of which (Table I) shows how much heavier (1.47 ×) those of the intraperitoneally-injected animals grew than those of their subcutaneously-injected brothers. This finding substantiates the earlier observation[3] made with 20 γ dosage which also resulted in larger seminal vesicles (by 1.22 ×) in intraperitoneally-injected animals than in their subcutaneously-injected controls.

The effect of testosterone propionate on testicular weight is also different for the two methods of administration. Here, however, the depressing effect is greater by subcutaneous injection (—52%) than by intraperitoneal administration (—41.9%). This response differs from that previously reported for 20 γ experiments. With the smaller dosage, the testicular depression was more marked by intraperitoneal treatment than by subcutaneous injections. As a matter of fact, the effect may be said to be quantitatively diametrically opposite. For example, with 20 γ dosage intraperitoneally, testes were depressed 26%; with 20 γ subcutaneously, testes were depressed 20%. This shows a 1.3 × greater depression by intraperitoneal than by subcutaneous injection. A similar comparison made for our 50 γ experiments shows a 1.26 × greater depression by subcutaneous than by intraperitoneal injection.

On the basis of our earlier experiments it was felt, with conservatism, that the effect of testosterone propionate was approximately the same whether the hormone was injected intraperitoneally or subcutaneously. The confirmation yielded by our 50 γ experiments as shown by the seminal vesicular response indicates that for some tissues the effects produced by intraperitoneal injections may be even more striking than those obtained subcutaneously.

[5] Rubinstein, H. S., and Solomon, M. L., PROC. SOC. EXP. BIOL. AND MED., 1940, **44**, 442.

[6] Shay, H., Gershon-Cohen, J., Paschkis, K., and Fels, S. S., *Endocrinology*, 1941, **28**, 877.

[7] Rubinstein, H. S., Jurland, A. A., and Goodwin, M., *Endocrinology*, 1939, **25**, 724.

There seems to be no doubt, therefore, that for experiments such as described testosterone propionate can be more potent for some tissues by the intraperitoneal route than when given subcutaneously. Interestingly enough, when similar doses are used for longer periods of time (*e.g.* from 26 to 80 days) the seminal vesicle may respond better to subcutaneous than to intraperitoneal injections.[8]

Summary. A comparative study of the potency of testosterone propionate administered intraperitoneally and subcutaneously in 45 respective litter mate male albino rats has been made. Injections of 50 γ daily dosage were given for 10 days from 22 to 32 days of age. Body weights before and after the experiment, final seminal vesicular- and testicular-weights were statistically compared. It was found that the intraperitoneally-injected animals gained 11% less weight, and showed a 274% *increase* in seminal vesicular growth, and a 41.9% *decrease* in testicular size over their controls. The subcutaneously injected animals showed practically no difference in gain in weight, a 185% *increase* in seminal vesicular weight, and a 52.8% *decrease* in testicular size compared to their controls. The differences observed for seminal vesicular and testicular weights were statistically "probably significant." The diminished weight increase observed for the intraperitoneally-injected animals while not statistically significant was sufficiently large to indicate a trend.

It is concluded that under the conditions of the experiments cited, testosterone propionate may vary in potency in accordance with its method of administration. But generalizations are as yet invalid since the greater testicular effect (depression) was observed by subcutaneous injection, and the greatest seminal vesicular response (stimulation) resulted from intraperitoneal administration.

The author acknowledges with appreciation the aid rendered by the Ciba Pharmaceutical Products, Inc., for helping defray the expense and for supplying the Perandren used in this study.

[8] Rubinstein, H. S., unpublished data.

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A Study of Clot Firmness in Viscometer Tubes.

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Determinations of clot firmness have been made by studying the tensile strength of clots. Fonio[1] prepared plasma clots with magnesium sulfate solution and ether. He pressed the clots into discs, suspended them, and determined their tensile strength. Kristenson[2] who criticized this method used clots from plasma which was prepared by centrifugation in ice jackets. Following incubation at 37° C. for 1 hour he wrapped both ends of the coagulum in linen cloth and tied a string around each end. He then measured the tensile strength by adding weights until the clot tore. Schnedorf[3] permitted blood to coagulate around two wire meshes which served as points of attachment. Five to 30 minutes after coagulation at room temperature, weights were added to measure the tensile strength. By employing different amounts of blood and using several modifications of the same principle, he was unable to obtain comparable results. To test clot firm-

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[1] Fonio, A., *Schweiz. med. Wchnschr.*, 1921, **11**, 146.

[2] Kristenson, A., *Acta med. Scandinav.*, 1932, **77**, 351.

[3] Schnedorf, J. G., personal communication, 1942.