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Inactivation of Methyl Testosterone in Castrate Male Rats.

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Methyl testosterone has been shown to be more effective on oral administration in man[1] and rats[2] than testosterone, testosterone propionate, and other related semi-synthetic androgens. This may indicate either a different route of absorption from the intestinal tract, or a different site of inactivation. To examine these possibilities, pellets of crystalline methyl testosterone* were implanted into the subcutaneous tissues, the normally situated spleen, and the transplanted spleen with pedicle tied, of groups of large castrated adult male rats of the Long-Evans strain. In the last group the spleen was transplanted at the time of castration between the overlying muscle and skin without impairing its vascular supply. Three weeks later the pellet was placed in the spleen, and at the same time a ligature was tied around the splenic vessels, which probably did not completely obstruct the artery. In all groups the pellet was inserted three weeks after castration. The animals were sacrificed 4 weeks after the pellets were implanted, the genital tract was removed, the seminal vesicles, prostate and bulbo-urethral muscles dissected free, and each of the organs was weighed on a damped balance. The contents of the seminal vesicles were carefully expressed before weighing. The remainder of each pellet was removed, cleaned, dried and weighed.

With the pellet implanted subcutaneously, the weights of the respective organs of the group show the usual significant increase when compared to the castrate control group, indicating that effective absorption from the pellet has taken place. In the group with the normally situated spleen, the weights of the respective organs are of the same order of magnitude as the castrate control group. The slight variation is explicable by the fact that the average weight of the animals in the former group is considerably more than in the latter group.

In Group IV, where the pellet was inserted in the transplanted

1 Foss, G. L., *Brit. Med. J.*, 1939, **2**, 11.

2 Miescher, K., and Tschopp, E., *Schweiz. Med. Wschr.*, 1938, **68**, 1258.

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spleen, the weights of the respective organs are of the same order of magnitude as in the group with the pellet in the subcutaneous tissues, indicating that absorption has taken place in the spleen, and that when the circulation from the spleen is shunted away from the portal into the general circulation enough is absorbed to be capable of exerting specific androgenic action. The average amount absorbed from any site from each pellet is .089 mg per day, which is greater than that absorbed from similar pellets of testosterone propionate, which averages .065 mg per day.[3]

Thus the same interpretations apply to this experiment as to the similar one in which testosterone propionate was tested;[3] namely, that transportation of the methyl testosterone through the liver from the normally situated spleen causes its inactivation. This experiment, like the previous one, has not completely excluded the possibility that the normal spleen may play a minor part in this process. Slight histological changes occur in the transplanted spleen which may conceivably be associated with altered function.

The results of the present observations indicate that the quantita-

TABLE I.
The Inactivation of Methyl Testosterone in the Castrate Adult Male Rat.

Animal No.	Seminal vesicles, mg	Prostate, mg	Bulbo-urethral muscles, mg	Animal weight, g	Pellet absorption, mg
I. Castrate controls					
1840	103	125	270	240	
1845	86	135	442	340	
1846	104	65	484	344	
1847	195	133	597	360	
1850	174	200	581	360	
1851	177	249	689	360	
1857	161	144	637	360	
Avg	143	150	528	338	
II. Methyl testosterone implantation in subcutaneous tissues					
1856	524	761	1315	380	.075
1858	498	659	1094	360	.091
1859	424	750	1214	250	.082
Avg	482	723	1208	330	.083
III. Methyl testosterone implantation in normally situated spleen					
1853	185	150	511	410	.078
1854	244	124	642	460	.107
1855	133	146	455	400	.105
Avg	187	140	536	423	.097
IV. Methyl testosterone implantation in transplanted spleen					
1838	410	440	900	340	.110
1839	707	1290	1255	470	.090
1843	640	910	1210	400	.060
1844	423	665	690	376	Broken
Avg	545	826	1014	396	.087

[3] Biskind, G. R., and Mark, J., *Bull. Johns Hopkins Hosp.*, 1939, **65**, 212.

tive differences in specific activity noted on oral administration of testosterone propionate and methyl testosterone may be related to a difference in the route of absorption from the intestinal tract, rather than to a lesser destruction of methyl testosterone by intestinal ferments as has been suggested.[2] If absorption is mainly by way of the lacteals and lymphatics, thus avoiding the liver, a greater specific effect should be present than if absorption occurs into the portal circulation. It is likely that the specific chemical structure influences the route of absorption. There is one other possibility, although a slight one. Methyl testosterone may be absorbed through the esophagus during ingestion and thus enter the systemic circulation by way of the esophageal veins; or if it is less rapidly destroyed in the gut, or less rapidly absorbed, enough might reach the lower gut to enter the systemic circulation by way of the hemorrhoidal veins.

Summary and Conclusion. Methyl testosterone, like testosterone propionate, does not exert its specific effect on the genital organs of castrate male rats when implanted in pellet form in the spleen. When the pellet is placed in the transplanted spleen, with the splenic vessels ligated, the specific effect returns. As both androgens appear to be destroyed in the liver, it is suggested that the differences in the specific effects of these two substances when administered orally may be due to different routes of absorption from the intestinal tract (*e. g., via* the lymphatics), rather than different sites of inactivation.

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Proof of Excitability of Mammalian Ventricles During Systole.

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In a recent paper[1] we reported that a single, short, strong, localized shock applied directly to different regions of the left ventricle of dogs anesthetized by sodium barbital can produce permanent ventricular fibrillation. The same results have since been obtained on dogs under chloralosane and in cats under dial anesthesia. A shock, if strong enough and given during the vulnerable period near the end of ventricular systole, produces one extra-systole followed by about 4 more or less coördinated beats and then by true ventricular fibrillation. If

1 Wiggers and Wégria, *Am. J. Physiol.*, in press.