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Bleeding Induced in Uterine Mucosa of the Rabbit by Estrogenic Hormone.

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By using gonadotropic hormone it is possible to produce in the rabbit a profuse bleeding which roots up the entire uterine mucosa.[1] The blood penetrates through the lifted areas of the epithelium into the uterine cavity and finally escapes into the vagina. This bleeding is observed especially after intravenous administration of the hormone and only rarely after subcutaneous administration. The most suitable dosage proved to be 100 RU gonadotropic hormone daily for 5 days. The bleeding appears on the 6th day. This effect was obtained with gonadotropic hormone from pregnancy urine or pregnant mare serum. The immature rabbit, weighing 1000-1400 g, is more suited for these experiments than when sexually mature. If the extirpated uterus is inspected against a strong light the blood can be recognized in the uterus with the naked eye but the macroscopical findings were not solely relied upon. Each preparation was examined histologically. In some cases the blood was found distributed over wide areas, sometimes there were only circumscribed spots. To be sure that bleeding had not been artificially produced by handling, the abdomen was opened, then filled with 4% formalin and the uterus was removed several hours later. It was possible to induce proliferation, and in some cases, progestational transformation in the mucosa uteri by administration of gonadotropic hormone for 5 days. In no instance was the bleeding found in the progestationally altered mucosa but only in the proliferative one. In the same uterine horn different areas may show different stages of development. Even in such cases the bleeding was always found in the proliferatively developed areas. From this we may deduce that progesterone counteracts the bleeding effect.

Bleeding could not be obtained in the castrated immature animal by the use of gonadotropic hormone, so it was obvious that the effect was produced *via* the ovary. The question now arose which of the two ovarian hormones was responsible for the production of the bleeding. The corpus luteum hormone could be eliminated, since no bleeding was ever encountered in the progestational mucous mem-

[1] Zondek, B., *J. of Obstr. and Gynæcol. of the Brit. Emp.*, 1938, **45**, 1.

brane; and experiments conducted with progesterone had also negative results. It is, therefore, the estrogenic hormone which should be considered in this connection. We injected into immature rabbits 100 IU of estrone in aqueous solution daily for 5 days. There was in some cases slight circumscribed bleeding, but we did not find the marked bleeding which spreads under the entire mucosa, eventually penetrating through the epithelium into the cavum uteri, as with gonadotropic hormone. Since it was not possible to produce bleeding of the uterine mucosa with either of the two ovarian hormones (estrone, progesterone) we suggested a third ovarian factor, hitherto unknown, which might be stimulated by gonadotropic hormone.[1] This assumption was found unnecessary, for it has been found possible to achieve the bleeding effect with estrogenic hormone, if a special experimental procedure is adhered to, taking into account the following factors:

(1) Dosage.
(2) Interval between administration of hormone and examination for the bleeding effect.
(3) Mode of application.

The most suitable dosage was 2 injections of 500 to 750 IU of estrone given at intervals of 12-24 hours. It is of prime importance that a powerful hormonal stimulus should be given in the course of one day, then wait several days. Usually the bleeding appears after an interval of 5 days. The most effective mode of application is by the intravenous route. The intravenous injection of estrogenic hormone is practicable in aqueous solution prepared in the following way: Dissolve 10 mg of crystallized estrone in a small quantity of absolute alcohol, add 1 cc of n/NaOH solution, after some time add water to 100 cc, so that the estrone is dissolved in n/100 NaOH. The alcohol is then evaporated *in vacuo*. One cc of this solution contains 1000 IU of estrone.

The experiments were performed with 13 immature rabbits. When estrone was injected subcutaneously in oily solution hyperaemia, but no bleeding, was observed (R. 604 and 606). When the hormone was spread over 4 days (R. 591) or when too large doses were used (3000 IU) bleeding was not obtained (R. 576, 579, 597). Adhering to the above described experimental procedure bleeding appeared in 5 of the experimental animals (Table I).

The estrone-produced bleeding is identical with that produced by means of gonadotropic hormone, yet does not seem to occur so regularly. The vessels show lacuna-like dilation, the blood penetrates the mucosa, lifts the epithelium and enters the uterine cavity and

TABLE I.
Bleeding of the Uterine Mucosa of the Rabbit Induced by Estrogenic Hormone.

Animal (rabbit) No.	Preparation	Dosage (IU)	Interval between injections	Mode of administration	Bleeding	Day when uteri were examined
565	Estrone aqu.	2x750	1 day	i.v.	+	4
566	"	2x750	1 "	i.v.	+	5
569	"	2x750	1 "	i.v.	+	4
588	"	2x750	1 "	i.v.	+	5
589	"	2x750	1 "	i.v.	+	5
605	Estrone ol.	2x500	1 "	s.c.	+	5
567	Estrone aqu.	1x750	—	i.v.	—	3
576	"	3x1000	18 hr	i.v.	—	5
579	"	3x1000	18 "	i.v.	—	5
591	"	4x300	4 days	i.v.	—	5
597	"	3x1000	18 hr	i.v.	—	5
604	Estrone ol.	2x250	1 day	s.c.	Hyperemia	5
606	"	2x750	1 "	s.c.	"	5

vagina. The anatomical picture greatly resembles that found in bleedings from a proliferatively developed mucosa in humans.

The sexual cycle, in the rabbit, is without bleeding. That it is possible to produce bleeding as in humans and monkeys, may provide the opportunity of studying the mechanism of the uterine bleeding in rabbits.

Summary. With estrone bleeding may be induced in the uterine mucosa of the rabbit. The blood penetrates through the lifted epithelial areas and eventually enters the uterine cavity and vagina. This effect may be obtained by two injections of 500 to 750 IU of estrone given intravenously during 12 or 24 hours. Bleeding appears after 4-5 days.

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Anterior Pituitary Extracts and the Brunn Reaction in Frogs.

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When pharmacopoeial extracts of the "posterior pituitary gland" are injected into frogs immersed in water there follows an increase in body weight due to an uptake of water which lasts 3 to 6 hours at room temperature. This reaction was first investigated by Fritz Brunn at Prague[1] and we shall refer to it simply as the Brunn reac-

[1] Brunn, F., *Zeit. f. exp. Med.*, 1921, **25**, 170.