

5220

Menstruation and the Anterior Pituitary.

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The prevailing gynecological opinion in the textbooks and the gynecological literature generally holds that menstruation is due to the degeneration of the corpus luteum and that the menstrual flow proceeds exclusively from a "pregravid" (swollen, congested, secreting) endometrium. We contend that this is a *post hoc, propter hoc* argument, a time relation mistaken for cause and effect, a conclusion without the slightest experimental evidence.

The chief facts that have called this generally accepted notion in question were the outcome of the work of Geo. W. Corner, who found that periodic uterine bleeding in monkeys often does occur from uteri not at all enlarged and unaccompanied by corpora lutea in the ovaries. This conclusion has been corroborated by a very extensive series of observations involving scores of laparotomies and hundreds of rectal palpations of the organs in fully adult monkeys of the Carnegie colony at Baltimore.

On the basis of these findings and other considerations which will not be taken up at this place, the senior writer has contended¹ that there is an active substance originating outside the ovaries that causes the periodic bleeding which we call menstruation. Over a dozen hypophysectomies (Dr. Firor*) have enabled us to announce that it is the anterior pituitary that elaborates the substance causing uterine bleeding. The evidence is as follows:

1. Ablation of the hypophysis abolishes the cycle, the sex organs atrophy, the sex skin becomes pale as in the pre-adolescent female.
2. Administration of ovarian hormone (Allen-Doisy in the form of Amniotin Squibb†) to a female monkey, whether ovariectomized or not, causes the bleeding. Even a one-year-old baby, of the "equivalent age" of a 3- or 4-year-old girl, can be made to bleed

¹ Hartman, C. G., *Am. J. Obst. and Gyn.*, 1930, **19**, 511.

* A description of the technique employed and the results of autopsies on the losses will appear in the *Contributions to Embryology*.

† These experiments were made possible through the kindness of E. R. Squibb and Son, through whose department of Biological Research the Amniotin and some of the alkaline extract of the anterior lobe was secured. Most of the anterior lobe extract was prepared by Dr. Geiling.

with as little as 90 rat units. The bleeding lasts for 10 to 15 days after the injections have stopped. This has been taken by other authors as a direct effect of the hormone on the uterus.

3. That the ovarian hormone acts through the hypophysis and not directly upon the genital tract is shown by the fact that if the animal is completely hypophysectomized the injections of Amniotin Squibb are without avail, that is, there is not the slightest bleeding whatever. In these experiments red blood cells are searched for in the vaginal lavage with the most meticulous care and may be found even when present in numbers that would absolutely escape notice by the ordinary smear method. Yet in one 1760-gm. baby hypophysectomized 3 weeks before and receiving 500 rat units of Amniotin Squibb over a period of 10 days not a single red blood cell was recoverable from the vaginal lavage. A control that had the brain retracted and compressed but the hypophysis left intact bled after receiving 160 rat units. These experiments establish beyond question a new function for the anterior lobe of the hypophysis. The experimental results are quite in line with clinical observations both before and after Fröhlich on the relation of menstrual anomalies and hypophyseal disturbances.

4. One adolescent female and one multipara gave a slight positive reaction to massive doses of Amniotin Squibb, a bleeding so meagre that it would have escaped notice by ordinary methods of examination. Presumably a small bit of the anterior lobe has been retained in these 2 animals. Tests for sensitivity to insulin bore out this assumption. The intensity of the menstrual flow may be more or less proportionate to the amount of active anterior lobe tissue.

5. Administration of anterior lobe hormone in any form—implants of fresh gland, or intraperitoneal injection of triturated gland tissue by trochar; or injection of acid or alkaline extract—all result in bleeding, whether the animal be normal, sick and amenorrhic, castrated or hypophysectomized, old or young.

6. The threshold for the bleeding phenomenon is immensely lower than that for growth and congestion of the uterus and ovaries. In most of the experiments no change in these organs took place; several times the Smith-Engle effect (stimulation of graafian follicles) took place along with the bleeding. Such difference points either to a separate hormone that conditions bleeding, or a mere difference in threshold of the affected organs. The fact that both acid and alkaline extracts bring about bleeding argues for the assumption of a distinct hormone.

7. Since bleeding is caused so much more readily than hyper-

plasia of refractory ovaries or a dormant uterus, the clinician must decide to what degree the patient is benefited whose amenorrhea is cured only to the extent of bleeding without a real awakening of the reproductive tract.

8. Upon these and similar facts a new theory of menstruation must be built. The sequence of events that occur in the ovulatory menstrual cycle, as determined by long and painstaking labor on the part of gynecologists during the last 100 years, will find a new explanation in the experiments here reviewed and menstruation will be placed upon an experimental footing.

5221

The Influence of Iodide of Iron on Rats Receiving a Vitamin A-Free Diet.

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In 1925, the senior author, who had been keenly interested in the endocrine glands since 1912, was struck by the fact that several medical writers had shown that thyroid extract was beneficial in cataract and certain other eye diseases involving keratization. Accordingly, he began experimenting with rats depleted of Vitamin A, using various iodine compounds.

Among the interesting discoveries was the fact that on a normal diet tiny quantities of iodine would induce greater growth. Subsequent studies carried on with various associates seemed to indicate quite definitely that xerophthalmia and other symptoms of Vitamin A deficiency would yield to iodine treatment, and the most effective combination proved to be with extremely small doses of ferrous iodide.¹

Our studies of the efficiency of ferrous iodide have been carried on during 1929 and 1930, and we are convinced that the action of iodine is largely responsible for the prevention and cure of xerophthalmia, in our rats. But as the present findings indicate, the iodine-iron combination which is so effective in curing the major symptoms of Vitamin A deficiency, cannot replace the growth factor, since the iodine introduced is not balanced by unsaturated fatty acids such as are also present in cod liver oil.

¹ Chidester, F. E., Eaton, A. G., and Thompson, G. P., *Science*, 1928, **68**, 432.