SOME METABOLIC EFFECTS OF ANDROGENIC SUBSTANCES

By Dr. D. PRICE, Dr. T. MANN and Dr. C. LUTWAK-MANN

Department of Zoology, University of Chicago;
Molteno Institute and Biochemical Laboratory, University of Cambridge

IT was previously shown that the secretion of both fructose and citric acid in the male accessory organs of reproduction is governed by, and responds readily to, the fluctuations in the level of the male sex hormone. This close relationship made it practical to use the estimation of fructose and citric acid, either in semen or in the accessory glands, as a 'chemical indicator test' for the male hormone[1,2,3]. Recently, in the course of a metabolic study of transplants from accessory glands of the rat, it was found that when small pieces of male glands were dissected from young rats and transplanted subcutaneously into male or female hosts, such transplants grew readily in response to testosterone propionate or normally secreted testis hormone, and when fully developed exhibited a high content of fructose and citric acid[4,5].

To determine whether the secretion of fructose and citric acid in accessory reproductive organs can be stimulated also by other androgens, we have now carried out further studies upon the metabolic processes in (1) female prostate glands in normal females and in those treated with testosterone propionate, (2) male accessory glands in castrated males treated with synthetic progesterone, and (3) male accessory gland transplants in female hosts treated with gonadotrophin.

Secretion of citric acid in the female prostate gland. A prostate gland develops spontaneously in some female rats, and the incidence varies in different strains. Histologically this organ resembles the ventral prostate gland of the male rat; it can be stimulated by normally secreted androgens from the testis, the ovary and the adrenal cortex and by synthetic male hormone[6,7]. To determine whether the analogy between the female prostate and the male ventral prostate also extends to metabolic properties, the female gland was analysed for its content of citric acid, which is a characteristic secretory constituent of the male ventral prostate[8].

The experimental material was collected from an inbred stock of rats maintained at the Department of Zoology, University of Chicago, which has an 80 per cent incidence of female prostate. It was found that in a 42-mgm. sample of female prostate representing an aggregate from eleven normal two-month-old rats, there was 46 mgm. per cent of citric acid, or 2 μgm. per organ. In response to stimulation with testosterone propionate, there was a remarkable increase in the level of citric acid as well as an increase in the gross size and a change in the histological appearance of the female prostate (compare Figs. 1 and 2). From eleven female rats injected for three weeks with 200 μgm. testosterone propionate daily and autopsied at 85 days of age, 1,236 mgm. prostate tissue was recovered; this contained 1,380 μgm. citric acid, which corresponds to 112 mgm. per cent or 125 μgm.

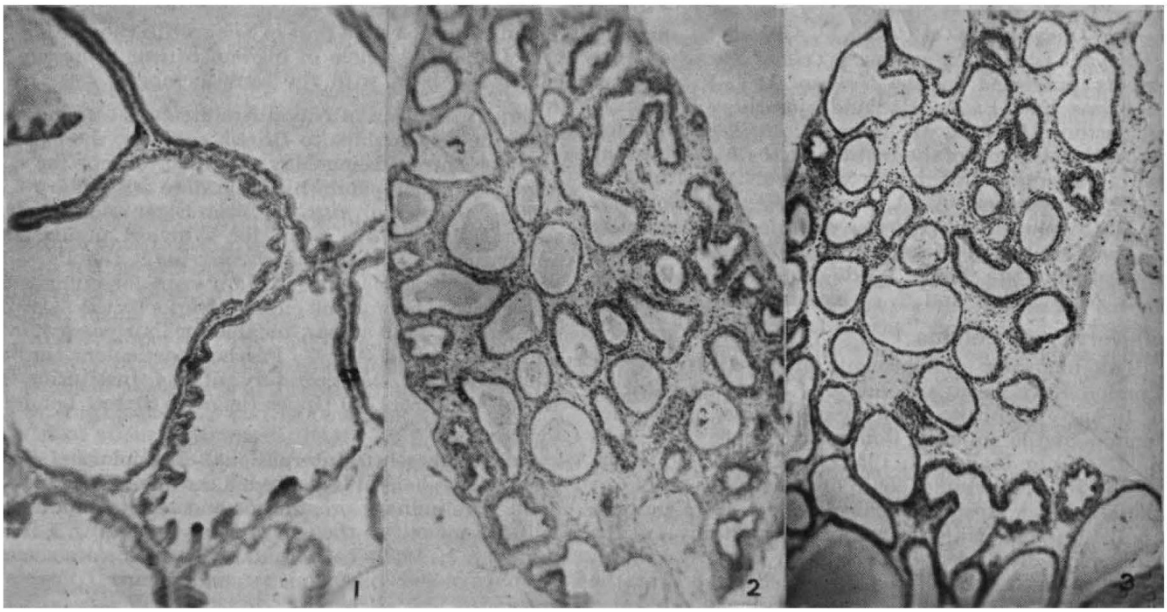

Fig. 1. Prostate gland of a female rat 85 days old injected with testosterone propionate for three weeks prior to autopsy. Note the distended acini and the tall columnar epithelium. × 56

Fig. 2. Prostate gland of a normal untreated female rat 85 days old. × 56

Fig. 3. Prostate gland of a normal untreated female of approximately sixty days of age showing the histological condition of the gland at the age at which testosterone propionate injections were begun. × 56

per organ. Another group of thirteen females received the same dose of hormone for two weeks; here the total tissue collected was 1,012 mgm., containing 1,427 μgm. citric acid, a concentration of 141 mgm. per cent or 110 μgm. per organ. For comparison, determinations were also made on the ventral prostate of male rats; thus in the ventral prostate of males 36–40 days old, there was 44 mgm. per cent or 29 μgm. per organ, in rats 85 days old 39 mgm. per cent or 121 μgm. per organ of citric acid.

These findings bear out the close metabolic resemblance between the male ventral prostate gland and the female prostate, and they show that the prostate of normal untreated females secretes citric acid.

Secretion of citric acid and fructose in male accessory glands in response to progesterone treatment. This series of experiments was carried out to ascertain whether administration of the corpus luteum hormone, progesterone, produces androgenic effects that are biochemically detectable. Effects of progesterone upon the weights and histology of the male accessory glands have been reported (see ref. 9 for recent literature). Twenty-one male rats were castrated at the age of eight to ten weeks, left for nine weeks, and then divided into three groups: (I) untreated; (II) 25 mgm. progesterone ('Proluton' Schering) injected daily for three weeks; (III) 5 μgm. testosterone propionate injected daily for three weeks; in addition there was group (IV) normal non-castrated rats of the same age as groups I, II and III. All animals were 20–22 weeks old at autopsy. Their accessory glands were analysed for citric acid and fructose, as well as for total nucleic acid phosphorus. In this experiment, unlike in our previous studies, the dorsolateral prostate was subdivided by careful dissection into its dorsal and lateral components, each of which was separately analysed. Results are summarized in Table 1.

Table 1. Behaviour of male accessory glands in response to progesterone

Organ	Group of rats*	Weight (mgm.)	Citric acid μgm./ organ	Citric acid mgm. %	Fructose μgm./ organ	Fructose mgm. %	Nucleic phosphorus μgm./ organ	Nucleic phosphorus mgm. %
Ventral prostate	I	14	1	8	0	0	19	133
	II	23	10	45	0	0	26	112
	III	16	4	28	0	0	16	97
	IV	339	232	69	0	0	246	73
Coagulating glands	I	7	0	0	0·3	4	14	197
	II	13	0	0	7	55	17	132
	III	8	0	0	1·4	18	12	152
	IV	132	0	0	348	263	84	64
Seminal vesicles	I	27	0·6	2	0	0	30	112
	II	40	5	12	0	0	39	98
	III	30	1·4	5	0	0	28	94
	IV	962	695	72	0	0	400	41
Lateral prostate	I	7	0·3	4	0·3	4	12	185
	II	29	0·4	1·6	8	28	26	89
	III	12	0·2	3	0·8	7	12	102
	IV	168	63	37	220	131	108	64
Dorsal prostate	I	9	0	0	0·3	4	11	124
	II	16	0	0	2	12	10	64
	III	9	0	0	0·3	3	9	104
	IV	75	0	0	56	75	38	51

* Experimental animals: Group I, castrated, untreated; Group II, castrated, treated with progesterone; Group III, castrated, treated with testosterone propionate; Group IV, non-castrated controls.

Treatment of the young male castrates with relatively large doses of progesterone brought about a distinct stimulation of metabolic activity in all accessory glands, and judging from the values for citric acid and fructose, it even exceeded that due to very small doses of testosterone propionate. The weight of the organs, on the other hand, and the nucleic acid phosphorus content, which presumably expresses the cellularity of these organs, were increased by progesterone in a less conspicuous manner than the secretion of fructose and citric acid. In connexion with nucleic acid phosphorus, it is interesting to note that whereas the absolute content of it in the accessory glands (μgm. per organ) was highest in normal non-castrated rats, its concentration (mgm. per cent) was lowest in this group, because of the considerable accumulation in these glands of secretory fluid which is itself devoid of nucleic acid.

It is clear from the results summarized in Table 1 that large doses of progesterone ('Proluton') were capable of producing androgenic effects in all accessory organs of male castrates.

Secretion of citric acid and fructose in transplants of male accessory glands in female hosts treated with gonadotrophin. In earlier studies it was shown that gonadotrophic treatment of female rats increased the production of ovarian androgens as judged by increase in weight and stimulation in the histological condition of the female prostate gland; in spayed females injected with gonadotrophin, no stimulation of the female prostate was found[7]. In addition, male ventral prostate transplants were strongly stimulated in pregnant and lactating female hosts, as were also the female prostate glands in some of the hosts[10]. To determine whether transplants of male accessory glands secreted fructose and citric acid in response to androgenic stimulation in female hosts, the following experiment was performed. Twenty female rats aged 27–70 days served as hosts; transplants were made of the coagulating gland, the ventral, lateral and dorsal prostate, from thirty-three male donors aged 27–70 days. Immediately following implantation, the female hosts were injected daily with 20 international units of equine gonadotrophin ('Gonadin', Cutter Laboratories) for 30–32 days.

It was found at autopsy that treatment with 'Gonadin' had a striking effect on the growth of the transplants and on the reproductive organs of the females. The behaviour of the transplants in regard to their metabolic activity is shown in Table 2.

Table 2. Transplants of male accessory glands in female hosts treated with gonadotrophic hormone

Transplant	Citric acid (mgm. %)	Fructose (mgm. %)	Nucleic phosphorus (mgm. %)
Ventral prostate	34	0	27
Coagulating gland	0	28	54
Lateral prostate	15	12	52
Dorsal prostate	4	17	53

The results demonstrate clearly that metabolically active transplants of male accessory organs were maintained in female hosts. The indications are that this metabolic effect is due to ovarian androgens.

A detailed histological examination of tissues was carried out in experiments 1, 2 and 3, and details will be published in due course.

[1] Mann, T., and Parsons, U., *Nature*, **160**, 294 (1947).
[2] Mann, T., *J. Agric. Sci.*, **38**, 323 (1948).
[3] Mann, T., Davies, D. V., and Humphrey, G. F., *J. Endocrinol.*, **6**, 75 (1949).
[4] Mann, T., Lutwak-Mann, C., and Price, D., *Proc. Soc. Exp. Biol. Med.*, **88**, 413 (1948).
[5] Lutwak-Mann, C., Mann, T., and Price, D., *Proc. Roy. Soc.*, **B.** (in the press).
[6] Price, D., *Anat. Rec.*, **82**, 93 (1942).
[7] Price, D., *Amer. J. Anat.*, **75**, 207 (1944).
[8] Humphrey, G. F., and Mann, T., *Nature*, **161**, 352 (1948).
[9] Colonge, R. A., and Baclesse, M., *C.R. Soc. Biol.*, **142**, 471 (1948).
[10] Price, D., *Phys. Zool.*, **14**, 145 (1941).