the endocrine system and consequently the development of secondary sex characters can be stimulated. Follicular growth seems never to follow and spermatogenesis is only incompletely restored. It is evident that the gonads of birds are even less responsive to pregnancy urine extracts than those of hypophysectomized rats. At the present it seems that this principle is entirely foreign to and not utilizable by the bird.

A most characteristic feature of the endocrinology of the seasonal cycles of the sparrow is the near coincidence of minima and maxima in hypophyseal and gonadal activity. Our experiments indicate that gonadal development is stimulated by increased hypophyseal activity; but on the other hand, gonadal involution and cessation of the production of sex hormones do not incite renewed production of gonadotropic hormones. The sexual cycle seems to be entirely and one-sidedly directed by seasonal changes in hypophyseal functions.

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Origin of Functional Differences Between Male and Female Hypophyses.*

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Recent investigations have shown that there is a functional, and even an histological difference between male and female hypophyses. This presupposes either (1) a primary difference which is genetical and determined by the sex genes, or, (2) a secondary difference which is determined by the gonad function and is, therefore, dependent upon whether an ovary or a testis is present.

In order to investigate these two possibilities, testes of new-born male rats were transplanted into littermate females and the resulting disturbance in the endocrine system followed by the vaginal smear method. Since in the newborn rat the heat regulatory mechanism has not been established, animals can be operated after being rendered insensible and immotile by cooling on ice. Out of 150 females raised to puberty, 56 had the grafts resorbed; 59 established normal oestrus cycles even though grafts persisted; however, 35 females, all with well-growing grafts, gave evidence of an altered

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endocrine function. The grafts were placed in various locations, but only those in the throat region will be further discussed here. In a later paper we intend also to report on the transplantation of ovaries of the newborn into newborn males and females and of gonads of the newborn into adults.

Of 48 females which had testes from litter-mate males grafted into the throat region, 10 were autopsied before puberty to serve for study of the development of graft and host gonads. Of the remaining 38, 30 carried growing grafts at the end of 7 to 9 months. Constant oestrus developed in 12 female hosts, 9 starting at puberty and 3 after various periods of irregular cycles. Of the animals which ran normal cycles, 6 were bred, and raised normal litters, which adds proof that these females are normal despite the presence of testis grafts. On the other hand, constant oestrus animals do not copulate unless, as may occur in rare instances, the constant oestrus is broken for a day or so. The animals may then copulate at the end of the nucleated epithelium stage but do not become pregnant.

Histological study demonstrates that this "constant oestrus" is in fact a suboestral condition. The ovaries contain follicles which in many cases are in excess of the number found in the normal ones. However, at about the time the follicles reach mature size the ova fragment and degenerate. Corpora lutea are not produced. The uterus remains in a quiescent condition and does not become distended with fluid as in normal oestrus or during the constant oestrus of a female in parabiosis with a castrate (Martins,[1] Witschi and Levine[2]). These conditions resemble those found in the case of an immature female rat responding to a minimal dose of follicle stimulating hormone. Therefore, this suboestral condition seems to indicate a constant low rate of production of follicle stimulating hormone by the hypophysis. Microscopically the hypophyses are normal, though cell counts were not made, nor was it attempted to decide whether the histological picture resembled more the male or the female type.

The grafts vary rather markedly in the type of tissues persisting. The germ cells disappear first, the tubules next, and the epididymis last. It is significant that in all cases of constant oestrus, testis tubules with numerous germ cells are present in the graft. However, spermatogenesis seems never to proceed beyond the secondary

[1] Martins, Th., *Endocrinol.*, 1931, **15**, 421.

[2] Witschi, E., and Levine, W. T., PROC. SOC. EXP. BIOL. AND MED., 1934, **32**, 101.

spermatocyte stage, where degeneration takes place. At any rate the implants maintain a more nearly normal condition in the "constant oestrus" than in the "normal oestrus" group. It is a surprising fact that without exception the removal of the graft does not alter the endocrine disturbance once established. The animal remains in constant oestrus until autopsy (which in some cases was 9 months after removal of the graft). In one case constant oestrus developed even though the testis graft was removed shortly *before* puberty.

Injection of large doses of oestrin decreases the output of follicle stimulator as evidenced by cessation of follicular development. The larger follicles disappear, and if the injections are discontinued, the animals go into dioestrus for a while then return to "constant oestrus" without the formation of corpora lutea. However, large doses of luteinizing hormone cause the formation of corpora lutea and a dioestrus condition of the vagina in 5 days. These facts show that the hypophysis of the "constant oestrus" animal has ceased producing luteinizing hormone.

Goodman[3] has described among other experiments the implantation of the ovary into the eye chamber of the adult male rat. Under the influence of the male hypophysis the ovary shows follicular development but no luteinization unless injected with antuitrin S which contains predominantly luteinizing hormone. This report is of great value as the first detailed description of the development of the ovary under control of a male hypophysis. The identical behavior of ovaries in Goodman's experiment and in our "constant oestrus" group is evident and supports the conclusion that in our experiment the hypophysis has been reversed to the male type.

Summary. Transplantation of testes of newborn males into the neck region of littermate females gives "takes" in 80% of the cases. In 48% the grafts do not interfere with normal endocrine or reproductive functions of the carrier, while in 32% the implanted testis assumes control of the sexual differentiation of the hypophysis. The male type hypophysis stimulates follicular development but not luteinization in the host ovary. These hosts start constant oestrus and maintain this condition after the removal of the testicular graft. It is concluded (1) that the cases with "constant oestrus" are those in which the implanted testis is sufficiently active to have a leading influence upon the hypophysis which responds with the male type of constant non-cyclic function; (2) that the hypophysis is permanently altered; (3) that the sex type of the hypophysis is secondary, depending upon the presence of differentiated sex glands.

[3] Goodman, L., *Anat. Rec.*, 1934, **59**, 223.