

The Action of Animal Extracts on Milk Secretion.

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Since the secretion of milk is known to proceed with the same regularity whether the nerves to the mammary glands are cut or intact*, it seems probable that it is provoked by other than nervous stimuli. It cannot, indeed, be contested that the secretion is influenced through the nervous system, but this may be indirect, if the formation and outpouring of the secretion can be shown to be produced by chemical agents (hormones) circulating in the blood, such as have been found to excite secretion in the pancreas,† which is stimulated to active secretion by a material obtained from the mucous membrane of the duodenum, and in the kidney,‡ which is stimulated by a material yielded by the posterior or infundibular portion of the pituitary body.

We have investigated the action of a large number of animal extracts upon the flow of milk from the mammary glands of lactating animals, chiefly cats, but including some dogs. The extracts, which were made with Ringer's solution, and were in most cases previously boiled, were injected slowly and in small amount (not more than 5 c.c. at a time) into a superficial vein, and the flow of milk, if any, was recorded by one of two methods, or by both methods simultaneously. The simpler method consists in recording the rate of exudation of milk from a small and superficial cut into one of the mammary glands (exudation method). The other method consists in recording the flow of milk led from a canula tied into a cut nipple (nipple method); in either case the milk is allowed to drop upon an electric recorder, and the drops are marked by an electromagnetic signal upon the paper of a kymograph. On this paper are also recorded at the same time in some of our experiments the blood-pressure, the volume of the kidney, and the rate of excretion of urine. The animals were anæsthetised either with chloroform alone or with chloroform followed by chloral, the latter being administered either intravenously or subcutaneously; after the complete effect of the chloral is established, the chloroform administration is stopped.

* Eckhard, 'Beiträge zur Anat. u. Physiol.,' 1855 and 1897.

+ Bayliss and Starling, 'Journ. Physiol.,' 1902, vol. 28, and 1903, vol. 29.

‡ Schäfer and Herring, 'Phil. Trans.,' 1906, B, vol. 199.

Until quite recently nothing had been ascertained regarding the influence of animal extracts upon milk secretion. But in a type-written notice inserted into a pamphlet on "Internal Secretions," by Dr. Isaac Ott, of Philadelphia, and dated October 28, 1910, the brief statement is made that "infundibulin is a rapid and powerful galactagogue."* This pamphlet came into our hands on November 20, and the statement in question furnished the starting point of our investigations.

The animal extracts which we have investigated are numerous, and include not only extracts of both parts of the pituitary body, but also extracts of placenta,† uterus in process of involution, mammary gland, duodenum, liver, spleen,‡ kidney, thyroid, ovary, testicle, thymus, and suprarenal capsules. In the ovary we investigated separately the ovarian substance proper and the substance of the corpora lutea. And in view of the growth of mammary gland substance which was found by Miss Lane-Claypon and Prof. Starling§ to be produced in the (virgin) rabbit by hypodermic injections of extract of rabbit-foetuses, we also tried the effect on the secretion of the mammary gland (of the cat) of intravenous injection of extract of cat-foetuses, with, however, a negative result. The most constant positive results which we have obtained have been those resulting from extracts of the posterior lobe of the pituitary body (of the ox) and of corpus luteum (of the sheep). Of these two materials that contained in the posterior lobe of the pituitary body is the more active. The accompanying curve (fig. 1) exhibits the effect produced by intravenous injection of a small amount of this extract. Prior to the injection no milk was passing from the gland; indeed, in the absence of a special stimulus the secretion almost always remains in abeyance. But within 20 seconds of the injection, drops of milk began to fall fast from the tube, the end of which was little, if at all, below the level of the gland with which it was connected, so that the flow was not assisted by suction, but must have been the result of the *vis a tergo* of the secretion. The effect

* "Infundibulin" appears to be a proprietary article and is described by Ott (p. 57) as "a 20-per cent. extract of the pituitary." But probably, as the name implies, the infundibular part of the gland is alone used in its preparation.

† Lederer and Pribram ("Report of Internat. Physiol. Congress, Vienna," 'Zentralbl. f. Physiol.,' 1910, vol. 24, p. 817) state that they have obtained increase of milk secretion in the goat as the result of intravenous injection of unboiled extract of placenta, but our results with this extract have so far been negative (in the cat and dog).

‡ In investigating the action of spleen extracts we have incidentally found that such extracts may produce marked diuresis, without either rise of blood-pressure (in point of fact the blood-pressure falls) or increase of kidney volume. The diuresis must therefore be caused by a direct stimulating action upon the secreting cells of the kidney.

§ 'Roy. Soc. Proc.,' B, 1906, vol. 77.

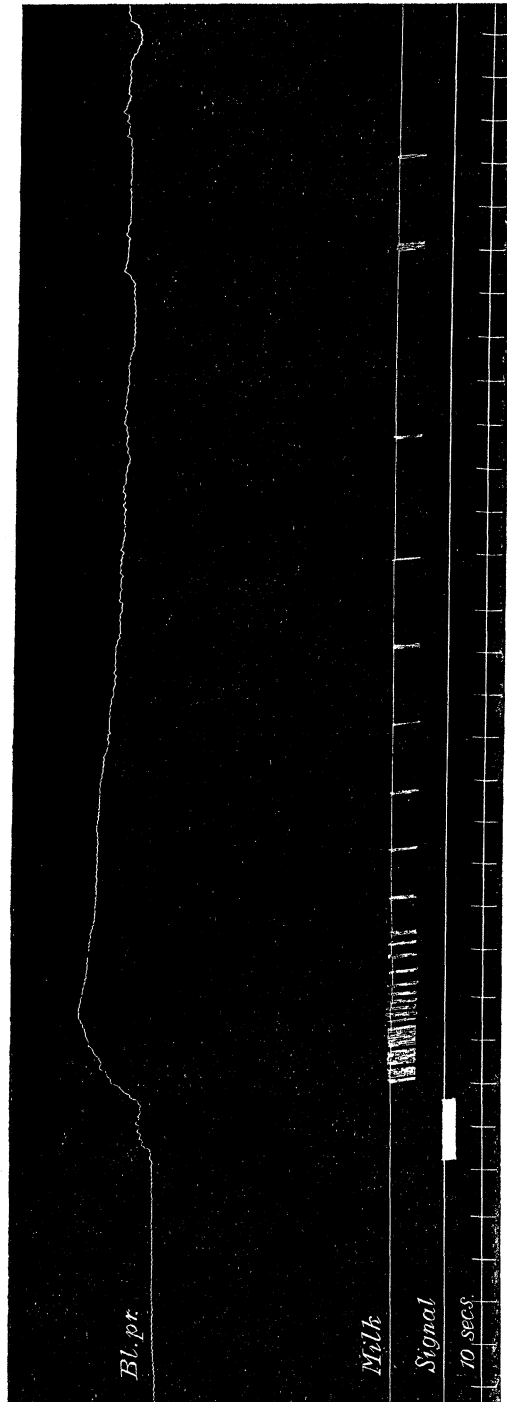


FIG. 1.—Graphic record of the milk secretion which was produced in a lactating cat as the result of intravenous injection of 4 c.c. Ringer's solution containing 1.5 c.c. of pituitrin solution (Parke, Davis and Co.) prepared from extract of posterior lobe of ox-pituitary. The uppermost line records the blood-pressure; the second the dropping of milk from a tube connected with a cut nipple; the drops fell at first so fast as to run together in the record; the third line marks the signal of injection; the fourth line time-intervals of 10 secs.

passed off after three or four minutes, during which time 30 to 40 large drops of milk were recorded. This, it must be remembered, was from two of the mammary glands only (usually two were led off to the one drop-recorder), representing about one-fifth of the whole glandular mass. But it lasts only a short time, in which respect it differs from the effect which the same extract produces upon the urinary secretion, the rate of which may be increased during many minutes after the injection, and even to some degree for a prolonged period. In the case of the urinary secretion, a second or "repeat" dose of posterior-lobe extract, given within a period of half an hour or less, causes a renewed increase of urine secretion, although this may be now unaccompanied by a repetition of the rise of blood-pressure which accompanies the first dose.* But the effect of a repeat dose upon the secretion of the mammary gland is much less than that produced by the first dose, and in some cases fails to be recorded by the "nipple method," although it can be sometimes observed by the "exudation method"; and such repetition produces a smaller result than the previous one.

We find that the galactagogue substance of the pituitary body is not present in the pars anterior, but only in the pars intermedia and pars posterior of the gland. It is not yielded to absolute alcohol, although a very small amount of water in the alcohol used will suffice to extract it. It is not destroyed by contact with absolute alcohol (at least within a reasonable period), nor by repeated boiling, nor by prolonged keeping in the dry state (we have obtained marked effect from dry posterior-lobe substance which has been kept some years in a stoppered bottle). The galactagogue action runs parallel in time with the action of the extract upon the systemic blood-vessels, which are contracted by posterior-lobe extracts.† It is probable, however, that, as in the case of the kidney, the blood-vessels of the mammary gland do not share in the general constriction which this extract produces. But we have not yet succeeded in definitely determining by a plethysmographic method whether the vessels of the gland dilate during the increased secretion, although to judge from the appearance of the cut gland this would seem to be the case. This is a point which must be the subject of further investigation.

Another extract which in our hands has yielded a definite positive result is extract of fresh corpus luteum, prepared with Ringer's solution. The effect is quite distinct but less decided than with extract of posterior lobe of pituitary: for, instead of some 30 to 40 drops, not more than 5 drops of milk were yielded by the nipple method after injection of 5 c.c. of a corpus

* Schäfer and Herring, *op. cit.*

† Oliver and Schäfer, 'Journ. Physiol.,' vol. 18, 1895.

luteum extract made up in the proportion of 1 part of the fresh tissue to 10 parts of Ringer's solution. One such result is shown in fig. 2, A. The active substance of the corpus luteum is probably not the same as that obtained from the pituitary, for its galactagogue action is unaccompanied by the same general rise of blood-pressure; indeed, there is usually a fall of a more or less decided character. As with the pituitary material, the galactagogue substance of the corpus luteum is not yielded to absolute alcohol, nor destroyed by contact with alcohol (at least for a short time) nor by repeated boiling. And, as with pituitary extract, a repeat dose is usually less effective as compared with the first dose; the amount of milk formed under its influence is often insufficient to cause the secretion to flow from the nipple, although secretion may be apparent when the exudation method is adopted. A second effect is, however, distinct in fig. 2, B.



FIG. 2.—Records of milk-flow from a nipple of a lactating cat as the result of the intravenous injection of 5 c.c. of Ringer's solution extract of corpus luteum from sheep's ovary. Two such injections were given. In the record of the first (A) six drops are shown; in that of the second (B) five drops. Signal and time tracings as in fig. 1.

In order to produce the galactagogue effect, it is not necessary to employ a lactating animal. In one instance we obtained a free flow of fluid—of serous appearance—from the incised mamma of a cat, apparently virgin, and not fully grown. This is illustrated in the tracing which is shown in fig. 3, which is from a small cat, weighing $2\frac{1}{2}$ kilogrammes and rather more than three parts grown. The mammary glands were very small and little developed, and confined to the neighbourhood of the nipples. The fluid which exuded from the incised gland was led by a wet cotton wick over a drop-recorder and the drops were marked in the usual way by electromagnetic signal. Prior to the injection (of the corpus luteum extract) no flow

was registered, but within less than a minute of the injection the flow began, and was, in fact, at first so rapid that two or three drops fell at the side and escaped registration. The galactagogue action in this case lasted about ten minutes. A second dose proved ineffective.

We have further investigated the action of a number of drugs which from their influence on other glands might have been expected to influence the secretion of the mammary gland; but with negative results. Amongst these may be mentioned pilocarpine, eserine, and nicotine. A dose of pilocarpine capable of producing intense salivation and lacrimation has no perceptible influence on milk secretion. Secretine also gives a negative result. Nor have we so far succeeded in obtaining any positive result from the electrical excitation of the nerves to the glands. Our experiments in this direction have not been sufficiently numerous for us to state definitely that no effect is under any circumstances so obtainable, but hitherto neither by reflex nor by direct stimulation have we been able to cause a flow of milk from the nipple. The work in this and in some other directions is, however, still in progress, and the results will be given in a later communication.

Within the last few days, and since the completion of our joint work upon this subject,* there has come into our hands the number of the 'Proceedings of the Society of Experimental Biology of New York,' which describes the communications made to that Society at its meeting on December 21, 1910. Amongst these communications are two by Drs. Isaac Ott and J. C. Scott, which deal with the galactagogue action not only of "infundibulin" but also of other animal extracts. These authors have used the goat as the subject of their

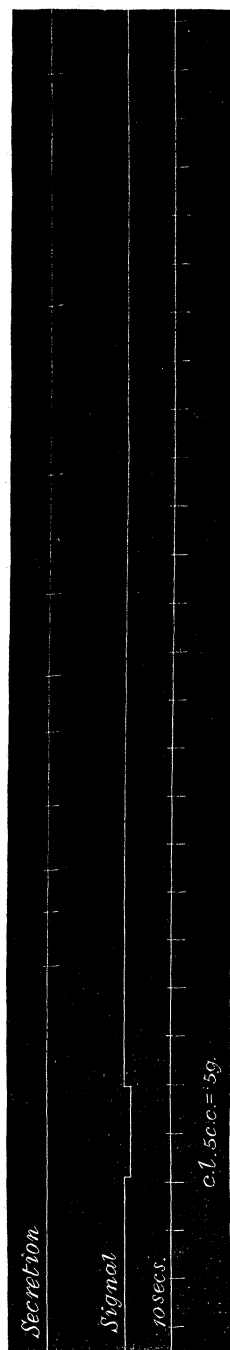


FIG. 3.—Record of flow of secretion from the mammary gland of a non-lactating and apparently virgin cat as the result of intravenous injection of 5 c.c. of Ringer's solution extract of corpus luteum from sheep's ovary (exudation method). The uppermost line shows the drops of secretion; signal and time tracings as in the preceding figures.

* The experiments are being continued by Dr. Mackenzie alone.

experiments, determining the amount of milk which could be drawn from the udder by an aspirator before and after the injection of various extracts into a vein of the ear. They record a very striking action of infundibulin, the amount of secretion being increased in one experiment as the result of a single injection from 5 drops to 400 drops of milk in periods of five minutes; they have also obtained a galactagogue action from extracts of corpus luteum, thymus and pineal gland. Although we have not been able to determine this action in the case of the two last mentioned glands, our experiments upon the pituitary and corpus luteum have yielded results, in the cat and dog, similar to those obtained by Drs. Ott and Scott in the goat, and we shall await with interest the publication of the details of their experiments. In any case the credit of the discovery of hormones which influence milk secretion belongs to them, and our results, although arrived at on other animals and by a somewhat different method, are in the main confirmatory of those which the American authors have established, at least for the early period of lactation.

[*Note added March 31, 1911.*—Since this paper was read, Dr. Mackenzie has found that extracts both of involuting uterine mucous membrane and of mammary gland itself are markedly galactagogue, and that with regard to the action of pituitary extract, the source of this extract appears to make no difference to its activity; the extract of the bird's pituitary being quite as active in promoting the mammary secretion as that of the mammalian pituitary itself. He has also determined that atropine does not interfere with the action of any of these galactagogues.]
