ANDROGENS IN THE MALE IN THE ABSENCE OF THE TESTES

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That the testes are not the only source of androgenic material has long been recognized. Before laboratory methods of androgenic assay were available, many females with striking male characteristics were observed. The above characteristics in themselves constitute a qualitative assay for androgens and indicate their presence in these cases. Precocious sexual maturity has also frequently been reported in young males and excessive development of characteristics dependent on androgenic stimulation has been observed in adult males, in which there appeared to be reason to believe that the source of the androgens was extratesticular. A typical observation of this kind is exemplified in a case to be reported by Dr. V. C. Laughlin and Dr. E. P. McCullagh. This report will describe a boy four years of age with a penis anatomically and functionally that of an adult, a considerable growth of pubic hair, unusual prostatic growth, a low voice, and other signs of precocious sexual maturity but with testes only the size of a pea. The androgenic output in the urine was considerably greater than that expected from an adult. The clinical diagnosis is that of androgenital syndrome. The experiments described below throw further light on the subject of testes-adrenal relationship.

Another publication[1] gave a summarized account of some of the work reported herein. It was stated that androgens could be found in the blood of castrated rabbits. This in itself is not surprising, since comb-growth producing material has been demonstrated in the urine of several castrates. However, the detailed study of the experimental animals adds considerably to the understanding of the physiology of this phenomenon.

The rabbits employed in this work were all mature, healthy males. In examining their blood for androgens, the blood was removed from the heart by means of a hypodermic needle and syringe. In each case approximately 40 cc. of blood was withdrawn for examination. The amount varied somewhat because of technical difficulties and the condition of the animals. The differences, however, are not consequential.

The extraction of the androgenic material was accomplished as follows: The blood was made up to 400 cc. with distilled water and acidified with 20 cc. of concentrated sulfuric acid. On the assumption that part of the hormone was probably in an inactive form, as is the case in both urine and in testes, the mixture was hydrolyzed by boiling for 15 minutes. It was then extracted twice by stirring or by violent shaking for 15 minutes with 200 cc. of dibutyl ether. The extraction was some-

what complicated by emulsification which was controlled by the addition of sodium taurocholate. The combined dibutyl ether extracts were washed twice with 50 cc. of 10 per cent sodium hydroxide or saturated sodium bicarbonate and twice with 50 cc. of water, the sodium hydroxide and water being discarded. The ether was evaporated to dryness in vacuo. The residue containing the hormone was removed from the flask to a small beaker by dissolving it in diethyl ether; 5 cc. of sesame oil were added and the ether removed by evaporation on a water bath.

The assay of the androgenic material contained in the sesame oil was carried out by the procedure of McCullagh and Cuyler[2], in which the oil is administered by inunction on the combs of capons. In each case 5 capons were employed, each bird receiving 0.2 cc. of oil daily for five days. The increase in size of the comb expressed in millimeters (length plus height) is a measure of the amount of androgenic material present. The results in this paper are expressed as comb-growth and not as international units.

The effect of castration on the amount of androgen in the blood of rabbits is demonstrated in tables 1 to 4. Normally, the androgens from 40 cc. of blood caused a comb-growth of 3.7 mm. in each of 5 capons. A few days following removal of the testes the comb-growth is decreased to about 1.7 mm. However, after a month or more, the amount of androgen in the blood is normal and is still at the same level two and one-half years later. Although the amount of androgen (in this case meaning

TABLE 1

ANDROGENS IN BLOOD OF NORMAL MALE RABBITS

Animal Number	*Volume of Blood Extracted*	*Average Comb-growth in 5 Capons*
	cc.	mm.
1	40	4.2
2	39	2.4
4	40	3.6
4	37	5.8
9	42	6.4
11	36	3.0
11	39	2.0
13	37	3.4
14	35	3.0
12A	45	3.4
15	45	3.4
16	44	5.0
12B	45	3.6
	Average 40 cc.	3.8 mm.

TABLE 2

ANDROGENS IN BLOOD OF MALE RABBITS CASTRATED LESS THAN ONE MONTH

Animal Number	*Length of Time Castrated*	*Volume of Blood Extracted*	*Average Comb-growth in 5 Capons*
		cc.	mm.
11	25 days	40	2.0
13	20 days	36	1.8
12	20 days	38	1.6
14	3 days	42	1.4
		Average 39 cc.	1.7 mm.

TABLE 3

ANDROGENS IN BLOOD OF MALE RABBITS CASTRATED FOR ONE OR MORE MONTHS

Animal Number	*Length of Time Castrated*	*Volume of Blood Extracted*	*Average Comb-growth in 5 Capons*
		cc.	mm.
4	4 weeks	40	4.8
9	4 weeks	38	1.8
9	4.9 months	45	5.4
4	4.9 months	45	3.0
14	3.5 months	45	5.0
		Average 44 cc.	4.0 mm.

TABLE 4

ANDROGENS IN BLOOD OF MALE RABBITS CASTRATED 2½ YEARS

Animal Number	*Volume of Blood Extracted*	*Average Comb-growth in 5 Capons*
	cc.	mm.
3	40	5.0
10	35	5.6
5	38	2.0
6	36	2.4
7	37	4.0
8	37	3.8
5	45	5.0
6	45	2.8
8	45	3.0
	Average 40 cc.	3.7 mm.

comb-growth producing material) in the blood of castrated rabbits becomes normal, the animals are by no means androgenically normal. That is to say, the changes usually associated with lack of testicular androgen remain quite evident after the blood androgens become normal. The weight of the pituitary gland increased from an average of 24 mg. to 34 mg. The prostate decreased from 570 mg. to 185 mg. and the seminal vesicles showed similar atrophy. The adrenals increased in weight from 340 to 864 mg.

Discussion

Although final proof is not as yet complete, it would seem very probable that the androgens found in the blood of castrated rabbits originate in the adrenal glands. It is well known that the adrenals contain androgenic tissue. This subject is reviewed by Grollman[3]. Although at one time it was thought that only man and mouse had androgenic tissue in the adrenals, it is now known that rabbit, rat, cat, and monkey also possess it. This makes it seem probable that it is common to most mammals. There is also evidence to indicate that an homologous tissue is to be found in birds. The androgenic tissue which is frequently referred to as the X-zone of the adrenals normally exists only during early life. It is the same morphologically as the accessory adrenals which are sometimes situated some distance from the main glands and which usually disappear at an early age.

The X-zone is embryologically and morphologically quite distinct from the rest of the adrenal glands, and there is no reason to believe that it is physiologically related to either the medulla or the cortex. Since the X-zone disappears normally early in life, its only function would seem to be confined to the fetal and infantile period of an animal's existence. At that time it is physiologically active, and according to Burrill and Greene[4], in the absence of the gonads in the immature male rat, the adrenals are responsible for the maintenance of the ventral prostate gland in a normal or nearly normal condition. These, however, demonstrate that the adrenals are not appreciably involved in the normal development of the prostate.

From a chemical point of view, adrenal products are closely related to the sex hormones. Several substances have been isolated from the adrenal gland which are closely related to the sex hormones, in that both the adrenal substances and the sex hormone are derivatives of cyclopentanoperhydrophenanthrene. At least one of these adrenal compounds, namely adrenosterone, has been shown by Reichstein to possess androgenic activity. Similarly, progesterone is androgenically active, and has been isolated from adrenal tissue.

The blood androgens were apparently normal but the secondary sex glands of the castrated rabbits showed no signs of the existence of any

androgens. This indicates either that the androgen in the blood of castrated rabbits is not in an active form and is activated during the process of extraction or that it is an androgen to which the capon's comb responds more readily than do the secondary sex glands of the rabbit, in that way differing from the testicular androgen.

Hall and Korenchevsky[5] have studied the changes in the rat adrenal following castration and have shown that several different androgens will correct those changes. Unfortunately, by present methods, it is not possible to determine whether the adrenal androgen output and hence blood androgen is normal when androgens are being injected into castrated animals. It would be interesting, however, to investigate the effect of non-androgenic steroids on the adrenals of castrated animals.

References

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