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Effect of Certain Hormones and Drugs on the Perfused Mammary Gland.*

W. E. PETERSEN.

From the Department of Dairy Husbandry, University of Minnesota.

Although Ott and Scott¹ demonstrated that an extract of the posterior hypophysis would cause an ejection of milk from the alveoli of the mammary gland this phenomenon was not associated with the natural let down of milk until the work of Ely and Petersen,² who demonstrated that both the oxytocic and vasopressor substances of the posterior pituitary would cause an ejection of milk in the cow. Turner and Cooper³ reported the same for the rabbit. Ely and Petersen observed fright or the injection of epinephrin inhibited the natural response to the milking stimulus. Petersen and Ludwick⁴ showed that the substance responsible for the ejection of milk is humoral in nature and that the blood from excited cows has great vasoconstricting properties in perfused bovine mammary glands.

As a result of these observations, it was deemed advisable to test the effects of a number of substances upon the blood flow and the milk ejection mechanism in the bovine mammary gland. This report deals with 9 substances: oxytocin, pitressin, epinephrin, histamine, atropine, ergonovine, acetylcholine, Mecholyl (acetyl- β -methylcholine) and Lentin (carbamylcholine).

The experiments here reported were on bovine mammary glands perfused according to the technic of Petersen, Shaw and Visscher.⁵ The glands were obtained from a packing plant. The teats were cannulated to permit drainage of the milk immediately after the perfusion started and the cannula left *in situ* during the experiment. The blood pressure was maintained at 110 mg Hg pressure at all times. The substances tested were injected into the arterial blood as it entered the gland.

The number of experiments, dosage of the substance, effect on the

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¹ Ott, I., and Scott, J. C., *Proc. Soc. Exp. Biol. and Med.*, 1910, **8**, 48.

² Turner, C. W., and Cooper, W. D., *Endocrinology*, 1941, **29**, 320.

³ Ely, F., and Petersen, W. E., *J. Dairy Sci.*, 1941, **24**, 211.

⁴ Petersen, W. E., and Ludwick, T. M., *Federation Proc.*, 1942, **1**, 66.

⁵ Petersen, W. E., Shaw, J. C., and Visscher, M. B., *J. Dairy Sci.*, 1941, **24**, 139.

blood flow and the effect on the ejection of milk are given in Table I for each substance tested. As the rate of the blood flow and the amount of milk in the glands varied greatly in the different experiments, it is not advisable to quantitate the data on such a basis. That ten units of Pitocin would quantitatively express the milk from a gland has been ascertained in many experiments. Pitocin injections following the use of any other substance was, therefore, resorted to as a test for the completeness of the milk ejection.

Only Pitocin and acetylcholine caused complete evacuation of milk from the gland. Of these acetylcholine did not affect the rate of blood flow while Pitocin caused a decrease. The vasoconstricting effect of Pitocin may be attributed to the pitressor principle which it contains. Pitressin (10 units) caused a marked decrease in blood flow and an incomplete evacuation of milk as in all experiments varying quantities of milk were obtained with Pitocin following pitressin.

The mammary gland seems to be unusually sensitive to epinephrin, for as little as 0.05 mg caused a 50% reduction and 0.1 and 0.2 mg completely stopped the blood flow. In all cases some milk was ejected with this hormone. Histamine also proved to be a powerful vasoconstrictor in the mammary gland and produced milk ejection of approximately the same magnitude as epinephrin.

Ergonovine in 0.2 to 0.6 mg doses proved to have no effect upon the ejection of milk but caused some vasoconstriction.

While acetylcholine caused a complete ejection of the milk acetyl- β -methylcholine (Mecholyl) in as large and larger doses caused but a partial evacuation of milk from the gland. Carbamylcholine in

TABLE I.
Effect of 9 Hormones and Drugs upon the Blood Flow and Ejection of Milk in the Perfused Mammary Gland.

Substance	No. of exper.	Amt used	Effect on blood flow	Effect on milk ejection
Pitocin	12	10 units	decrease 8-20%	complete
Pitressin	6	10 "	" 40-60%	partial
Epinephrin	10	0.05-0.2 mg	" 50-100%	partial
Histamine	10	0.5-10 mg	" 50-100%	partial
Ergonovine	6	0.2-0.6 mg	" 10-20%	no effect
Acetylcholine	5	4.0-100 mg	no effect	complete
Acetyl- β -methylcholine	4	25.0-150 mg	" "	partial
Carbamylcholine	4	2-8 mg	slight increase	no effect
Atropine	8	2-4 mg	" "	" "
Acetylcholine following atropine	3	100 mg	no effect	" "
Acetyl- β -methylcholine following atropine	2	250 mg	" "	" "

2 to 8 mg doses had no effect upon milk ejection. Atropine tended to increase blood flow slightly and completely prevented any response to acetylcholine and acetyl- β -methylcholine but had no effect upon the action of Pitocin or pitressin.

From these observations it would appear that the mammary gland is innervated with the parasympathetics as well as the sympathetics.

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Studies on the Toxicity of Protamine.

WALTER B. SHELLEY, MYRTLE P. HODGKINS AND M. B. VISSCHER.

From the Department of Physiology, University of Minnesota.

The parenteral administration of protamine has been suggested by Jorpes¹ and Ravdin² as a clinical method of terminating the action of administered heparin. Since the toxic effects of the protamines have not been extensively studied, further investigations seemed desirable.

Thompson³ and later workers have shown that relatively large doses of protamines produce dyspnea, a marked fall in the blood pressure, diminished blood coagulability, and in sufficient dosage, death. These symptoms were observed in several animal species. Thompson felt that the action of protamines could best be explained on the basis of a general toxic effect on the cardiovascular and respiratory systems. Postmortem studies on rabbits and mice, killed by subcutaneous injection of protamine, have been performed by Vartiainen and Marble.⁴ Hemorrhages in the thymus, lungs, and kidneys were the most constant findings.

Although Kern and Langner⁵ and earlier workers⁶ had failed to produce anaphylaxis with protamine, Walther and Ammon⁷ recently claimed to have produced fatal anaphylactic shock in guinea pigs

¹ Jorpes, E., Edman, P., and Thaning, T., *Lancet*, 1939, **237**, 975.

² Ravdin, I. S., *Am. J. Med. Sc.*, 1941, **201**, 299.

³ Thompson, W. H., *Trans. Roy. Acad. Med. in Ireland*, 1900, **18**, 426.

⁴ Vartiainen, I., and Marble, A., *J. Lab. and Clin. Med.*, 1941, **26**, 1416.

⁵ Kern, R. A., Langner, P. H., *J. A. M. A.*, 1939, **113**, 198.

⁶ Wells, H. G., *Physiol. Rev.*, 1921, **1**, 44.

⁷ Walther, G., and Ammon, R., *Klin. Wschr.*, 1939, **18**, 288.