TABLE I.

Material	B.P. °C	Sp. gr., 25°C	MeO %
Creosote	200-215	1.085	12.5
Phenols extracted from rabbit urine after creosote administration	192-215	1.085	11.6

Summary. 1. Calcium creosotate administered either in single doses of 0.5 to 2.0 g or in amounts and at intervals approximating its therapeutic application (0.5 g every 2 hours) did not produce bacteriostatic urine in normal human subjects. 2. Evidence was obtained that practically all of orally administered calcium creosotate which is excreted in rabbit urine is present in conjugated form. 3. Data are presented to show that after hydrolysis of the conjugates a portion of orally administered creosote could be recovered in rabbit urine. This indicates that the methoxy compounds are not more readily destroyed in the body than the other phenols of the mixture.

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Some Effects of Testosterone on Sexual Differentiation of Female Albino Mice.

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Early investigators observed that the persistence of testicular transplants in oöphorectomized rodents produced hypertrophy of the clitoris. Since male sex hormone became available in crystalline form, it has been demonstrated that varying degrees of intersexuality may be induced experimentally in guinea pigs,[1, 2] mice,[3, 4, 5] rats,[6–10] and rabbits.[10] Although the previous findings of Raynaud indicated that a pronounced degree of masculinization of genetic

1 Dantchakoff, V., *Compt. Rend. Soc. de Biol.*, 1936, **123**, 823.

2 *Ibid.*, 1937, **124**, 195.

3 Lacassagne, A., and Raynaud, *A.*, *Compt. Rend. Soc. de Biol.*, 1937, **125**, 351.

4 Raynaud, A., *Compt. Rend. Soc. de Biol.*, 1937, **126**, 866.

5 Raynaud, A., and Lacassagne, A., *Compt. Rend. Soc. de Biol.*, 1937, **126**, 868.

6 Greene, R. R., and Ivy, A. C., *Science*, 1937, **86**, 200.

7 Greene, R. R., Burrill, M. W., and Ivy, A. C., *Science*, 1938, **87**, 396.

8 *Ibid.*, PROC. SOC. EXP. BIOL. AND MED., 1938, **38**, 4.

9 *Ibid.*, 1938, **38**, 1.

10 Hamilton, J. B., and Gardner, W. U., PROC. SOC. EXP. BIOL. AND MED., 1937, **37**, 570.

female mice resulted from both prenatal and postnatal administration of androgens, it was thought that more detailed and extensive studies on the mouse were justifiable.

The present work is based on dissections, wax reconstructions and histological studies of a total of 94 genetic female mice which displayed varying degrees of intersexuality. Forty-four adults received subcutaneous or intraperitoneal injections of testosterone propionate* between the time of copulation and parturition. Sixteen of these pregnancies were terminated by resorption or by the delivery of dead fetuses; 28 of the treated mothers produced a total of 74 viable offspring (Table I). Eighteen of the young (8 litters) which received prenatal treatment also received postnatal injections of 0.5 mg of testosterone at 48-hour intervals from birth until autopsy. Twenty offspring (7 litters) received only postnatal treatment, the testosterone being administered subcutaneously or massaged into the skin (Table I).

The prenatal administration of testosterone, if present in the organism at the period when both Müllerian and Wolffian systems are first differentiated, leads to the persistence of Wolffian duct derivatives and to the inhibition of the distal portion of the vagina. Five milligrams of testosterone administered to the mother on the fifth day of gestation did not influence the genital organs of the offspring (litter 13). A similar amount of testosterone injected on the seventeenth day of gestation (litter 3) did not maintain the Wolffian ducts in genetic female offspring nor prevent vaginal introitus, but did result in a mild modification of the clitoris. Animals receiving postnatal treatments (Table I) from birth until autopsy possess an enlarged clitoris dorsal to which is present a fold of skin surrounding the minute vaginal orifice; the genital tract is not otherwise appreciably modified. The most pronounced modifications are produced when the hormone is administered between the tenth and fourteenth days of pregnancy. There are, however, some variations among genetic females of the same litter even when large amounts of testosterone are administered at the critical period of pregnancy. In well affected offspring, subjected only to prenatal treatment, there is persistence of epididymides, ductuli efferentes extending from the rete portions of the ovaries to the epididymides, vasa deferentia, prostatic lobes, vesicular glands, Cowper's glands, and enlarged preputial glands. The clitori of such animals are hypertrophic, possess os priapi, cavernous bodies, and are perforated by penile urethrae. Except for their smaller size, the modified clitori of affected animals

* We wish to acknowledge the generous supply of testosterone propionate (Perandren) provided by the Ciba Pharmaceutical Products, Inc.

TABLE I.
Summary of Animals Receiving Testosterone Treatment.

Litter No.	No. females in litter	Day of gestation	Amt of testosterone prenatal, mg	Postnatal treatment	Autopsy, days after birth
		(a) Prenatal Injection of Androgen.			
1	2	10	2	None	0*
2	1	10	5	"	0
3	3	17	5	"	0, 36, 143
4	4	10	5	"	1, 10, 30
5	3	12	2.5	"	0
6	4	10	1	"	0, 28
8	5	13	5	"	0, 10, 41
9	2	10	5	"	
		12	3	"	41
10	1	14	5	"	0
12	3	6	1		
		14	3	"	0, 20
13	3	5	5	"	0, 28
15	2	8	5		
		12	2.5	"	124
25	1	12	5	"	0
26	3	11	5	"	30
27	3	10	5	"	0, 60
28	2	12	5	"	0
29	3	12	10	"	10, 30
30	4	14	2	"	0
31	3	10	4	"	10, 15
32	4	10	5	"	0, 30
		(b) Prenatal and Postnatal Androgen.			
14	4	10	1	15 (0.5 mg)	30
17	3	10	2	9 " "	18
18	2	10	1	14 " "	28
19	1	5	5		
		8	2.5		
		10	2.5		
		13	2.5	40 " "	92
20	2	12	5	10 " "	21
21	3	9	5		
		13	2.5	10 " "	23, 112
22	2	7	5		
		10	2.5		
		12	5		
		15	2.5	40 " "	48
23	1	12	5		
		14	5	12 " "	30
		(c) Postnatal Androgen Only.			
11	1	None	None	22 " "	48
16	4	"	"	10 " "	21
33	5	"	"	30 " "	10, 20, 30
34	2	"	"	10 " "	10
35	3	"	"	10 " "	10, 30
36	3	"	"	Massaged	30
37	2	"	"	"	21

* "0" designates individuals autopsied within a few hours subsequent to birth.

are indistinguishable from the penes of normal littermate males. To date we have observed no indication of inhibition of the female tract other than the caudal vagina and the ovary. The ovaries of intersexes

produced by prenatal androgen are abnormally small and are frequently anterior to the kidneys. We have observed no normal luteinization in the ovaries of our intersexed mice, although some were allowed to become mature (Table I, litter 15). Vesicular and non-vesicular follicles, in various stages of atresia, are frequent. In the 2 animals of litter No. 15, autopsied at 124 days of age, introitus did not occur, the uterine horns and proximal vagina were distended with fluid, epididymides persisted bilaterally, the vas deferens did not persist, and remnants of prostatic lobes were present. The ovaries of these 2 animals contained no corpora lutea but possessed a moderate number of vesicular follicles and many atretic ones. Cords of epithelioid cells penetrated the interfollicular areas. The uterine mucosa was metaplastic and consisted of a stratified squamous epithelium, the outer layers of which were highly keratinized. Many leucocytes had infiltrated into the lumina of the uterine horns.

Some of our animals received postnatal injections of androgen in addition to prenatal treatment (Table I). This stimulated the Wolffian duct derivatives and built them up to such degree that they equalled or surpassed the condition present in males of comparable ages. The 2 genetic females of litter No. 22 may be used as examples. Both individuals received prenatal testosterone on the seventh, tenth, twelfth and fifteenth days of pregnancy and 40 small doses (0.5 mg at each injection) of testosterone from birth until autopsy on the forty-eighth day postpartum. Both possessed atrophic ovaries consisting mostly of atretic follicles. The fallopian tubes were normal, ovarian bursae were absent, and there was no indication of pyometria in the uterine horns. The uterine horns fused to form a short duct which is apparently the cranial portion of the vagina. The vaginal canal opened into the prostatic urethra by means of a single orifice. The epididymides, ductuli efferentes, vasa deferentia, ejaculatory ducts, and vesicular glands persisted bilaterally. The prostatic lobes and Cowper's glands were distended by secretions. The penes were perforated for their entire extent by a penile urethra and they were histologically similar to the penes of males of similar ages.

Summary. Fifty-six genetic female mice have been examined subsequent to the prenatal administration of testosterone; 18 subsequent to both prenatal and postnatal treatment; and 20 subsequent to postnatal treatment alone. When testosterone is present in the pregnant mother, at a critical period, Wolffian duct derivatives persist and vaginal differentiation is inhibited. With sufficient testosterone treatment the clitoris is modified into a veritable penis and the utero-vaginal canal opens into the prostatic urethra.