

The Age Factor in the Castration of Male Rabbit Fetuses.

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In previously reported experiments on intra-uterine surgical castration of rabbits, it was ascertained that the fetal gonads play some part in somatic sexual differentiation. In controls, the first somatic sexual differences appear on the 20th day;¹ and prostate buds appear at 21 days. At 27-28 days, genital organogenesis is practically completed; all control and experimental fetuses were dissected and preserved at that age. The following observations were published recently: (1) males gonadectomized at 23 days (4 cases) acquired nearly all male characters, but the deferent ducts and ampullae were partly involuted;^{2,3} (2) in males castrated at 22 days (2 cases) the wolffian ducts had disappeared, but vestiges of mullerian ducts were present; the prostate was reduced and the external genitalia were abnormal.⁴ (3) In a group of males castrated at 21 days, 3 out of 8 retained some wolffian vestiges; the other 5 had none; the mullerian ducts persisted and had differentiated into mullerian vagina, uterine horns, and sometimes, oviducts. In microscopic sections, the external genitalia presented a feminine aspect. Only 2 rudimentary prostatic buds had developed; they correspond to the cranial prostate, which is first to appear in normal development. (4) There were great similarities between fetuses of both sexes castrated at this age, but only the males had prostatic buds.⁵

It was the aim of the now to be presented new series of experiments to determine: (1) whether male fetuses may acquire and retain normal male characters, if castrated after the

23rd day, and (2) whether their prostate development may be suppressed completely, if castrated before the 21st. The following results were obtained.

Two males, gonadectomized at 24 days, continued to develop according to the male type, retaining their deferent ducts and ampullae. The size of the prostate is somewhat below normal.

In fetuses operated before the age of 21 days, the following conditions were observed: 3 males castrated at 20 days developed and retained female genital tracts, but also had 2 prostatic buds. In 2 males gonadectomized at 18 days 19 hours, and 19 days 5 hours, *i.e.*, before the initiation of somatic sexual differentiation, prostatic development was entirely suppressed. Another male, castrated at the same age, and treated with testosterone propionate, exhibited a large prostate.

Thus, in order to suppress completely the formation of prostates, it is necessary to castrate the embryos before the development of their primordia. After primordia have reached a certain stage of development, especially from the 23rd day on, they continue growing and branching, in spite of the absence of the testes. However, they are somewhat reduced in size; this point should be checked by a quantitative study like that devoted to the rat by Wells.⁶ One may wonder whether Moore's opossums were already too old for prostate development to be suppressed when they were gonadectomized.⁷

Three groups of facts suggest that the testis exerts its influence by means of actual secretions: (1) in males unilaterally castrated at 22 or 23 days, the wolffian ducts are fully

¹ Jost, A., *C. R. Soc. Biol.*, 1943, **137**, 586.

² Jost, A., *C. R. Soc. Biol.*, 1946, **140**, 774.

³ Jost, A., *C. R. Soc. Biol.*, 1946, **140**, 938.

⁴ Jost, A., *C. R. Soc. Biol.*, 1947, **141**, 126.

⁵ Jost, A., *C. R. Soc. Biol.*, 1947, **141**, 135.

⁶ Wells, L. J., *Proc. Soc. Exp. Biol. and Med.*, 1946, **63**, 417.

⁷ Moore, C. R., *J. Exp. Zool.*, 1943, **94**, 415.

maintained;^{3,4} (2) androgens have a reparative influence;⁸ (3) the results of one especially favorable case of testis graft in a female showed localized inhibition of the oviduct, more extensive persistence of the wolffian duct.

Some new observations contribute complementary data on the manner of action of the testicular secretion. In 3 males unilaterally castrated between the ages of 19 days 6 hours and 20 days 21 hours, the prostate and the external genitalia are well developed, but the single testis acts less effectively on the primordia of the opposite side. In a fetus with only a right testis, of somewhat under normal size, the vas deferens is present only on the right side, while on the left, a uterine horn persists. It follows that after early unilateral gonadectomy the action of the fetal testis is relatively localized. A single testis or a fragment of a testis (as appears in the case of an incomplete castration) does not seem to undergo compensatory secretory hypertrophy;

⁸ Jost, A., *C. R. Soc. Biol.*, 1947, **141**, 275.

with regard to this point, it should be remembered that the hypophysis is not indispensable for embryonic sexual differentiation.^{9,10,11} Lastly, some of our observations suggest that more testicular secretion is required to completely inhibit the mullerian ducts, than to maintain the wolffian ducts.

Conclusion. In the male rabbit, early fetal castration (before the 21st day) prevents the formation of male secondary sex characters such as the prostate. At a later stage (24 days) established primordia continue their development even after ablation of the testes; the resulting structures are usually subnormal. The effects induced by testicular secretions are sometimes regionally restricted. Earlier observations on the differentiation and persistence of female genital ducts after early orchidectomy are confirmed and extended.

⁹ Ancel, P., *Les Hormones Sexuelles*. Colloque Singer Polignac, Paris, 1937, Hermann.

¹⁰ Wolff, E., and Stoll, R., *C. R. Soc. Biol.*, 1937, **126**, 1215.

¹¹ Fugo, N., *J. Exp. Zool.*, 1940, **85**, 271.

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The Lymphoid Tissue and Antibody Formation.

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Several early investigators in immunology considered the possibility that the spleen was the main site of antibody formation, but conclusive evidence for this was not found. Hektoen,¹ using the well-known fact that X-ray produces a destructive effect on all lymphoid tissue, demonstrated that antibody formation is restrained to a marked degree in X-rayed animals. He concluded from this observation that the spleen, lymphoid tissue and bone marrow were the principal sites of immune bodies. Murphy and Sturm² confirmed Hek-

toen's findings but considered that they had eliminated the bone marrow as of first importance in the process. This conclusion was based on the fact that depletion of the lymphoid tissue was effected by repeated, small doses of X-ray of low penetration which produced no detectable damage to the bone marrow or other tissues. Yet animals treated in this manner were found deficient in the production of antibodies. In addition, these investigators demonstrated that rabbits, after stimulation of the lymphoid system by dry heat treatment, had an enhanced ability to produce immune substances. Hussey³ in this

¹ Hektoen, L., *J. Infect. Dis.*, 1915, **17**, 415; 1918, **22**, 28; 1920, **27**, 23.

² Murphy, J. B., and Sturm, E., *J. Exp. Med.*, 1925, **41**, 245.

³ Hussey, R. G., *Proc. Soc. Exp. Biol. and Med.*, 1921, **19**, 22.