the types of the diabetic curves are the same, the average values are of the same order, and the percentages of diabetic animals in the age groups are similar except for the group 101-140 days. Here only 44% of the females but 66% of the males are diabetic, and a statistical analysis of these data (Table II) shows that the chances are 100 to 1 that the difference is real. Thus, the females lag behind the males in the development of a low glucose tolerance and reach their maximum, 62% of diabetic curves, around 140 days of age. Attention should be called to the fact that the glucose tolerance of the males is normal to 50 days of age,[1] but thereafter the incidence of diabetic curves increases until it reaches 66% at 100 days of age with only a questionable additional increase after 240 days (Table II).

Relevant to the problem of whether or not the diabetic curves become more severe with age, Table III lists the averages for 307 tests made on males of the "Y" strain ranging in age from 90 to 730 days. The data suggest that after 240 days there is a further decrease in the glucose tolerance of the diabetic males. Normals of the "Y" strain do not show a similar change.

Summary. 1. Females of the "Y" strain exhibit a low glucose tolerance similar to that of the males. 2. The estrous cycle has no conspicuous effect on the glucose tolerance. 3. After 240 days of age, the severity of the diabetic curves in the males appears to increase.

11043 P

Androgenic Function of APL Stimulated Ovaries in Immature Rats.*

R. R. GREENE AND M. W. BURRILL. (Introduced by A. C. Ivy.)

From the Department of Physiology and Pharmacology, Northwestern University Medical School, Chicago.

The present authors have reported that the administration of chorionic gonadotropic hormone (APL) to very young, immature female rats causes definite growth of the clitoris.[1] This gross enlargement was associated with modifications in the male direction as

* Supported in part by a grant from the Josiah Macy, Jr., Foundation. We wish to thank Dr. Charles Mellish and Dr. C. O. Miller of Lakeside Laboratories for the Anterior Pituitary-like Gonadotropic Hormone used in this study.

1 Greene, R. R., and Burrill, M. W., PROC. SOC. EXP. BIOL. AND MED., 1939, **40**, 514.

shown by microscopical evidence. The ovary was indicated as being the probable source of the substance responsible for this androgenic activity. Bradbury and Gaensbauer[2] made similar observations and, in addition, noted that continuation of treatment beyond 30 days of age caused no further growth of the clitoris.

Inasmuch as clitorine growth is a relatively slow process and is not readily evaluated quantitatively, another method was devised for testing the production of androgens in the treated immature female. This method is based on two facts, (1) that the ventral prostate of the rat is very sensitive to androgens and (2) that histological evidence of androgenic stimulation of the prostate is definite and unequivocal. Although ventral prostatic lobes sometimes occur in normal female rats, the incidence is too low to be of practical value in approaching the present problem.[3, 4, 5] Furthermore, it has been shown that the ventral prostate of the immature female has a lower threshold to androgens than the prostate of the immature male, inasmuch as the ventral prostate of the normal immature female of a certain age shows evidence of activity when a male prostate implanted into the same female shows negative cytology.[5] The male prostate, therefore, by virtue of its higher threshold of response, when implanted into the treated immature female should provide a good indicator for the formation of androgenic substances in excess of the quantity normally produced by the immature female. The functional state of the implanted prostates should also determine whether or not the production of androgens by the immature female in response to treatment is definitely age-limited as indicated by Bradbury and Gaensbauer.[2]

Accordingly male ventral prostates were implanted intraperitoneally into 36 female rats at 10 days of age. The donors, in all cases, were litter mates of the recipients. These females were then given 25 to 100 RU of chorionic gonadotropin daily until they were sacrificed. Enlargement of the clitoris occurred as in previous experiments. The animals were killed at 15 to 38 days of age (5 to 28 days after implantation). Viable implants were recovered from 15 of them. The recovered tissue was fixed in Bouin's fluid, sectioned and studied microscopically. In the youngest prostate recovered (5 days post-implantation) the acinar epithelium was high but showed none of the

2 Bradbury, Jas. T., and Gaensbauer, F., PROC. SOC. EXP. BIOL. AND MED., 1939, **41**, 128.

3 Witschi, E., Mahoney, J. J., and Riley, G. M., *Biol. Zentralb.*, 1938, **58**, 455.

4 Price, Dorothy, PROC. SOC. EXP. BIOL. AND MED., 1939, **41**, 580.

5 Burrill, M. W., and Greene, R. R., PROC. SOC. EXP. BIOL. AND MED., 1939. **42**, 764.

characteristic light areas which are indicative of androgenic stimulation.[6] The next age group included 7 animals, 18 to 25 days old. In 6 of these the implants were positive for androgenic function. The negative prostate was in an animal 23 days old. The oldest group included 7 animals, 28 to 38 days old. Only one implant in this group was positive. This was from one of 3 animals which were killed at 28 days of age.

In order to show that the ovary is necessary for the observed effects, 11 females were castrated at the time of implantation (10 days of age) and were then treated in the same manner as the preceding group. No clitorine enlargement was observed in these castrates. Viable implants were recovered from 8 of these animals at 20 to 35 days of age (6 at 25 days). None of these prostates showed evidence of androgenic stimulation.

Implants in the normal treated animals were a great deal larger than those observed in treated castrate controls. Due to the difficulty of making a clean dissection of the implanted tissues the prostates were not routinely weighed when recovered. However, several implants in the treated animals were over 30 mg and one, from a 25-day-old animal, weighed 60 mg. The average weight of the ventral prostates (both lobes) in the normal males of our colony at 26 days is 29.23 mg.

From these data it is evident that chorionic gonadotropin stimulates the ovaries of young, immature female rats to produce androgens in amounts sufficient to cause enlargement of the clitoris and to elicit a functional response in the implanted male prostates. The absence of functional activity in the implant at 15 days of age is probably due to insufficient time allowed for the response (5 days). In the period between 18 and 25 days of age, the stimulated ovaries produced sufficient androgen to induce a functional state in the implanted prostates. The negative state of the implants in the older group (28 to 38 days) implies that the output of androgens by the stimulated ovaries at this age is no longer adequate to maintain the prostates. However, the conclusion that the ovaries are no longer producing androgens is not warranted. It is also possible that the ovaries of the older animals are producing sufficient estrogens to antagonize directly the effect of the androgens on the prostatic epithelium.

The exact nature of the androgen produced by these stimulated ovaries is not known. It is probably similar to the androgen produced by chorionic gonadotropin-stimulated ovaries in the guinea

[6] Moore, C. R., Price, D., and Gallagher, T. F., *Am. J. Anat.*, 1930, **45**, 71.

pig[7, 8] and also to the androgen produced by ovaries transplanted to the ears of untreated castrate mice[9, 10] and rats.[11] In a previous publication the present authors suggested that the androgen involved may be progesterone[1] since this substance has been shown to have androgenic potency in the rat.[12, 13] Experiments to test this hypothesis are in progress.

Summary. Ventral prostates from male littermates were implanted into female rats 10 days of age. Daily treatment with chorionic gonadotropin produced no evidence of androgenic stimulation in the prostates when the females were castrated. When the ovaries were not removed the prostates of the treated animals showed evidence of stimulation at 18 to 25 days, but not after 28 days of age.

11044 P

Androgen Production in Normal Intact and Castrate Immature Female Rats.*

M. W. BURRILL AND R. R. GREENE. (Introduced by A. C. Ivy.)

From the Department of Physiology and Pharmacology, Northwestern University Medical School, Chicago.

In the female white rat the homologue of the male ventral prostate is sometimes found. Witschi, Mahoney, and Riley[1] reported that in one strain of rats the incidence of female prostates was 8.8% and in another strain, of Wistar origin, it was 26.7%. They also found that, by selective breeding, the incidence of female prostates was increased to 77.3%. Price[2] has reported a low incidence (under 2%) for the rats of her colony. In our own colony, examination of 333 females has placed the incidence at 13.8%.

Contrary to the conditions in the male, the female prostate is not

7 Papanicolaou, G., and Falk, E. A., PROC. SOC. EXP. BIOL. AND MED., 1934, **21**, 750.

8 Papanicolaou, G., and Falk, E. A., *Science*, 1938, **87**, 238.

9 Hill, R. T., *Endocrin.*, 1937, **21**, 495.

10 Hill, R. T., *Endocrin.*, 1937, **21**, 633.

11 Deanesly, Ruth, *Proc. Roy. Soc.* (Series B), 1938, **126**, 122.

12 Lamar, J. K., *Anat. Rec.*, 1937, **70**, Suppl. p. 45.

13 Greene, R. R., Burrill, M. W., and Ivy, A. C., *Endocrin.*, 1939, **24**, 351.

* Supported in part by the Josiah Macy, Jr., Foundation.

1 Witschi, E., Mahoney, J. J., and Riley, G. M., *Biol. Zentralb.*, 1938, **58**, 455.

2 Price, Dorothy, PROC. SOC. EXP. BIOL. AND MED., 1939, **41**, 580.