

mination in a rough way of the potency of various extracts, it was deemed advisable to undertake a series of experiments to determine the effect of excessive dosage of the hormone upon both normal and pregnant animals. Up to this time we had tentatively accepted the hypothesis that the maturity-provoking factor of the placenta was identical with the anterior-pituitary gonad-stimulatory principle. As the investigation proceeded, however, it became apparent that a theory according to which the placenta is considered as the ductless gland of pregnancy, producing by an active process a pregnancy hormone with both physiological and chemical properties peculiar to itself, would fit the observed facts much better. While we do not feel that we have as yet sufficient evidence available to prove this theory conclusively, we are nevertheless of the opinion that there are many observations which support it. Some of this evidence may now be considered.

1. Extracts which have been prepared from anterior pituitary lobes by the use of acetone, as in the case of placenta, have been found to be non-œstrogenic in character. These extracts have been prepared from small amounts of tissue. It is possible, however, that by the use of large amounts of these glands an active principle similar to that herein described may be obtained.

2. It has been repeatedly shown that the placental œstrogenic hormone is effective by the oral route, and it is proposed ultimately to standardize the extract which may be made available for clinical use in terms of oral rat units.

3. Considering the limitations of accuracy in potency testing with a limited number of immature rats, we have observed no decrease in potency following treatment of active extract with either pepsin or trypsin.

4. The prolonged treatment of normal adult rats with large doses of the hormone has not resulted in any noticeable effect upon the cycles or upon impregnation or lactation. Moreover, such treated rats have shown no evidence of marked hypertrophy of the ovaries, nor has there been any evidence of superfetation. Abortion has not been produced. The hormone viewed as a pregnancy principle could not of course be expected to cause abortion.

The following condensed protocols of four experiments are of interest in this connection:

*Rat No. 1:* Weight 191 gm.

Nov. 8. Started daily injection of 50 per cent acetone extract = 3 gm. human placenta.

Nov. 14. Litter.

Dec. 4. Injections every second day.

Dec. 20. Male placed in cage.

Jan. 11. Equivalent of 5 gm. of placenta (85 per cent alcohol soluble) injected every second day.

Jan. 16. Litter (7).

Feb. 12. Male placed in cage.

March 17. Weight 187 gm. Killed for microscopic study of genital tract. Ovary normal (see Fig. 6).

*Rat No. 2:* Weight 175 gm.

Nov. 8. Started daily injection equivalent to 3 gm. human placenta.

Nov. 18. Litter (6).

Dec. 4. Injection every second day.

Dec. 20. Male placed in cage.

Jan. 11. Litter (8). Standard injections, equivalent to 5 gm. of placenta, every second day.

March 21. Weight 176 gm. (See Chart 1, No. 14, for cycles).

*Rat No. 3:* Weight 137 gm.

Nov. 6. Started daily injection equivalent to 3 gm. of placenta.

Dec. 7. Injections every second day.

Dec. 24. Male placed in cage.

Jan. 11. Equivalent 5 gm. of placenta every second day.

Jan. 31. Litter.

Feb. 4. Eating poorly.

Feb. 26. Injections stopped on account of poor condition of animal.

March 8. Dead of respiratory infection. Weight 91 gm. Ovaries normal. (See Chart I, No. 13, for cycles).

*Rat No. 4:* Weight 136 gm.

Nov. 6. Started daily injection equivalent to 3 gm. placenta.

Dec. 6. Injection every second day.

Dec. 24. Male placed in cage.

Jan. 11. Equivalent 5 gm. placenta every second day.

Jan. 16. Litter (8).

Feb. 10. Male placed in cage.

March 10. Litter (7).

March 21. Weight 200 gm. Normal.

Also Charts 1 and 2 show the results of 17 experiments in which the hormone was administered daily or bi-daily, and in varying dosage. In general it may be said that we have little or no evidence of any interference with the normal sex functions in normal adults as a result of treatment with even massive doses of this hormone.