THE PHYSIOLOGICAL RESPONSE OF PROSTATIC AND VESICULAR TRANSPLANTS IN THE ANTERIOR CHAMBER OF THE EYE

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Markee (1) with Schochet (2) first used transplants of tissue in the eye for physiological observations. With transplants of endometrium in the rabbit, they observed the color changes in the estral cycle and the relation of the vascular changes to muscular contractions (3). Later, Markee and Andersen (4) devised a method for measurement of the size of the transplants by camera lucida drawings and observed a definite series of changes during pregnancy. Litt (5) placed placental tissue in the eyes of pregnant rabbits and observed no effect on the subsequent lactation. After 30 days of growth and establishment of vascularity, there was gradual degeneration and absorption. Goodman (6) with homoiotransplants of immature ovaries in intact and spayed male and female rats observed a number of physiological phenomena. A successful take in a spayed female was accompanied as a rule by regular estral cycles. In the male rat, follicles were formed but corpora lutea did not appear unless extracts of pregnancy urine were administered. The administration of the female sex hormone in the male and female was followed by complete or partial atrophy of the ovarian grafts.

From this incomplete review of the literature, it is clear that, at least with certain organs, transplants in the eye are functioning viable tissues and may be used for physiological observations. With the photographic method which has been described in the preceding paper, it has been possible to follow accurately changes in the size of seminal vesicular and prostatic transplants under the influence of parenterally administered hormones in intact and castrated male rabbits.

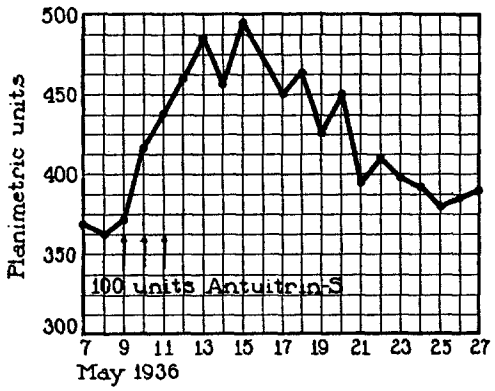
Methods

The methods of transplantation and observations of size were identical with the procedure outlined in the preceding paper (7). The hormones used were those

available on the market. As examples of the gonadotropic substance of pregnancy urine, the trade products of antuitrin-S and follutein were employed. The female sex hormone was represented by theelin and progynon or progynon B. The male sex hormone was employed in the form of oreton or oreton B. The alkaline extract of the anterior lobe of the pituitary was that commercially manufactured by Squibb. Proluton was the example of the hormone of the corpus luteum. The units shown on the graphs were those printed on the labels and in all instances conform to well recognized standards. Differences in the response of seminal vesicular and prostatic transplants have not been observed.

EXPERIMENTAL OBSERVATIONS

Single Injections of the Gonadotropic Substance of Pregnancy Urine in Intact Animals (Text-Fig. 1).—Following three injections each of 100



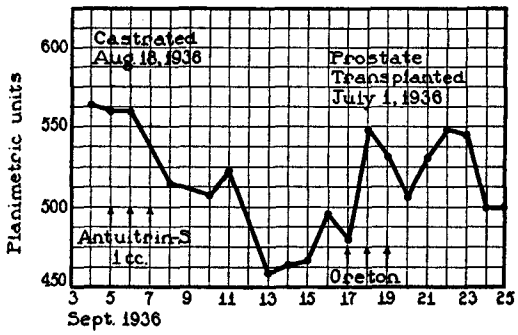
TEXT-FIG. 1. The size of an ocular transplant of the prostate after the injection of the gonadotropic substance of pregnancy urine in an intact rabbit.

rat units of this substance there is a prompt increase in size, manifest within 24 hours of the first injection and reaching a maximum 48 to 96 hours after the third injection. The increase is rapid and continuous but during the subsequent decrease in size there are fluctuations which probably represent superimposed normal fluctuations. The return to the preinjection level is reached in from 10 to 15 days after the injections.

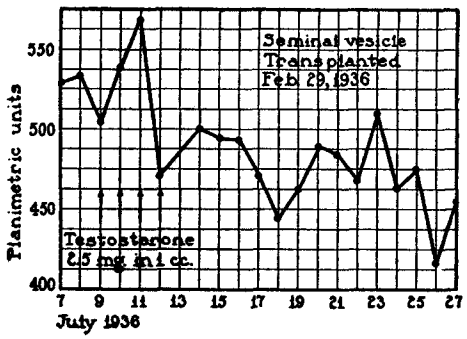
Repeated Injections of the Gonadotropic Substance of Pregnancy Urine in Intact Animals.—With one exception, a second series of injections of similar amounts of this substance fails to invoke a response greater than the normal variation, if given within a few months. In one

animal a second series after 3 months gave a typical response but all other attempts have been unsuccessful.

The Gonadotropic Substance of Pregnancy Urine in Castrated Animals (Text-Fig. 2).—In castrated animals this substance in amounts up to 300 rat units is uniformly ineffective and has no influence on the cas-



TEXT-FIG. 2. The effect of the gonadotropic substance of pregnancy urine and of the male sex hormone on the size of an ocular transplant of the prostate in a castrated rabbit.



TEXT-FIG. 3. The size of an ocular transplant of the prostate after an injection of the male sex hormone in an intact rabbit.

tration atrophy. This is true regardless of whether or not the animal has had a previous injection of the same substance.

Male Sex Hormone in Intact Animals (Text-Fig. 3).—The response of intact animals to the male sex hormone is difficult to evaluate because the response is slight and in many instances does not exceed

the observed normal variation of the animal. However, after three injections of 2.5 mg. each, there is always an increase in size on the 1st or 2nd day following the first injection. The increase is rarely sustained and there may be a subsequent fall below the preinjection level.

Male Sex Hormone in Castrated Animals (Text-Fig. 2).—In contrast to the slight response in intact animals, the male sex hormone in castrated animals, in amounts up to 7.5 mg., will within 24 hours decrease the velocity of the castration atrophy and within 3 to 4 days restore the transplant to the precastration size. This restoration lasts for several days and the progressive decrease in size due to castration does not again appear for 10 to 15 days.

The Gonadotropic Substance of Pregnancy Urine and Male Sex Hormone in Intact Animals.—The simultaneous administration of these hormones in the amounts given above results in a prompt increase in size and a slow decrease to the preinjection level, identical with that of the gonadotropic substance alone.

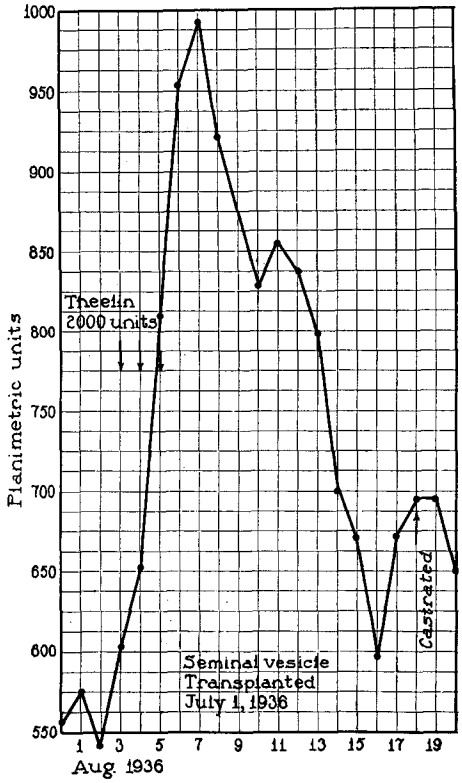
The Gonadotropic Substance of Pregnancy Urine and Male Sex Hormone in Castrated Animals.—In castrated animals which have not received injections of the gonadotropic substance there is a prompt increase in size, analogous in magnitude and velocity to that of the male sex hormone alone.

Alkaline Extract of the Anterior Pituitary Gland in Intact Animals.—This extract (three injections of 1 cc. each) evokes a prompt increase in size within 24 hours after the first injection with a slow decrease over a period of 2 to 3 weeks. The general features of the curve with a smooth increase and irregular decrease are similar to those secured with the gonadotropic substance of pregnancy urine. Repeated injections of the extract give irregular responses but in general less stimulation than the first injection.

Alkaline Extract of the Anterior Pituitary Gland in Castrated Animals.—As in the experiments with the gonadotropic substance of pregnancy urine there is no response to the extract in castrated animals.

Female Sex Hormone in Intact Animals (Text-Fig. 4).—The female sex hormone in three injections each of 2000 international units provokes a conspicuous increase in size, usually slight in 24 hours, but

rapidly increasing after the second and third injections. In contrast to the other hormones, the peak of the reaction is only 24 hours after the last injection. Subsequent decrease in size is always rapid during the first few days but in some animals this is followed by a slower decrease over a period of 10 to 20 days. The form of the curve during



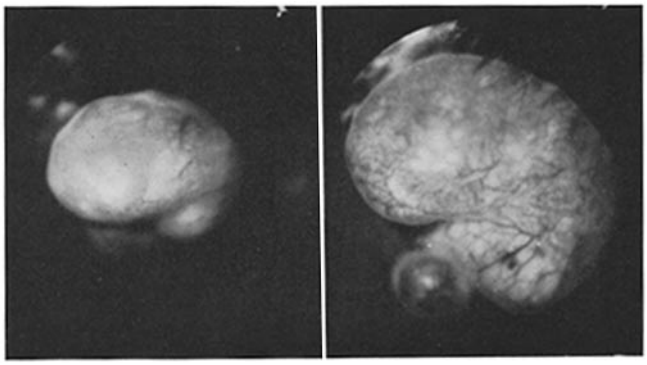
TEXT-FIG. 4. The effect of the female sex hormone on the size of an ocular transplant of the seminal vesicle in an intact rabbit.

the decrease is usually smoother than with the other hormones and shows only occasional and transient periods of slight increase in size. In one of 21 experiments in which this reaction has been tested, there was only a slight increase in size, followed by a decrease below the preinjection level. Both the increase and the decrease were slightly

greater than the normal variation and were probably related to the injection.

Female Sex Hormone in Castrated Animals.—An increase in size, entirely analogous to that in intact animals, results from the injection of the same quantity of this hormone in castrated animals. Repeated injections in both intact and castrated animals result in responses, which in general show no evidence of tolerance or resistance, but the exact percentage increase in size is not always proportional to the units of hormone injected in amounts up to 2000 units.

Male Sex Hormone and Female Sex Hormone in Intact and Castrated Animals.—These two hormones in the above amounts injected simul-



TEXT-FIG. 5. Increased vascularity of a transplant after the injection of the female sex hormone. ×25. (Photographs on infrared plates after intravenous injection of trypan blue.)

taneously provoke a response in both intact and castrated animals which in general is similar to that of the female sex hormone alone.

Corpus Luteal Hormone in Intact and Castrated Animals.—The injection of this hormone, up to 3 international units, fails to show any change in the size of the transplants either before or after castration.

Vascular Changes with Alterations in Size.—Any increase in the size of the transplant in the normal animal or as the result of the injection of a hormone is associated with an increase in the number and size of the visible blood vessels within the graft. In Text-fig. 5, two photographs on infrared sensitized plates show the effect of an injection of the female sex hormone. The pictures were taken after an intra-

venous injection of trypan blue in order to secure a color with maximum sensitivity on the infrared sensitized plates.

Control Observations

When the results described above are reviewed in the light of previous investigations, it is certain that the responses are the result of the action of a hormone. However, there are several possible mechanisms which must be eliminated by control experiments.

Foreign Protein Shock.—The elicitation of a slight to moderate inflammatory reaction in the eye or cornea with prompt healing following foreign protein injections is well known and frequently used in the treatment of corneal lesions. The work of Seegal and Seegal (8) on local tissue hypersensitiveness in the eye also points to the same general type of reaction. In order to eliminate this possibility, animals have been injected with an amount of human serum protein containing nitrogen equivalent to that contained in the injected gonadotropic substance from human pregnancy urine. There was no change in the size of the transplants and therefore this possibility may be eliminated as an explanation of the results.

Hormones from the Same Species.—It may be said that the reactions are in part due to the fact that the hormones have been derived from another animal species and therefore give reactions not analogous to those in a normal animal. In order to eliminate this, implants of eighteen desiccated rabbit pituitary glands were made in one rabbit on 3 successive days and a 25 per cent increase in size resulted.

Focal Inflammatory Reaction.—It is not the purpose of this paper to detail the histological changes in the eye transplants, but sufficient evidence must be presented to eliminate inflammation as the cause of the increase in size. The injection of the female sex hormone results in hypertrophy of the smooth muscle fibers, and marked edema of the connective tissue, but no infiltration with cellular or other elements which would indicate an inflammation in the usual sense.

DISCUSSION

The effects of the injection of hormones on the eye transplants, with the exception of that with the female sex hormone, are entirely in agreement with previous morphological and physiological observa-

tions and need not be discussed in detail. This agreement with other studies indicates that the method is a reliable one and should be useful in other endocrinological investigations.

The lack of response on repeated injections of the gonadotropic substance of pregnancy urine confirms the general thesis of resistance to successive injections of this hormone, but of course throws no further light on the mechanism of the resistance.

The slight response to the male sex hormone in intact, as compared with castrated animals, is in support of the general thesis that a hormone is less effective in an animal that possesses adequate amounts of the functioning tissue elaborating the hormone.

With this method there is no evidence of the synergistic action of the pituitary gonadotropic and testicular hormones which is observed in immature rats and mice. The explanation may lie in the fact that only adult animals were used. Likewise there is no evidence that the two sex hormones are antagonistic. This is an additional fact to be added to those marshalled by C. R. Moore and Price (10) to dispose of the older idea of a fundamental antagonism of the two sexes.

The possibility of an effect of the female sex hormone in the male animal was first shown by Lacassagne (11), who produced carcinoma of the male breast of mice by long continued injections. In the same animals (12), he noted an enlargement of the prostate and microscopically found advanced atypical squamous metaplasia. The diffuse increase in size is conspicuous and may cause urinary obstruction (13). The enlargement has suggested that the female sex hormone may be responsible, at least in part, for benign enlargement of the prostate in man (14), but no convincing proof has yet been given. Recently Zuckerman and Groome (15) have studied a case of benign "hypertrophy" in a dog, in which the histological appearance was identical with the changes induced in dogs by the injection of estrogenic hormones.

In none of the above observations are there described changes within a few days after the hormonal injections analogous to those which are recorded in this paper. Further studies are required to relate the two types of reaction.

SUMMARY

1. With a photographic method for the determination of the size of prostatic and vesicular transplants in the anterior chamber of the eye, it has been possible to follow continuously the response to an injection of a hormone.

2. The results may be briefly summarized as follows: (*a*) One injection of the gonadotropic substance of pregnancy urine produces a moderate increase in size; (*b*) subsequent injections of this same substance for a period of at least 3 months are without effect; (*c*) an alkaline extract of the whole anterior pituitary gland produces a similar increase; (*d*) all pituitary derivatives are ineffective in the castrated animal; (*e*) castration brings about a decrease in size that gradually loses velocity; (*f*) the male sex hormone produces a slight increase in intact, and a variable, at times conspicuous, increase in castrated animals; (*g*) the female sex hormone provokes a conspicuous increase in both intact and castrated animals; (*h*) the hormone of the corpus luteum has no effect; and (*i*) there is no evidence of synergism of the pituitary and male sex hormones nor of antagonism of the male and female sex hormones in adult rabbits.

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