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.

tion. It has been shown[2] that the uptake of water in the Brunn reaction is 2 to 3 times as great in the summer as in the winter months in this locality. No exogenous factor was found to account for this seasonal variation which was tentatively ascribed to variation in some endogenous mechanism.[2]

Zahl[3] has reported that there is a seasonal variation in the histological picture of the pars distalis of the frog with more acidophilic cells in the winter than in the summer. The acidophilic cells of the buccal lobe are believed to elaborate growth hormone and possibly other hormones such as the thyrotropic and gonadotropic factors.[4, 5] We therefore considered it possible that an excessive production of anterior pituitary principles might have accounted for the depression of the Brunn reaction in our winter frogs. That anterior and posterior pituitary hormones antagonize each other upon certain phases of mammalian water balance has been known since the initial experiments of Harvey Cushing and his colleagues, von Hann and others.[6] Elmer writing from Lwöw quotes Carter as stating that a "Ringer extract of the whole pituitary . . . . produced the winter condition in a summer heart" of frogs.[7] Biasotti[8] found that an extract of the anterior part of the pituitary body had no immediate effect on the body water of a South American amphibian, *Leptodactylus ocellatus.*

If anterior pituitary hormones account for the winter depression of the Brunn reaction, they may act in one or both of two ways, either by directly neutralizing the water balance component of pituitary (posterior lobe) extract or by so altering the receptor cells upon which this extract acts that it cannot effect as great an uptake of water into the body. We wish to report experiments bearing upon the first possibility. Using the same technic as in previous studies of the Brunn reaction,[2] we injected into frogs in water pituitary (posterior lobe) extract without and with several commercial anterior pituitary, human pregnancy urine and pregnant mare serum preparations, the latter in doses corresponding by weight to 1 to 1000 times

[2] Boyd, E. M., Mack, E. G., and Smith, A. E., *Am. J. Physiol.*, 1939, **127**, 328.

[3] Zahl, P. A., PROC. SOC. EXP. BIOL. AND MED., 1935, **33**, 56.

[4] Van Dyke, H. B., *The Physiology and Pharmacology of the Pituitary Body*, Univ. of Chicago Press, 1936, and Vol. 2, 1939.

[5] Symposium: *The Pituitary Gland*, Williams and Wilkins, Baltimore, 1938.

[6] Fisher, C., Ingram, W. R., and Ranson, S. W., *Diabetes Insipidus and the Neurohormonal Control of Water Balance*, Edwards Bros., Ann Arbor, 1938.

[7] Elmer, A. W., *Iodine Metabolism and Thyroid Function*, Oxford Univ. Press, London, 1938.

[8] Biasotti, A., *Comp. rend. Soc. de biol.*, 1923, **88**, 361.

the average recommended single injected human dose. These preparations used included Gonan and Serogan (B.D.H.), Antophysin (Winthrop), Antuitrin-G (P.D.&Co.) and the gonadotropic, thyrotropic and lactogenic fractions marketed by Ayerst, all of these preparations being generously provided us by the companies concerned. A grant which defrayed part of the expenses of the investigation was provided by Parke, Davis and Co. through Dr. E. A. Sharp.

None of these preparations had any effect upon the Brunn reaction in the doses employed. To illustrate this, the percentage uptake of water was averaged in all groups of frogs receiving the same human dose equivalent of the preparations and 1 international unit of pituitary (posterior lobe) extract per 10 g body weight, giving a total of 96 frogs to each group and the mean values so obtained have been compiled in Table I. Similar experiments made with lower doses of pituitary (posterior lobe) extract down to 0.1 units per 10 g yielded similar negative results. These results indicate that that fraction of pituitary (posterior lobe) extract which produces the Brunn reaction is not directly neutralized by any of the anterior pituitary or anterior pituitary-like hormones present in the preparations used.

It seemed unlikely that any of these anterior pituitary or anterior pituitary-like preparations could of themselves affect body water during the 5-hour interval after their injection when body weight was being measured. To be sure of this, we injected them without pituitary (posterior lobe) extract and in a dosage range similar to that used above and found in some 500 frogs that changes in body weight were not significantly different from those in controls.

Conclusion. A number of anterior pituitary and anterior pituitary-like preparations were found to have no effect during 5 hours after their injection into frogs in water either on normal body water or upon the Brunn reaction.

TABLE I.

Uptake of Water by Leopard Frogs in Water Injected with Pituitary (Posterior Lobe) Extract with and without Increasing Doses of Anterior Pituitary Preparations (AP).

Group	% uptake of water (Mean 96 frogs)			
	2 hr	3 hr	4 hr	5 hr
Pituitrin alone	14.1	15.6	13.5	9.9
" + equivalent human dose AP	13.1	15.4	13.1	9.9
" + 10X equivalent human dose AP	11.8	15.2	13.8	10.4
" + 100X " " " "	10.0	14.4	12.8	9.4
" + 1000X " " " "	10.3	15.1	13.5	10.8