10942

Gonadotropic Activity of Ant. Pituitary of the Finback Whale.

H. JENSEN, E. M. K. GEILING AND SIBYLLE TOLKSDORF.

From the Squibb Institute for Medical Research, New Brunswick, N. J., and the Department of Pharmacology, University of Chicago, Ill.

The gonadotropic activity of anterior whale pituitary has been determined by Valsö[1] and by Wallen-Lawrence.[2] Using normal immature female rats, these investigators demonstrated the presence of the follicle-stimulating (FSH) and luteinizing (LH) factors. We have repeated these standardizations in hypophysectomized as well as normal rats, testing the whale pituitary samples at the same time for their ability to repair the ovarian interstitial tissue (ICSH) in hypophysectomized female rats and to act as a gonadotropic antagonist. As shown recently,[3, 4] these 2 properties are characteristic of the hypophyseal LH factor.

Three different samples of acetone-dried anterior whale pituitary and 40% alcohol extracts thereof[3] were tested at different dose levels in normal and hypophysectomized rats in the routine manner, giving one injection daily for 3 days with autopsy 72 hours after onset of therapy. The first sample injected either subcutaneously or intraperitoneally into hypophysectomized rats, at dose levels ranging from 2 mg to 0.25 mg, produced only follicular development. The M.E.D. was found to be 0.25 mg. No repair of the interstitial tissue was observed at any dose level between 2 mg and 0.25 mg and no pronounced antagonism was manifested when given at these dose levels intraperitoneally to normal rats in combination with pregnant mare serum.* The simultaneous absence of the interstitial stimulating and antagonistic effects of this preparation agrees with our assumption of their identity.

On the other hand, 40% alcohol extracts of samples II and III which had been collected later were found to contain both the FSH and LH (ICSH) factors and to give varying degrees of antagonism

[1] Valsö, J., *Klin. Wochenschr.*, 1934, **13**, 1819; *Hvalradets Skrifter Norske Videnskaps—Akad. Oslo*, 1938, **16**, 5 (*Chem. Ab.*, 1938, **32**, 6707).

[2] Geiling, E. M. K., *Bull. Johns Hopkins Hosp.*, 1935, **57**, 123.

[3] Jensen, H., Simpson, M. E., Tolksdorf, S., and Evans, H. M., *Endocrin.*, 1939, **25**, 57.

[4] Evans, H. M., Simpson, M. E., Tolksdorf, S., and Jensen, H., *Endocrin.*, 1939, **25**, 529.

* It has been found[4] that purified FSH preparations may also act as an antagonist against the gonadotropic potency of pregnant mare serum.

TABLE I.
40% Alcohol Extract of Anterior Whale Pituitary, Sample II. Ovarian Response in 72-hr Test after Intraperitoneal Injection.

Hypophysectomized Rats 2 mg	Normal Rats	
	2 mg + PMS*	PMS* alone
9.2 mg slight foll. development, hypertrophy of interstitial tissue	71 mg (avg 6 rats)	119 mg (avg 6 rats)

* PMS: 1 mg total dose of a pregnant mare serum preparation.

when tested against pregnant mare serum (Table I). The gonadotropic activity of preparations II and III corresponds to that of similar preparations obtained from sheep and pig pituitary. Sample II (40% alcohol extract) when tested at 10 mg produced luteinization of the ovaries and stimulation of the thyroids and adrenals in hypophysectomized rats. In addition, 40% alcohol extracts of samples II and III were tested for thyrotropic activity in day-old chicks according to the method described by Smelser[5] and showed, at 4 and 2 mg total dose, approximately the same potency as similar extracts from sheep pituitary.

We are unable to give an explanation for the different results obtained with various whale pituitary samples. It is possible that in sample I the LH (ICSH) factor was destroyed by autolysis during the time which elapsed between the killing of the animal and the removal of the gland. In order to test this possibility, we studied the effect of autolysis on the gonadotropic content of anterior beef and whole sheep pituitary. The fresh glands were incubated at 37°C for periods varying from 2 to 6 hours and for 24 hours. Our assays of the incubated material are, however, not very conclusive and are, therefore, not given in detail. It seems that 6 hours' incubation causes a considerable reduction of the FSH and ICSH activities while incubation for 24 hours destroys practically all gonadotropic potency. We are under the impression that both factors are inactivated at approximately the same rate and that there is no sufficient differential destruction to allow a separation of the 2 factors. It might be desirable to study the rate of inactivation at incubation periods between 6 to 24 hours.

Summary. Three samples of acetone dried whale anterior pituitary and 40% alcohol extracts thereof were assayed in normal and hypophysectomized female rats. In the first sample, only the presence of FSH could be demonstrated, no interstitial cell stimulating, luteinizing, antagonistic or thyrotropic activity was observed at the dose

[5] Smelser, G. K., *Endocrin.*, 1938, **23**, 429.

levels employed. Samples II and III showed the presence of both FSH and ICSH, concurrently with luteinizing, antagonistic and thyrotropic activity. Sample II was also tested for adrenotropic activity and it was found that this factor was present. The gonadotropic activity of 40% alcohol extracts of samples II and III is of the same order as that of similar preparations obtained from sheep and pig pituitary. The absence or presence of the multiple properties of the LH (ICSH) factor agrees with our assumption that they are due to one principle only.

10943

Alkyl Nitrites V.
The Pharmacology of the High Molecular Weight Alkyl Nitrites.*

JOHN C. KRANTZ, JR., C. JELLEFF CARR AND SYLVAN E. FORMAN.
From the Department of Pharmacology, School of Medicine, University of Maryland.

In previous studies[1] the pharmacology of a series of new brominated and non-brominated alkyl nitrites of relatively high molecular weight was described. The properties and action of 2-ethyl-n-hexyl-1-nitrite[2] prompted a more complete investigation of this compound, which resulted in its use as a therapeutic agent in angiospastic disease. Cash and Dunstan[3] many years ago studied the activity of the primary and secondary alkyl nitrites from methyl to amyl. In general, they found that the higher nitrites, butyl and amyl, gave a greater fall in blood pressure than those of lower molecular weight. On the other hand, they found a greater duration of response when the lower molecular weight esters were administered. These investigators expressed the view that the magnitude of the fall in blood pressure was a function of the instability of the higher members and not of their molecular weight. The greater duration of the response of the lower members was attributed to their greater degree of stability. It oc-

* The expense of this investigation was defrayed in part by a grant from the Committee on Therapeutics of the Council on Pharmacy and Chemistry of the American Medical Association.

1 Krantz, J. C., Jr., Carr, C. J., and Forman, S. E., *J. Pharmacol. and Exp. Therap.*, 1938, **64**, 298.

2 Krantz, J. C., Jr., Carr, C. J., and Forman, S. E., *J. Pharmacol. and Exp. Therap.*, 1938, **64**, 302.

3 Cash, J. Th., and Dunstan, W. R., *Phil. Trans. Roy. Soc.*, 1893, **184** B, 505.