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Ott, Isaac, 1847-1916.
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Publication/Creation

[Philadelphia] : [publisher not identified], 1912.

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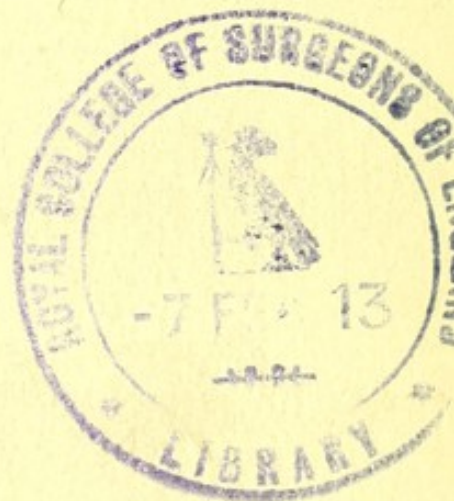
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CONTRIBUTIONS
FROM THE
PHYSIOLOGICAL LABORATORY
OF THE
MEDICO-CHIRURGICAL COLLEGE
OF PHILADELPHIA

BY
ISAAC OTT, A.M., M.D.
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PART XIX
OF
OTT'S CONTRIBUTIONS TO PHYSIOLOGY

1912



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[Reprinted from the *American Journal of Obstetrics and Diseases of Women and Children*, Vol. LXI, No. 5, 1910.]

THE EFFECT OF ANIMAL EXTRACTS UPON UTERINE CONTRACTIONS.

BY

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AND

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(With one illustration:)

In a paper published in the *Journal of Experimental Medicine*, vol. xi, No. 2, 1909, we stated the action of animal extracts upon the uterus by the method of Magnus. In this method a piece of the uterus is excised, placed in Ringer's solution at a temperature of 37.5° C. with oxygen bubbling through it. A segment of the uterus was attached to a lever which recorded the contractions.

In this communication we have studied the action upon the uterus *in situ*. The experiments were made upon rabbits and cats. The animals received paraldehyde by the mouth and ether by inhalation. Fifteen experiments were performed. The animals after being under the influence of ether were fastened upon the holder, the abdomen opened

in the median line in its lower segment, the head of the Malassez holder elevated, and the pelvic cavity filled with normal saline solution, which kept the uterine tissue bathed. The sides of the abdominal walls incised were elevated by ligatures

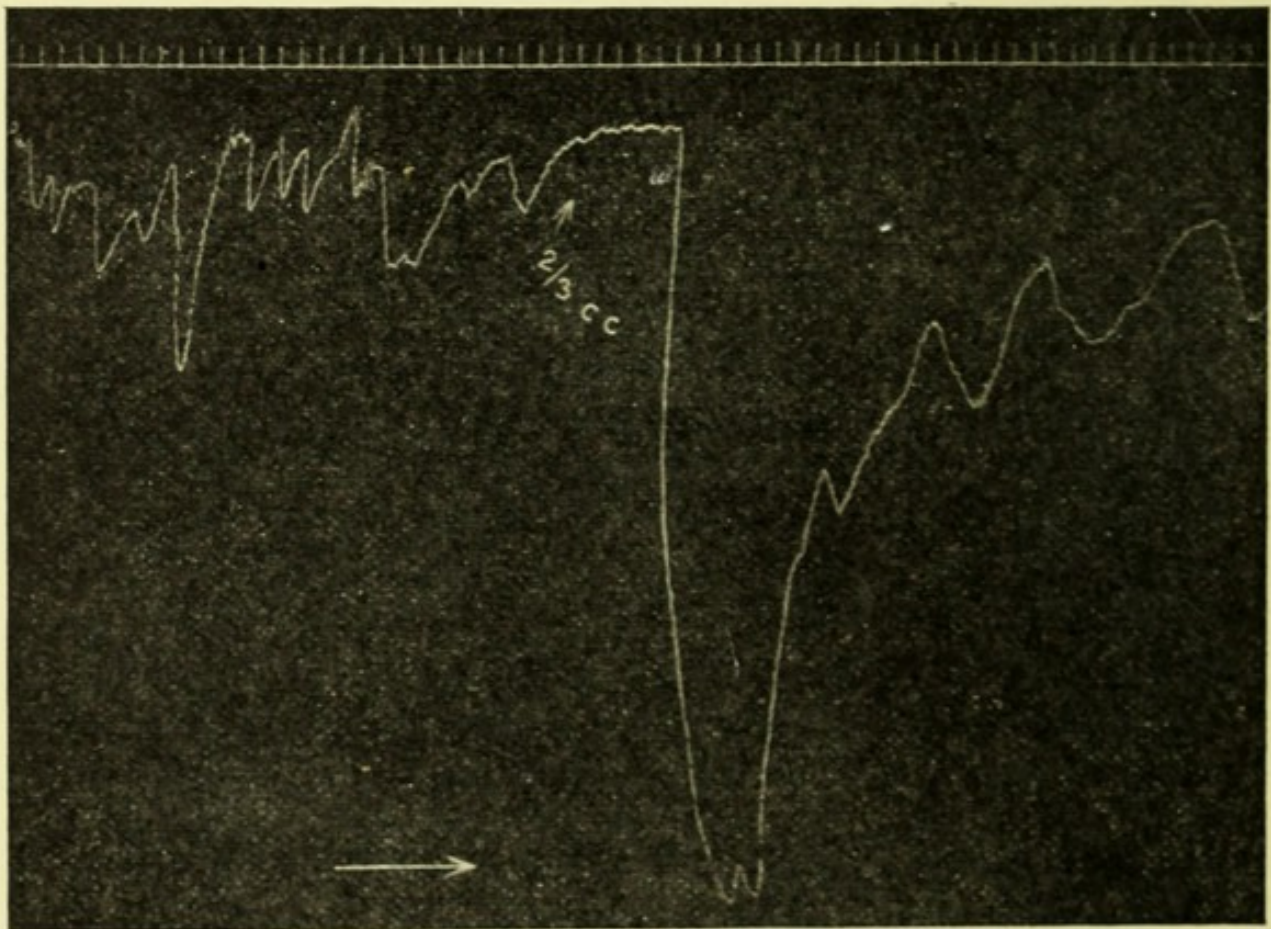


FIG. 1.—Rabbit: parous uterus $\frac{2}{3}$ of 1 c.c. of infundibular extract of pituitary per jugular. The downward curve shows the contraction of the uterus after infundibulin.

to a horizontal bar. This aided in the retention of the normal saline. The temperature of the saline was kept at the temperature of body by means of frequent additions of the heated saline solution.

The uterus was attached by two threads to a myocardiographic lever which inscribed the quite regular uterine contraction with the respiratory movements upon a smoked drum. The dried extracts were rubbed up with distilled water filtered through cotton and injected per jugular. We have obtained a marked uterine contraction with a 20 per cent. extract of the infundibular lobe of the hypophysis. Fig. 1. This has been previously observed by Dale and Bell.

Brain ($\frac{1}{2}$ grain) per jugular produced marked uterine contractions in the pregnant uterus.

The mammary gland ($\frac{1}{3}$ grain) in the parous uterus caused marked uterine contractions.

Spleen ($\frac{1}{2}$ to 1 grain) in the virgin uterus and in pregnant uterus caused marked contraction.

Parathyroid (1 grain) with the parous uterus was followed by increased uterine contraction.

Iodothyryn (2 grains) in virgin uterus produced contractions and in pregnant uterus produced marked uterine contraction.

The parotid (1 grain) in pregnant uterus produced fair uterine contraction.

Pancreas (1 grain) in pregnant uterus produced very marked contractions.

Thymus ($\frac{1}{4}$ grain) caused some contraction in pregnant uterus.

Prostate ($\frac{1}{4}$ grain) in pregnant uterus produced marked contraction.

Spermine (Poehl) 10 drop doses, caused some contraction in pregnant uterus of cat.

The ovary ($\frac{1}{4}$ grain) in the virgin uterus caused slight contraction.

Testicle ($\frac{1}{4}$ grain) produced slight contraction of the virgin uterus.

Of the above-named agents—infundibulin, brain, mammary gland, spleen, parathyroid, prostate, pancreas, and iodothylin have the most marked activity upon the contractions of the uterus.

When we compare these experiments with those obtained upon the excised uterus we find about the same results.

Bell and others have used the infundibular extract in postpartum hemorrhage. It stopped the bleeding in about three to four minutes. It has also been used in placenta previa with excellent results.

The contractions of the human uterus by it are more prolonged than those produced by any other preparation, not excluding the extremely active preparation of ergot. In two cases of Cesarean section after a single injection the uterus contracted like a bleached ball and subsequently relaxed only to a moderate degree. The preparation used was a 20 per cent. extract of which 1 c.c. given intramuscularly was the dose. It can be repeated in an hour.

Reprin'ed from Medical Bulletin, February, 1910.

WHICH PREPARATION OF THE PITUITARY IS THE BEST TO USE IN TETANY?

BY ISAAC OTT, M.D., and JOHN C. SCOTT, M.D.

The removal of the pituitary in part causes even in man an enlargement of the thyroid. Extirpation of the thyroid causes an increase in the size of the pituitary. In a paper (*New York Medical Journal*, Dec. 10, 1908) we have shown in feline tetany that the pituitary gland given in distilled water subcutaneously had an effect at least equal to the calcium salts in alleviating the tetany after complete parathyroidectomy. As calcium has failed in several instances to cure tetany in man it is necessary to seek other agents to combat the disease.

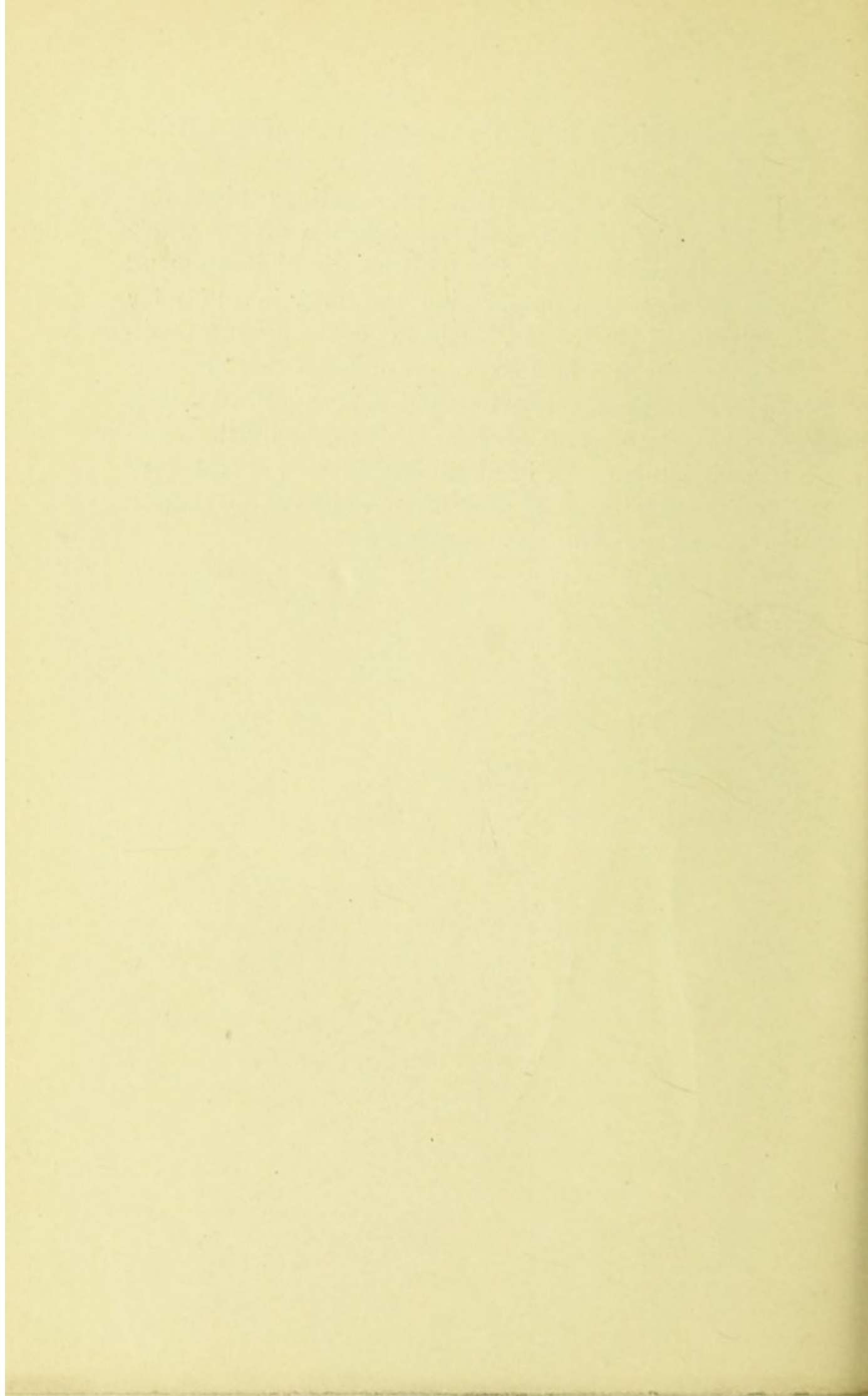
Prof. Pal, of Vienna, reports (*Wiener Klinische Wochenschrift*, July 8, 1909, No 27, p. 983) a case of severe tetany in a boy. He gave pituitrin and the tetany disappeared in 24 hours, while the other symptoms retrograded. We have made experiments with pituitrin in feline tetany and find it has some effect which is, however, quite fugitive. We then tried the infundibular extract (of Burroughs, Wellcome & Co., 20%). It had a much more prolonged action than pituitrin, even when we gave the latter in ounce doses subcutaneously.



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But neither pituitrin nor infundibular extract had the continued power that the whole gland exerts. We used all these preparations subcutaneously. As the boiled filtered infusion of the whole gland cannot be readily used we would recommend as the next best preparation the 20% infundibular extract of Burroughs, Wellcome & Co. by intramuscular injection in doses of seven drops three times a day. It should not be used subcutaneously as it might cause some necrosis of the skin by the vasoconstriction. As infundibular extract is not very poisonous, it can be used oftener than three times a day if the conditions necessitate it.



Reprinted from The Alienist and Neurologist, May, 1910.

GLYCOSURIA DUE TO SOME GLANDULAR EXTRACTS.

By ISAAC OTT, M.D., Professor of Physiology, Medico-
Chirurgical College, of Philadelphia,

and

JOHN C. SCOTT, M.D., Demonstrator of Physiology.

Blum was the first to show that the adrenal when given subcutaneously produced glycosuria. Borchardt¹ has proved that the hypodermic use of the pituitary produced a small amount of sugar in the urine. He used the boiled filtered infusion of the gland, which was injected hypodermically in rabbits and dogs. The quantity of sugar obtained by him varied from a trace to 4.2 per cent. The absolute quantity of sugar was very small, not more than a centigram. The sugar usually began to appear in the urine three hours after the injection. The amount of sugar excreted was extraordinarily variable and to a great degree independent of the amount of the gland injected. He found that pituitary produced glycosuria more easily in rabbits than in dogs.

¹ Zeitschrift für Klinische Medizin, 1908, Band 66, page 332.

INFUNDIBULIN.

We have also studied the effect of injections of infundibulin, pancreas and parathyroids in rabbits and cats. The number of our experiments was thirty-five. The tests for glucose were Fehling's, fermentation and the phenyl hydrazine tests. The injection of these extracts of the glands proceeds on the theory that they act like a hypersecretion of the gland. The first extract used was infundibulin twenty per cent. extract of the pituitary (Burroughs Wellcome & Co.) Borchardt used the whole gland to produce sugar. Falta was unable to obtain in rabbits any glycosuria with pituitrin, which is obtained from the infundibular part of the pituitary.

We have made several experiments with infundibulin, of which we injected 1 c.c. into the muscles of the rabbit, as Meltzer has shown that adrenalin is more rapidly absorbed here than under the skin. In all cases at the end of two and a half hours we found glucose in the urine, the amount being about one-eighth of one per cent.

In cats intra-muscular and intra-peritoneal injection of the infundibulin produced similar results. In akromegaly Hinsdale found in an analysis of 130 cases that 10.8 per cent. had sugar. Borchardt from an analysis of 176 cases of akromegaly holds that glycosuria is more regularly associated with this disease than with any other.

However, there are cases of tumor of the hypophysis without akromegaly and which are not complicated with diabetes. Kollaritz has collected 51 cases of this nature. From our experiments we must infer that the glycosuria is due to a hypersecretion of the infundibular part of the hypophysis, perhaps of the pars intermedia.

DRIED PANCREAS.

Pariset² injected pancreatic juice into the portal vein of dogs, using 20 c.c. of the juice. He made analyses of the amount of sugar in the portal vein and hepatic vein before and after the injection. He found after the injection of the pancreatic juice that sometimes the amount of sugar in the hepatic vein was doubled. Pariset³ proved that it was not due to the alkalinity of the pancreatic juice. He also boiled the juice and injected it into the portal vein; then analysis of the blood in the hepatic vein showed that the increase of glucose was very small. He also injected into the portal vein a very active diastase, the vegetable amylase of the extract of malt. Then he obtained a considerable increased amount of sugar in the hepatic vein. From these data Pariset infers that the hydrolysis of the glycogen in the liver by the pancreatic juice is due to an amylolytic ferment which it contains.

² Comptes Rendus de la Société de Biologie, 1904, page 720.

³ C. R. de la Société de Biologie, 1905, page 268.

Pariset⁴ injected secretin into the portal vein; it increased the biliary secretion, but did not augment the glucose in the blood.

We tried not the juice but the dried powdered pancreas subcutaneously. It was rubbed up with distilled water and used upon rabbits and cats. In a few hours the urine was withdrawn and one-eighth of one per cent. of sugar was found to be present. The amount of pancreas injected was about 15 grains.

The question now arises, Was it due to the ferment amylopsin or to choline? When we boiled the pancreatic infusion and then injected it we obtained no sugar in the rabbit. These experiments would lend support to the theory of Pariset that it is amylopsin in the pancreas which produces the sugar after injection of powdered pancreas. It might be choline.

Gautrelet⁵ found by the reaction of Florence (the reagent of Florence is made of two parts of iodine, six parts of iodide of potassium and 100 parts of water) the presence of choline in the pancreas, thyroid, kidney, ovary and liver. But it was especially in the pancreas and kidney that crystals of iodo-choline were the largest and most abundant. When Gautrelet removed the choline from the pancreatic extract as a chloroplatinate and injected the extract then adrenalin

⁴ C. R. Société de Biologie, 1906, page 66.

⁵ C. R. Société de Biologie, 1908, page 174.

injected into the rabbit produced sugar. When the pancreatic extract did have choline in it, then the pancreatic extract injected prevented the glycosuria by adrenalin. Gautrelet⁶ found when a rabbit had a half a milligram of adrenalin subcutaneously that it caused sugar to appear in the urine at the end of two hours. If he mixed 0.20 gram of choline with the half milligram of adrenalin and then injected both subcutaneously then no sugar was found in the urine at the end of 3½ to 7 hours. Blanchetrière and Chevalier⁷ have shown that the presence of fatty acid is a cause of error in the reaction of Florence used by Gautrelet. They found no choline in the pancreas and only traces of it in thyroid.

Gliken⁸ states that neurin, betain, muscarin and the purin bases give the same reaction to the reagent of Florence as choline does. Parisot⁹ also concludes that choline is not the principal cause of the fall of tension in the blood vessels by injection of the grandular extracts into the vein.

W. Webster¹⁰ has shown that it may even be doubted whether any of the micro-chemical tests at present in use are specific for choline. The choline theory from nerve degeneration is not seriously considered by several chemists. Frank

⁶ C. R. Société de Biologie, 1908, page 173.

⁷ C. R. Société de Biologie, 1909, page 249.

⁸ Oppenheim, Biochemie, Part I, page 154.

⁹ C. R. Société de Biologie, 1909, page 753.

¹⁰ Bio-Chemical Journal, 1909, page 117.

and Isaac¹¹ have made various kinds of experiments with choline both in dogs and rabbits. They found it had no influence on the hyperglycaemia and the glycosuria of adrenalin.

We tried the subcutaneous use of $\frac{1}{8}$ of a grain of choline in rabbits but it produced no sugar in the urine.

Hence, as the presence of choline in the pancreas is doubtful, and as Gautrelet has shown, choline prevents adrenalin glycosuria, or according to Frank and Isaac had no influence on the glycosuria of adrenalin, and our experiments show it does not produce glycosuria, we must infer that dried pancreas does not produce glycosuria by any possible choline in it. As to the actual body which does produce it, we are unable to state what it is.

PARATHYROIDS.

We found that 10 to 15 grains of powdered parathyroid rubbed up with distilled water and subcutaneously injected into rabbits produced in $2\frac{1}{2}$ hours glycosuria. When it was injected intraperitoneally in cats the same result ensued. The percentage of sugar obtained in the rabbit was about one-eighth of one per cent.

SEAT OF THE GLYCOSURIA.

(1) *Removal of Thyroid.* In etherized cats we

¹¹ Wiener Klinische Wochenschrift, 1909, No. 27, page 988.

extirpated the thyroid, leaving two or more parathyroids. On the following day we found sugar in the urine in a few cases. A similar result after the removal of the thyroid has been found in dogs by Falkenberg and Rahel Hirsch¹². Falta, however, did not obtain it in dogs. We found, however, that the injections per jugular of the same dose of infundibulin, or of pancreas or of parathyroid in the cat after the absence of the thyroid was followed by a decrease in the amount of sugar as compared with those animals whose thyroid was intact. Before the removal of the thyroid these agents caused 3 to 4 per cent. of sugar in the urine; after the removal, 1 to 2 per cent. The pancreas and parathyroid in the jugular injections were rubbed up with distilled water and filtered through cotton. We took care that the binding down and etherization did not produce glycosuria.

(2) *Removal of Adrenals.* In the etherized cat we removed the adrenals with the most careful antiseptic precautions. As they usually died on the following day, we injected immediately on the same day the infundibulin, pancreas and parathyroid. They were given by the jugular. The pancreas and parathyroid were rubbed up with distilled water and filtered through cotton. In all cases sugar appeared in the urine. However,

¹² Zeitschrift für Klinische Medicin, 1908, page 6.

Nishi has shown that removal of adrenals is followed by hyperglycaemia.

(3) *Splanchnicotomy*. In cutting both splanchnics in the cat we followed the procedure of Schultze¹³. The animals were etherized and the strictest antiseptic precautions followed. The abdomen was closed by suture and the animals placed in the cage until the next day. Then they were again etherized, jugular prepared and infundibulin and the watery infusion of the pancreas and parathyroid injected. But at no time afterward did we observe any sugar in the urine. Pollak¹⁴ in a classification of the glycosurias found that adrenalin produces sugar in the urine after splanchnicotomy being an agent which stimulates the terminals of a sympathetic nerve. The glycosuria of caffein does not ensue after splanchnicotomy. According to Macleod, curare does not cause any sugar in the urine after section of the splanchnics.

As section of the splanchnics arrests glycosuria we must consider it due to an action on the diabetic center in the medulla acting through the splanchnics on the glycogen of the liver. If the sympathetics influence the adrenals, who then actuate the glycogen in the liver is a question not decided by these experiments.

¹³ Archiv. für Experimentelle Pathologie und Pharmakologie, Band 43, 1897.

¹⁴ Archiv. f. ex. Path., u. Pharmakol, 1909, Band 61, p. 376.

PRELIMINARY NOTE ON THE ACTION OF SOME INTERNAL SECRETIONS UPON ERECTILE TISSUE.

By ISAAC OTT, M.D., and JOHN C. SCOTT, M.D.

To study the action upon erectile tissue we employed the penile organ of the dog. The length of it was measured by a pair of compasses, from the bulb to the tip. The width of the bulb of the organ was measured in the same way. Then the filtered infusion made with distilled water was injected into a vein and the dimension of the organ measured as before. It was found that the prostate increased the length 25 millimeters, and the width of the bulb 25 millimeters. The orchitic extracts gave an increase in length of 15 millimeters, and an increase in width of bulb of 23 millimeters. The ovarian extract gave an increase in length of 21 and an increase in width of bulb of 23 millimeters. The parathyroid extract gave an increase in length of 15 and an increase in width of bulb of 15 millimeters. The thymus extract gave an increase in length of 15 millimeters and an increase in width of bulb of 12 millimeters. Pituitary extract, as a whole, gave an increase in length of 11 millimeters and an increase in width of bulb of 6 millimeters. Infundibulin gave an increase in length of 5 millimeters and an increase in width of bulb of 6 millimeters. Pineal gland gave no increase in length but increase in width of bulb of 7 millimeters. The corpus luteum increased the length 15 millimeters and the width of the bulb 28 millimeters.

THE HISTORY OF THE UNITED STATES

OF AMERICA

FROM THE FIRST SETTLEMENTS TO THE PRESENT TIME

BY

JOHN F. JOHNSON

OF THE

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[Reprinted from *American Medicine*, March, 1911.]

ACTION OF ANIMAL EXTRACTS UPON INTESTINAL MOVEMENTS.

BY

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AND

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In 1884, one (*Medical Bulletin*) of us showed that adrenal extract enlarged the lumen of the intestine at the moment of the injection of the filtrate; when the arterial tension is mounting the intestine is relaxing. Drs. Ulman and Ott studied some of the animal extracts upon the excised intestine by the method of Magnus. Here a small piece of the intestine is attached by one end to a fixed point in warmed Ringer's solution, through which oxygen is bubbling. The other end of the intestine was attached to a heart lever which recorded the contractions. Ott (*Medical Bulletin*, 1897) first noted that a filtered watery infusion of the spleen injected into the circulation increased the frequency

and force of peristalsis. Ulman and Ott noted a similar effect by the Magnus method. We also found by the method of Magnus that a drop of the filtered infusion of the pancreas relaxed the muscle and slowed the movements of the intestine. At the same time the force of the contractions was increased. We also found in the same manner that thymus occasionally increased the force of the contraction.

In this study we used a glass cannula upon one end of which a balloon of the thinnest rubber was tied. This balloon was inserted through an opening in the small intestine of an etherized rabbit, not far from the stomach. The other end of the cannula was attached to Albrecht's piston recorder. The animal extracts used were rubbed up with distilled water, filtered through absorbent cotton and injected per jugular. The number of the experiments was twenty-five.

Iodothyrene (5 grains) increased the frequency and extent of intestinal contractions. Powdered thyroid (1 to 2 grains) also increased it.

Ovary ($\frac{1}{2}$ to 1 grain) had no effect as a rule, occasionally (1 to 2 grains) increased the peristalsis.

Infundibulin (10 gtt to 18 gtt) increased the extent of the contractions of the intestine.

Mammary gland ($\frac{1}{2}$ grain) increased the height of the waves of peristalsis.

Prostate ($\frac{1}{2}$ grain to 1 grain) increased the height of the intestinal contractions.

Thymus ($\frac{1}{4}$ to $\frac{1}{2}$ grain) augmented the frequency and extent of peristalsis.

Spleen ($\frac{1}{4}$ to $\frac{1}{2}$ grain) increased the height and frequency of the intestinal contractions.

Parathyroid ($\frac{1}{2}$ to 1 grain) increased the rate of peristalsis and the height of it.

Pancreas ($\frac{1}{4}$ grain) also augmented the extent of the contractions. One grain of cortex of the kidney had no effect.

Dried brain (1 to 2 grains) also increased the height of the contractions.

Parotid ($\frac{1}{2}$ grain) increased the extent of the intestinal contractions.

[Reprinted from *Monthly Cyclopaedia and Medical Bulletin*, July, 1911.]

THE ACTION OF ANIMAL EXTRACTS UPON THE BLADDER.

BY

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AND

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DALE¹ states that when pituitary extract is injected intravenously the bladder of the cat usually exhibits a temporary weakening, followed by a more prolonged increase of tone. Neither state is of any great extent. A guinea-pig's bladder suspended in Ringer's bath contracted feebly when pituitary extract was added. The plain muscular coats of the intestine and the bladder contract, then, like other plain muscle in response to pituitary extract, but their sensitiveness thereto is small in comparison with that of some other organs.

¹ Bio-Chemical Journal, 1909, p. 438.

Von Frankl-Hochwart and Fröhlich found that pituitary caused strong contraction of the bladder, and that it increased the irritability of the pelvic nerves. The nervous supply of the bladder is, 1, by the pelvic nerves; 2, by branches from the hypogastric; 3, by intrinsic ganglia mainly situated in the trigonum.

Roth has shown that when the spinal nerves are injured the sympathetic ganglia in the pelvis take care of the bladder. When the pelvic and hypogastric nerves are cut, it has been shown by Kehrer that the reflexes between the bladder and uterus are carried on by an independent nervous system, the ganglia of the bladder.

Our experiments were made upon cats. Their number was 45. The animals were etherized, an incision made in the median line, the bladder exposed, a right-angled cannula inserted into the neck of the bladder, and a ligature applied a little distance from the neck of the vesical reservoir. The other end of the cannula was attached to a water manometer. The bladder, previously filled with warm Ringer's solution, was returned to the abdominal cavity, and the abdomen closed except where the rubber tubing projected. The rhythmic contractions of the bladder were recorded. We first tried a 20 per cent. solution of infundibulin from the posterior part of the pituitary body. It was injected by the jugular vein. We found it to produce weak contractions of the bladder. If,

however, in cats we divided the nervi pelvici a day or two in advance of the experiment we found infundibulin to produce much stronger contractions. According to Langley, the nervi pelvici in the cat contain motor and inhibitory fibers; hence, the weak action following the immediate division of the pelvic nerves may be due to an excitation of the vesical inhibitory nerves, which would prevent a marked action by the infundibulin. This view may explain the marked action of infundibulin on the bladder when the nervi pelvici are cut forty-eight hours previously. We have repeated the experiments of von Frankl-Hochwart and Fröhlich and can confirm their statement that infundibulin raises the irritability of the nervi pelvici. While one of us (Ott) has expressed the view in a brochure² that infundibulin acted mainly on the vesicospinal center and only slightly on the unstriated muscle of the bladder, we now wish to state that we believe from further experimentation on bladders whose nervi pelvici have been cut for a day or two that it acts mainly and strongly on vesical unstriated muscle and has a weak action on the vesico-spinal center and the nervi pelvici.

The other animal extracts were prepared by rubbing them up with water and filtering them through absorbent cotton. The filtrate was injected through the jugular vein.

² Internal Secretions, 1909, E. D. Vogel, publisher, Easton, Pa.

Thyroid extract produced strong contractions of the bladder, with the pelvic nerves intact.

Prostate ($\frac{1}{4}$ to 1 grain) increased the contractions of the bladder and also augmented their frequency.

Parathyroid ($\frac{1}{2}$ grain) increased the tonus and height of contractions of the bladder.

Adrenalin relaxed the bladder.

Mammary gland ($\frac{1}{2}$ to 1 grain) had no action upon the bladder.

Pancreas (1 to 2 grains) produced strong contractions of the bladder; in one case it caused a tetanic contraction four days after section of the nervi pelvici.

Ovary ($\frac{1}{2}$ grain) increased the contractions of the bladder to a slight extent.

Orchitic extract increased the contractions.

Parotid (1 grain) considerably increased the extent and frequency of the contractions.

Thymus ($\frac{1}{2}$ grain) increased the extent of the contractions.

Brain extract increased the extent of the contractions.

[Reprinted from MONTHLY CYCLOPEDIA AND MEDICAL BULLETIN,
p. 207, April, 1912.]

THE ACTION OF CORPUS LUTEUM AND OF THE PINEAL BODY.

By ISAAC OTT, M.D., Professor of Physiology, Medico-
Chirurgical College, of Philadelphia,
and
JOHN C. SCOTT, M.D., Demonstrator of Physiology.

A. CORPUS LUTEUM.

Busquet,¹ in April, 1910, found that intravascular injections of extracts of the corpus luteum in the dog caused a considerable fall of blood-pressure, an acceleration of the heart, and a want of excitability in the vagus.

Villemin,² in May of the same year, similarly found that intravenous injection of extracts of the corpora lutea in the dog produced a general lowering of blood-pressure, acceleration of the heart rate, and loss of excitability of the vagus.

A. Weymeersch³ states that extirpation of the corpora lutea is followed by a vasoconstriction of the uterine vessels. He holds the corpora lutea to be vasodilators.

N. Beloff⁴ found the corpus luteum to lower arterial tension and slow the pulse.

¹ C.-r. de la Société de Biologie, lxxviii, 18, p. 874.

² Zentralblatt f. Physiologie, xxiv, 13, p. 585, 1910.

³ Zentralblatt f. Physiologie, xxv, 18, p. 831, 1911.

⁴ Journal de physiologie et de pathologie, xiii, 2, p. 292.

Champy and Gley⁵ found the corpus luteum to be highly toxic, but it is absolutely necessary that it should be very fresh and prepared very rapidly. They found that the extract of corpus luteum injected into the vein of the rabbit, in a dose not immediately lethal, immunizes the animal rapidly in five minutes, so that a second injection can be made ten times as large as the toxic dose. They call this rapid immunity "tachyphylaxia."

Champy and Gley⁶ found that the extracts of the corpora lutea of menstruation in the cow have but little activity on the circulation. The commercial extracts prepared by desiccation *in vacuo* at a low temperature do not have any effect on the circulation. The extracts of the corpora lutea of the pregnant cow, however, are very active even when prepared by desiccation *in vacuo* at a low temperature, and preserve their activity. The extracts of the corpora lutea of pregnant sheep are equally active. Those of the mare are less active. The extracts of the corpora lutea of the sow are most active. The corpora lutea lower the blood-pressure, and slow and weaken the heart in dogs. There is a difference in activity between the corpora lutea of menstruation and the corpora lutea of pregnancy.

We used the dried powdered corpus luteum of the cow rubbed up with water and filtered through cotton. Our experiments on the circulation were performed exclusively on cats, which, as is well known, have a circulatory apparatus unusually responsive to pharmacologic agents.

⁵ C.-r. de la Société de Biologie, lxxi, 26, p. 159.

⁶ C.-r. de la Société de Biologie, lxxi, 32, p. 442.

The *pulse rate* was practically unchanged. The initial action was to depress the *blood-pressure* (20 to 40 mm. of mercury), which then immediately rose above normal for a short time.

Urinary Secretion.—Corpus luteum was found to have no perceptible action upon diuresis. However, it caused the appearance of 0.5 per cent. of glucose in the urine of the rabbit, as shown by the fermentation test.

Uterine Contractions.—Corpus luteum increased the contractions in an unimpregnated uterus. In the pregnant uterus it increased the contractions. A uterine strip of the rabbit *in situ* was used, being kept in a bath of warm Ringer's solution of the temperature of the body and attached to a lever.

Intestinal Contractions.—A portion of an etherized rabbit's intestine was excised and suspended in Ringer's solution, through which oxygen was kept bubbling. It was attached to a lever. Corpus luteum, when added to the solution, increased the height of the contractions to a marked degree.

B. PINEAL BODY.

Exner and Boese⁷ extirpated the pineal body in rabbits, but no results ensued after the first twenty-four hours.

Von Cyon⁸ found that the intravenous injection of small doses of extracts of the pineal gland had no action upon blood-pressure. The rate of the heart was accelerated. Larger doses were found to increase the strength of the heart beat,

⁷ Deutsche Zeitschrift f. Chirurgie, cvii, 143, p. 182, 1910.

⁸ "Die Gefäßdrüsen," p. 226.

slow it, and induce irregularity. There was a *pulsus trigeminus*, due to irritation of the central end of the vagus.

Ott and Scott showed that pineal extract and corpus luteum cause vasodilation in the male genitalia.

Eyster and Jordan⁹ found that an aqueous extract of the pineal body of the sheep on intravenous injection in various animals caused a fall of the mean arterial blood-pressure. This fall was accompanied by vasodilation in the intestine. On the excised heart the pineal had no important effect, and, as it did not change the pulse, they think the fall of pressure is due to the dilation of the intestinal arterioles. They also observed transitory diuresis.

Our experiments were made upon cats, with the dried powder rubbed up with distilled water and filtered through cotton. Pineal body did not affect the *pulse rate* to any extent. The *arterial tension* fell below normal, then rose above normal, and remained there for some time.

Urinary Secretion.—Eyster has shown that the pineal body produces a transitory diuresis. We have found in the cat, with the renal oncometer and a registering apparatus, that during this diuresis there is an increase in volume of the kidney due to vasodilation.

Intestinal Contractions.—An excised piece of intestine of an etherized rabbit was used according to the Magnus method. Pineal body increased the height of the intestinal contractions to a slight extent.

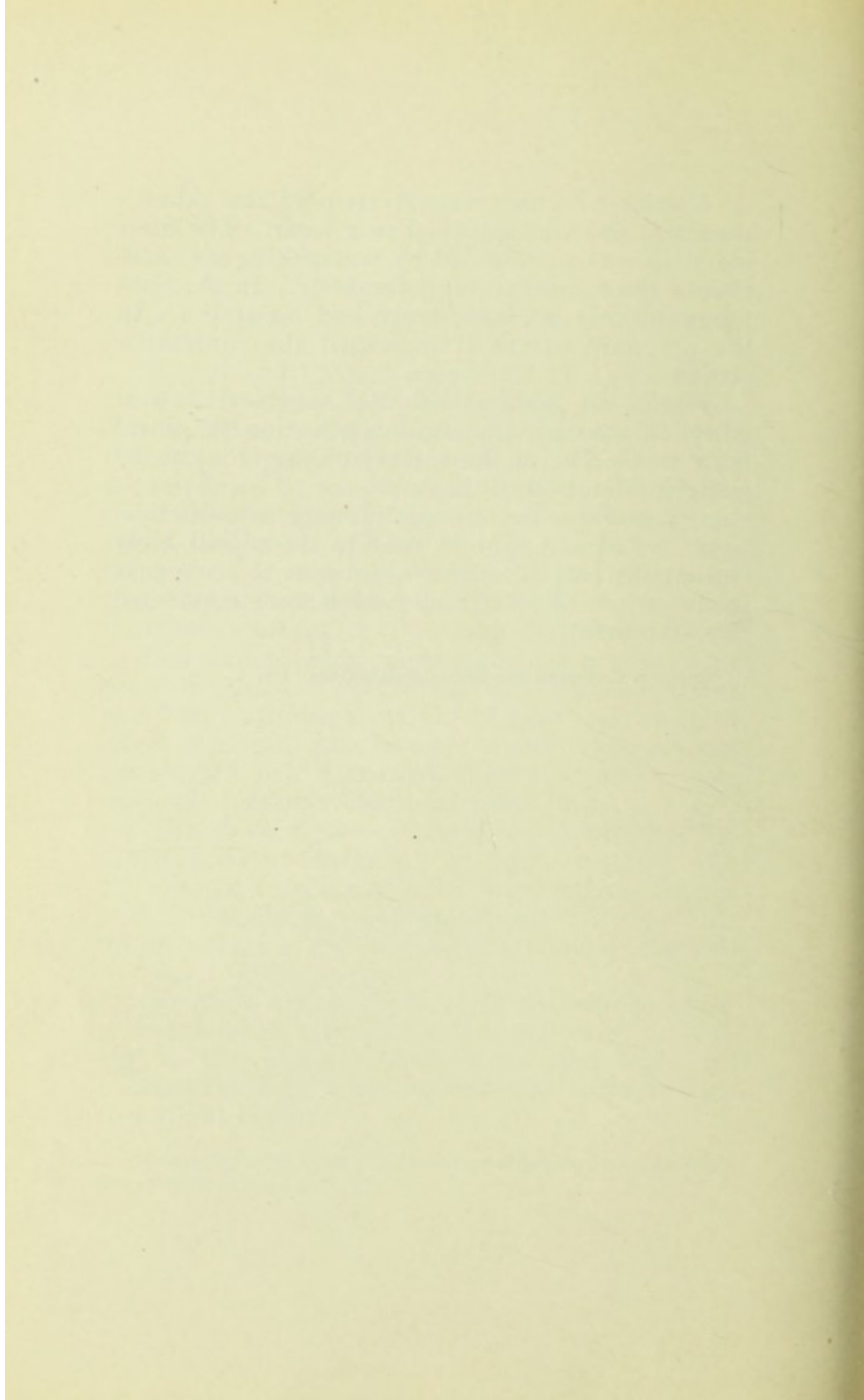
⁹ Proceedings of the American Physiological Society, xxiii; American Journal of Physiology, xxvii, 4.

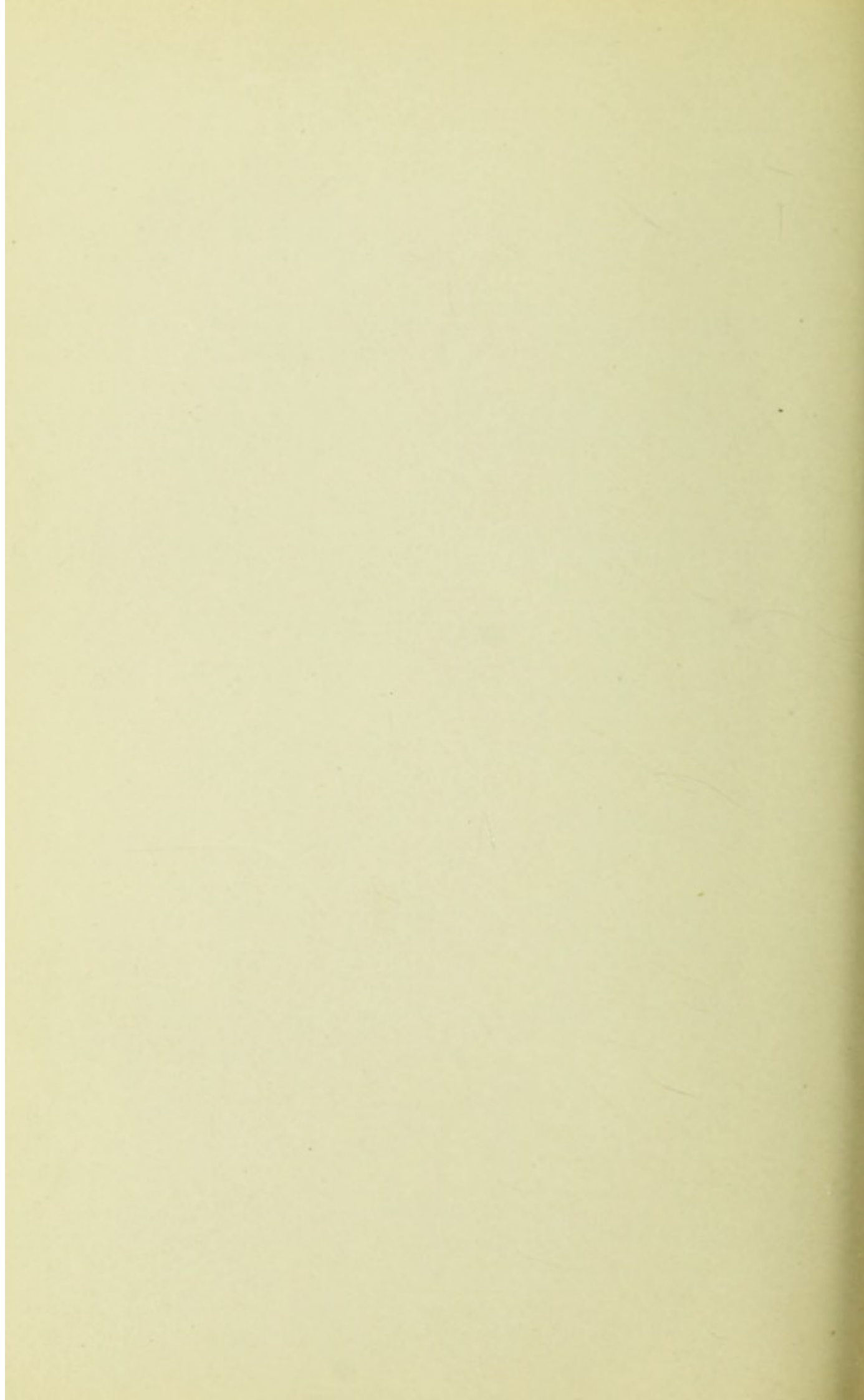
Uterine Contractions.—A strip of the rabbit's uterus *in situ* was attached to a lever. The uterine strip was surrounded by warm Ringer's solution of the temperature of the body. In the non-pregnant uterus pineal body had no action. In the pregnant uterus it increased the contractile power.

Pupil.—In rabbits with the superior cervical ganglion excised, the local application of pineal body to the eye of the corresponding side caused a slight dilatation of the pupil.

Glycosuria.—In our preliminary communication¹⁰ we stated that in rabbits the pineal body caused one-half of 1 per cent. of glucose to appear in the urine. Eyster and Jordan have confirmed this statement.

¹⁰ Monthly Cyclopedia and Medical Bulletin, Sept. 1911.





[Reprinted from *Monthly Cyclopaedia and Medical Bulletin*, September, 1911.]

THE SPLEEN AND CHRONIC CONSTIPATION, AND A PRELIMINARY NOTE ON THE PINEAL GLAND AND THE CORPUS LUTEUM.

BY

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AND

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The Spleen and Chronic Constipation.—In the *Medical Bulletin*, 1897, one of us (Ott) stated that the spleen, of all the animal extracts, has the most marked effect on peristalsis. It produces the largest peristaltic waves. When the spleen was removed, peristalsis decreased. If, now, spleen extract was injected, peristalsis was restored, to a considerable extent above normal.

In 1908, Zuelzer,¹ with others, confirmed the preceding results. He prepared an extract of the spleen for intravenous and intramuscular injection in man for the cure of chronic constipation, and reported marked success in this condition. This statement has been confirmed by Saar, Henle, Unger, and several others.

¹ Dohrn, Marxer, and Zuelzer: "Specifische Anregung der Darmperistaltik," etc. *Berliner klinische Wochenschrift*, 1908, No. 48.

We have tried the action of the Zuelzer extract of the spleen by the Magnus method. This consists in immersion of an excised segment of the intestine from an etherized animal in Ringer's solution through which oxygen is bubbling. The intestine is attached to a heart lever and the contraction registered. The spleen extract showed a marked action. In another method a balloon was inserted into the small intestine of an etherized animal and the contractions registered by Albrecht's piston recorder. This method also exhibited an increase of contractions in the intestine. They are not so marked, however, as when a watery filtered infusion of the spleen is used.

The Pineal Gland and the Corpus Luteum.—In a series of experiments we have found the pineal gland to have a marked diuretic action, as previously noted by Eyster. At the time of each injection per jugular, the volume of the kidney increases considerably, while, after a temporary fall, the pressure in the carotid shows some increase. About one-half of 1 per cent. of glucose appears in the urine after the injection of pineal extract and after the use of corpus luteum.

Corpus luteum does not markedly change the pulse-rate, but elevates the blood-pressure for some time.

The intestinal peristalsis is markedly increased by corpus luteum.

In the pregnant uterus, corpus luteum increased the contractions.

[Reprinted from *Therapeutic Gazette*, October, 1911.]

THE ACTION OF ANIMAL EXTRACTS UPON THE SECRETION OF THE MAMMARY GLAND.

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Röhrig, Strumpf, Hammerbacher, and Cornevin sought to excite the milk secretion by chemical agents, as pilocarpine.

Foges (*Centralblatt fuer Physiologie*, Bd. 19, S. 233, 1905) found that the development of the mammary gland depended upon the presence of functionally active ovaries, but that the production of milk was dependent on the abrogation of the ovary.

Knauer found that upon removal of the ovaries the mammary gland atrophied, but by subsequent transplantation remained the same.

L. Fraenkel thought that the internal secretion of the corpus luteum had a certain influence upon lactation.

Marshall thought the cause of the excitation of the milk secretion resided in the changes of the uterine mucous membrane during pregnancy.

Starling and Jane Lane Claypon (*Proceedings of the Royal Society of London*, 1909, Bd. 77) injected subcutaneously into rabbits extract of the embryo of rabbits. These injections were repeated at short intervals. They found it caused an enlargement of the mammary gland and produced a secretion of milk. Extracts from the uterine mucous membrane, ovaries, and placenta were without effect. They believed that a hormone was generated in the embryo, and through the placenta passed into the blood and then to the gland.

Karl Basch used saline extracts subcutaneously of human or homologous placenta. These extracts were repeatedly injected. By dogs, cats, rabbits, guinea-pigs, and goats he obtained a secretion of milk independent of pregnancy. Basch found, by injection of extract of the fetus of the rabbit and of the dog, in rabbits a secretion of milk. It was less in quantity than that obtained by injection of extracts of placenta (*Monatsch. f. Kinderheilk.*, 1909).

Lederer and Pribram (*Pflueger's Archiv f. Physiologie*, Band 144, Heft. 9 and 10, p. 591) made a series of experiments upon goats. They inserted a cannula into the nipple and counted the amount of milk excreted. An aspirating bottle was attached to the cannula. They injected into the vein of the goat fresh placental extracts and obtained a marked increase of the milk secre-

tion. They also state that probably ovarian extract is without effect. Surely liver extract has no action in accelerating the secretion of milk.

Foa confirmed the statement of Starling and Lane Claypon. He studied the influence of extracts of the fetus of the cow upon young rabbits, and found fresh extracts caused a marked increase of the parenchyma of the mammary gland with the formation of new acini, whilst boiled extracts were without effect.

Arthur Biedl and Koenigstein (*Zeitschrift f. Experimentelle Pathologie und Therapie*, Achter Band, Zwölftes Heft, p. 358) found that the intraperitoneal injection of fetal and placental extracts was followed by perceptible appearances in the milk gland. They also used intraperitoneal implantation of the placenta or embryo, so that the chemical messenger, the hormone, could be continuously supplied to the organism as in the natural state of affairs. The embryo and placenta were obtained by Caesarian section from rabbits in the second half of pregnancy. This method was not productive of any effect upon the mammary gland secretion.

Much safer was the histological observation of the mammary gland. The animals with placenta implanted showed no development of the mammary gland tissue. But in all animals with the embryo implanted there was more or less development of the gland. These changes, as a rule, were more marked when more extract or more implantation material was used. They found the injection method to produce greater

hypertrophy than the implantation intraperitoneally. Injections of the fetal extract cause hypertrophy of the breast in castrated females.

Biedl and Königstein state that although the placenta physiologically excites a secretion of milk, yet the true source of it is in the fetus and not in the placenta.

Ott and Scott at the meeting of the Society for Experimental Biology and Medicine, December 21, 1910, announced that the corpus luteum by the vein in the goat increased the quantity of milk fourfold in five minutes.

Ancel and Bouin (*Journal de Physiologie et de Pathologie Generale*, No. 1, Jan. 15, 1911, p. 31) have made researches upon the functions of the corpus luteum in gestation. They used rabbits. They produced a follicular rupture and the apparition of the corpus luteum in a certain number of rabbits either by coition or by rendering them more sterile for a long time by ligature of the spermatic canals. The animals were killed at different periods after the sexual act, and their mammary glands examined microscopically and macroscopically. They also examined the mammary glands in rabbits during the period before puberty and during the first period of "heat." They also used rabbits which were pregnant, and thus made a comparison between the development of the mammary gland in normal conditions and the state of the gland only under the influence of the corpus luteum. They also destroyed with the fine point of the cautery all the corpora lutea at various times after their appearance, and

found that the mammary glands did not develop or their development was arrested.

They show that the corpus luteum exercises a kinetic stimulation upon the constituent elements of the mammary gland. As to the secretory phase following this form of development, the cause is to be sought not in the corpus luteum but in one of the other factors which appear in the course of gestation.

Our experiments were made upon goats. They were bound down, not etherized, and the plan of Röhrig followed. An oiled metal cannula was inserted into the nipple and the milk aspirated into a graduated flask. A water aspirator was used. The goat was in the nursing period, and activity of secretion was maintained by means of the young nursling. The amount of milk was noted every five minutes. The animal extracts were rubbed up in a mortar with distilled water, filtered through cotton, and injected into a vein in the ear or into a vein in the leg. For three five-minute periods the amount of milk was noted. After this time the animal extracts were injected and the amount of milk again noted every five minutes. The following experiment shows the effect of infundibulin:

Experiment 1.—Goat, right nipple.

2:25	P.M.	
2:30	"	4 drops of milk.
2:35	"	5 " " "
2:40	"	5 " " "
2:41	"	5 drops of infundibulin by the vein.

2:45	"	405	drops	of	milk.
2:50	"	15	"	"	"
2:55	"	22	"	"	"
3:00	"	12	"	"	"
3:05	"	8	"	"	"
3:10	"	4	"	"	"
3:11	"	5	drops	of	infundibulin by the vein.
3:15	"	75	drops	of	milk.
3:20	"	15	"	"	"
3:25	"	15	"	"	"
3:30	"	7	"	"	"
3:35	"	6	"	"	"
3:40	"	5	"	"	"
3:45	"	4	"	"	"

Infundibulin starts the flow in about one minute from the beginning of the injection, and it reaches its height in four minutes, after which it rapidly falls to normal. When a feverish condition arose in the goat, infundibulin acted very feebly.

We also found the corpus luteum (10 grains), pineal body (5 grains), and the thymus (1 grain) increased the quantity of milk fourfold in five minutes. The ovary minus the corpus luteum had no effect. The amount of butter-fat was about the same in the augmented secretion by the thymus, corpus luteum, and infundibulin. The determinations were made with the Soxhlet apparatus. Boiled thymus had an activity upon the secretion of milk.

About fifty experiments were performed. Appended are a few of them:

Experiment 2.—Goat.

2:55	P.M.				
3:00	"	8	drops	of	milk.
3:05	"	7	"	"	"
3:10	"	7	"	"	"
3:15	"	112	"	"	"
					1 grain of thymus.

3:20	P. M.	44	drops	of	milk.
3:25	"	20	"	"	"
3:30	"	14	"	"	"
3:35	"	6	"	"	"

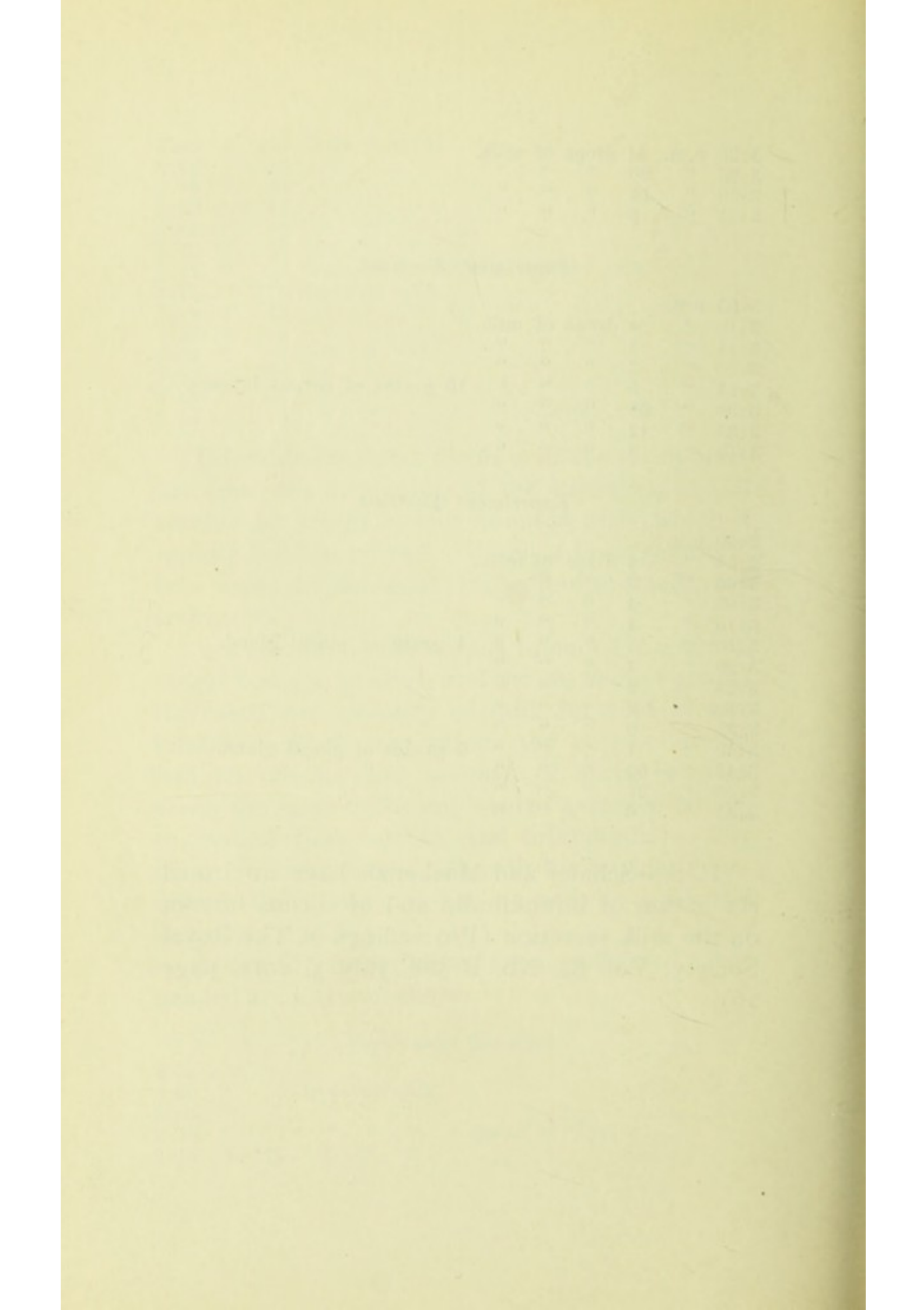
Experiment 3.—Goat.

3:05	P.M.				
3:10	"	4	drops	of	milk.
3:15	"	3	"	"	"
3:20	"	3	"	"	"
3:25	"	5	"	"	" 10 grains of corpus luteum.
3:30	"	65	"	"	"
3:35	"	12	"	"	"
3:40	"	3	"	"	"

Experiment 4.—Goat.

2:50	P.M.				
2:55	"	4	drops	of	milk.
3:00	"	3	"	"	"
3:05	"	4	"	"	"
3:10	"	4	"	"	"
3:15	"	3	"	"	" 1 grain of pineal gland.
3:20	"	3	"	"	"
3:25	"	2	"	"	"
3:30	"	2	"	"	"
3:35	"	0	"	"	"
3:40	"	1	"	"	" 5 grains of pineal gland.
3:45	"	63	"	"	"
3:50	"	27	"	"	"
3:55	"	6	"	"	"

P. S.—Schäfer and Mackenzie have confirmed the action of infundibulin and of corpus luteum on the milk secretion (Proceedings of The Royal Society, Vol. 84, No. B 568, July 3, 1911, page 16).



[Reprinted from THE THERAPEUTIC GAZETTE, p. 310, May, 1912.]

ACTION OF DIFFERENT AGENTS UPON THE SECRETION OF MILK.

By ISAAC OTT, M.D., Professor of Physiology, Medico-
Chirurgical College, of Philadelphia,
and
JOHN C. SCOTT, M.D., Demonstrator of Physiology.

Among the earlier experimentalists upon this subject was Roehrig.¹ He used goats, and an aspirator to empty the udder. He found strong muscular movements increased the milk secretion from 9 to 40 drops. Jaborandi also increased the secretion. Chloral reduced it, but after repeated doses it occasionally increased it to a considerable extent. It was given subcutaneously.

Atropine arrested the secretion. Strychnine by the vein increased the milk in a curarized goat. Digitalin and caffeine also increased the secretion. Bromide of potash reduced it. He also irritated several of the nerves going to the mammary gland in the goat, and thought that specific secretory nerves were improbable.

Bouchacourt² found that the placenta of the sheep when fed to women increased the milk secretion.

Lederer and Prizbram³ found that injections

¹ Virchow's Archiv, Band 67, S. 119.

² Société de Biologie, Feb. 1, 1902.

³ Pflüger's Archiv of Physiologie, Band 144, Heft 940, S. 591.

of extracts of the fresh placenta of the goat into the vein of a goat called out in three to ten minutes an increased milk secretion, which disappeared in a half to two minutes. Heating placenta at 60° to 65° C. from half an hour to an hour destroys its milk-producing activity. We used the placenta of woman, which immediately after delivery was placed in a sterile jar and chloroform added to it. It was then dried carefully at air temperature. Some of the powder was rubbed up with distilled water, filtered through cotton, and injected into the vein of the goat. It increased the secretion. Basch⁴ injected extracts of the placenta into adult animals who at one time had lactated and produced milk. He also injected these extracts into children in whom the milk secretion had ceased, but the placenta renewed it. He concludes that the so-called "witches' milk" is due to a passage into the fetus of a hormone circulating in the blood of the mother.

Aschner and Grigoriu⁵ experimented upon guinea-pigs. They used the placenta subcutaneously for several periods. The injection was not in the vicinity of the mammae. In animals who had been mothers they found in three to four days' colostrum and at the end of the week considerable milk. Heating the watery extract of the placenta or the placenta itself for ten minutes did not prevent the galactagogue action of the placenta. In virginal guinea-pigs the daily subcutaneous injection of placenta called out a marked secretion of milk. They also found

⁴ Münchener med. Wochenschrift, 1911, lviii, p. 2266.

⁵ Archiv f. Gynäkologie, Band 94, Heft 3, S. 766, 1911.

fetal extract subcutaneously called out a milk secretion. Pilocarpine had no effect in animals who had been mothers but were free of milk. They also found watery extracts of fresh ovaries minus the corpus luteum by subcutaneous injection produced a marked milk secretion. With corpus luteum they obtained no actual secretion of milk. They also found in milk-free animals, but who had undergone lactation, that every lymphagogue when given subcutaneously called out a marked secretion of milk.

Schaefer and Mackenzie⁶ found that boiled infundibulin and boiled corpus luteum increased the secretion of milk and that the anterior part of the pituitary had no effect. They obtained no effect from pilocarpine, eserine, or nicotine. Infundibulin elevated the blood-pressure, whilst corpus luteum generally caused a fall of arterial tension.

Dr. Mackenzie has found extracts of both the involuting mucous membrane and extracts of the mammary gland itself to have a marked galactagogue action. He also found that atropine did not interfere with the action of any of the above internal secretions which acted as galactagogues.

Our experiments were fifty in number, and were made on lactating goats. The same plan in experimentation was followed as described in a previous paper.⁷ We made experiments with boiled thymus and boiled pineal body. We found both increased the secretion of milk. We also found that boiling the mammary gland did not prevent its galactagogue action, which has been

⁶ Proceedings of the Royal Society, Series B 568, vol. 84, p. 16.

⁷ Therapeutic Gazette, October, 1911.

shown by Mackenzie to increase the flow of milk. We then tried the effect of a dose of atropine, $1/50$ of a grain by the vein, before the injection of the corpus luteum, infundibulin, and pineal gland, but they still increased the milk secretion, although not to as great an extent as before the atropinization. We have previously shown that the injection of the second dose of infundibulin is not followed by as great a secretion of milk. In the lactating goat we tried several successive injections by the vein of $1/2$ Cc. of infundibulin. The normal milk secretion was 4 drops every five minutes. The first increase was 101 drops, the second 32 drops, the third 12 drops, the fourth 20 drops, the fifth 10 drops, and the sixth 7 drops.

The mammary gland is very sensitive to infundibulin; even $1/1000$ of a drop increased the milk secretion a drop, whilst $1/100$ of a drop increased it 5 drops.

We found pilocarpine, $1/20$ grain by the vein, to increase the milk secretion to a marked degree. If, however, $1/50$ grain of atropine was given just previous to the injection, then the pilocarpine was without effect. If we waited forty-eight hours after the venous dose of atropine ($1/50$ gr.) and then injected $1/3$ grain of pilocarpine intravenously, then the flow of milk increased to a small extent. Digitalin increased the secretion of milk. Caffeine citrate, eserine, nicotine, and muscarine had no effect in augmenting the milk secretion.

Atropine arrested the milk secretion. Antipyrin reduced the flow one-half. We also studied the effect of proto-albumose and deuterio-albumose. They caused a considerable increase in

the secretion of milk. Peptone increased the secretion, but not so much as the albumoses. Glucose (gr. xx) caused a marked increase. Sodium chloride increased it to a marked degree. Potassium chloride also increased it, whilst calcium chloride only slightly augmented it.

The question now arises, how do these agents increase the secretion of milk? Is it nervous, vascular, or cellular, or a combination of all of them? Goltz and Ewald⁸ after previous extirpation of the lumbar cord in dogs found milk to be secreted after pregnancy. Starling and Jane Lane-Claypon from experiments found a hormone which they believed to be generated in the embryo, and through the placenta passed into the blood and then to the mammary gland. The Blazek twins had a common circulation, but independent nervous systems, yet pregnancy and delivery in one was followed by lactation in the glands of both. Mackenzie found that atropine, which paralyzes secretory nerves, did not prevent the galactagogue action of infundibulin and corpus luteum. We have found the same to be true for thymus and the pineal gland.

Mironoff,⁹ in 1895, a Russian physiologist, in a primiparous goat resected to the length of two centimeters all the nerves of the mammary gland a month and a half before the time of delivery. When this arrived the mammary glands nevertheless enlarged as in a normal animal and secreted in the usual manner. He repeated the experiment with a similar result. In experiments

⁸ Pflüger's Archiv, Band 63, S. 385, 1896.

⁹ Gley's Physiologie, p. 722.

upon goats¹⁰ on the external spermatic nerve, independently of the branches whose excitation caused erection of the nipple, there were two other branches whose irritation caused at the same time a secretion and a change in the circulation. In another experiment upon a bitch the excitation of the peripheral end of the mammary nerve resulting from the union of the fourth and fifth lumbar pair lowered blood-pressure in the mammary artery and gave out an abundant jet of milk when the nipple was compressed. Compression of the nipple of the other breasts was followed by only a few drops of milk. It would seem that this nerve was both dilator and secretory. But Eckhard and Von de Sinety after cutting the external spermatic nerve found no influence of any account upon the quantity and composition of the milk.

Roehrig, by electric and all possible chemical irritation of the nerves going to the milk ducts, could not find any secretory nerves. It is probable that the positive results in the goat and bitch, which have been just described as evidence of secretory nerves, are vasodilator effects. The flow of milk by suction and its continuance in man can also be due to reflex vasodilator effects.

Schaefer thought he saw a greater vascularity than normal in the mammary glands when laid open, after the use of infundibulin. There is no doubt that the hormones of the internal secretions cause increased lactation, and that there is probably a vasodilation in the gland itself which plays the major part in the augmented secretion, aided by a stimulation of the gland cells, rather

¹⁰ Gley's *Physiologie*, p. 722.

in a direct manner than through any secretory nerves acting upon the cells. Ott and Scott have shown that corpus luteum, thymus, pineal body, and infundibulin are vasodilators in the male genitalia, hence it is probable that they are vasodilators in the mammary gland. Infundibulin is a vasodilator for the kidney; pineal body also dilates the renal vessels.

Transplanted glands can secrete milk, and certainly no nervous agent is concerned in this case.

Appended are some of the experiments.

Experiment 1.—Lactating Goat.

P. M.	Gtt.
3.00	12 in 5 minutes.
3.05	10
3.10	11
3.15	53 Two grains of mammary gland by the vein.
3.20	40
3.25	15
3.30	10

Experiment 2.—Lactating Goat.

P. M.	Gtt.
2.40	11 in 5 minutes.
2.45	12
2.50	11
2.55	59 1-20 grain of pilocarpine.
3.00	16 Profuse salivation.
3.05	10

Experiment 3.—Lactating Goat.

P. M.	Gtt.
2.45	9 in 5 minutes.
2.50	8
2.55	8
3.00	5 1 grain antipyrin by vein.
3.05	2
3.10	0
3.15	3

3.20	1 1 grain antipyrin.
3.25	2
3.30	0

Experiment 4.—Lactating Goat.

P. M.	Gtt.
3.05	4
3.10	4
3.15	3
3.20	17 4 grains of deutero-albumose.
3.25	12
3.30	6
3.35	4

Experiment 5.—Lactating Goat.

P. M.	Gtt.
2.45	8
2.50	9
2.55	8
3.00	20 10 grains glucose by vein.
3.05	9
3.10	5
3.15	4
3.20	4

Experiment 6.—Goat.

P. M.	Gtt.
2.55	12
3.00	8
3.05	10
3.10	8 30 grains of sodium chloride in 5 Cc. of water.
3.15	33
3.20	10
3.25	10
3.30	9

Experiment 7.—Goat.

P. M.	Gtt.
2.45	5
2.50	4
2.55	4
3.00	5

3.05	15	15 grains calcium chloride.
3.10	10	
3.15	5	

Experiment 8.—Goat.

P. M.	Gtt.	
3.00	6	
3.05	5	
3.10	5	
3.15	10	10 grains of potassium chloride.
3.20	5	
3.25	4	
3.30	3	
3.35	2	

Experiment 9.—Lactating Goat.

P. M.	Gtt.	
3.50	4	
3.55	4	
4.00	4	
4.05	½	Cc. of a 20-per-cent extract of the posterior part of the pituitary gland
4.10	30	
4.15	4	
4.20	36	½ Cc. infundibulin.
4.25	10	
4.30	22	½ Cc. infundibulin.
4.35	6	
4.40	26	½ Cc. infundibulin.
4.45	16	
4.50	26	½ Cc. infundibulin.
4.55	20	
5.00	18	½ Cc. infundibulin.
5.05	25	
5.10	16	
5.15	10	

Experiment 10.—Lactating Goat.

Infundibulin is a 20-per-cent extract of posterior part of the pituitary.

P. M.	Gtt. every five minutes.
2.55	4
3.00	4
3.05	4

3.10	5	1/1000	of a drop of infundibulin.				
3.15	3	1/1000	" " " "	"	"	"	"
3.20	1	1/500	" " " "	"	"	"	"
3.25	1	1/100	" " " "	"	"	"	"
3.30	6						
3.35	1						
3.40	5	1/100	" " " "	"	"	"	"
3.45	3						
3.50	3						
3.55	2						

ORIGINAL COMMUNICATIONS.

[Reprinted from THERAPEUTIC GAZETTE, p. 761, November, 1912.]

THE ACTION OF THE INTERNAL SECRECTIONS UPON THE MILK SECRETION.

By ISAAC OTT, M.D., Professor of Physiology, and JOHN C. SCOTT,
Lecturer upon Experimental Physiology, Medico-Chirurgical
College of Philadelphia.

We¹ found that the hormones exciting the secretion of milk were those from the posterior part of the pituitary, the pineal gland, the thymus, and the corpus luteum. These experiments were confirmed by Schaefer and Mackenzie² except in the case of the thymus. They used the cat. We used the goat.

On the lactating cat we obtained no results with thymus. On the goat we then tried three different specimens of thymus, one of which was ten years old and kept in an unopened box. Every specimen produced a great increase in the secretion of milk. It is evident the cat is not so suitable for this work as the goat. Ancel and Bouin³ discovered what they call a myometrial gland in the uterus of the pregnant rabbit. It exists only during the second half of gestation. In the rabbit they hold that in the course of gestation the mammary gland goes through two phases: first, a rapid development of the gland during the first half of pregnancy; second, the characteristic secretory phenomena. They hold that the phenomena of the mammary gland during the first half of pregnancy are conditioned by the corpus luteum. The secretory phenomena of the second

half of gestation are caused by the appearance of a gland called the myometrial and located in the uterine muscle. Mackenzie⁴ found that a saline extract of the uterus of a cat killed within a week of parturition was found to have a powerful galactagogue action. This secretory activity was absent from the uterus except after parturition and during lactation. These experiments might be construed as confirmatory of a myometrial gland.

That substances inhibitory of lactation exist in the blood was rendered probable by an experiment of D'Errico's.⁵ He injected into lactating bitches the defibrinated blood of pregnant bitches and found that the secretion of milk was considerably diminished. Lombroso and Bolaffio⁶ by a parabiotic procedure sutured rats together in pairs so that a vascular anastomosis was established between them. They joined a virgin female rat with one in an early stage of pregnancy, but no change took place in the mammary glands of the former as pregnancy advanced in the latter.

Morpurgo⁷ performed a similar experiment and obtained the same result.

In the case of the Blazek twins of Prague, united by a common sacrum with a common circulation, but with separate nervous systems, the pregnancy of one was followed by enlargement of the breasts and a secretion of milk in both.

In our experiments we followed the plan used by Mackenzie to test the inhibitory action of the animal extracts upon the secretion of milk. He injected a solution of the pituitary body, noted the quantity of milk, then rested thirty minutes,

when the solution of the pituitary was again injected and the quantity was found to be the same. Then he tried the same experiment, but injected a small dose of another animal extract just before the second injection of the pituitary solution by the vein. He then waited another half-hour and injected the third dose of the hypophysis. If the first and third doses produced a marked effect and the second much less, it is inferable that the animal extract is inhibitory of the pituitary activity. Mackenzie in this way found that extracts of the placenta and fetus had an inhibitory action upon the milk secretion in the cat. But Miss Lane-Claypon and Starling⁸ have shown in the rabbit that the injection of a fetal extract enlarged the mammary gland in the rabbit and also produced milk. Foa⁹ and Biedl and Koenigstein¹⁰ have confirmed this fact.

It has also been shown by Ancel and Bouin¹¹ that destruction of the corpora lutea in the pregnant rabbit arrests the development of the mammary gland. Bouchacourt¹² states that women fed with sheep's placenta had an increased secretion of milk. Basch¹³ found that the subcutaneous injection of the placental and fetal extracts increased the milk secretion. Basch¹³ found a placental extract produced milk in virgin animals and in children about four months old. Lederer and Pribram¹⁴ and Ott and Scott¹⁵ have found that a solution of the placenta by the vein augmented the secretion of milk in the goat. We have here discordant results, perhaps due to the different animals employed.

We studied the inhibitory agents of the secretion of milk upon the goat. We found that a so-

lution of 0.108 gramme of the ovary minus the corpus luteum rubbed up with distilled water, filtered through cotton, and injected by the vein inhibited the action of infundibulin, the pineal, thymus, and corpus luteum upon the milk secretion. If, however, orchitic extract in the same dose and prepared in the same manner like the ovary was injected, then the second dose of infundibulin was followed by a considerable increase. The orchitic extract is a synergistic agent to infundibulin. We also found the pancreas, spleen, adrenalin, and iodothyron to inhibit the secretion of milk excited by infundibulin. That this inhibitory action was not due to albumen was shown by injection just previous to the second injection of 0.108 gramme of egg-albumen, when we obtained a slight increase of secretion. With 0.018 gramme of liver and infundibulin we obtained no decrease, but a very marked increase of the secretion of milk. As several of the glands contain cholin we tried the effect of 0.00128 gramme of cholin and obtained no increase of the milk secretion.

Now as neither egg-albumen nor liver retards the action of infundibulin, we feel sure that it is not the albuminous constituents of the glandular extracts which inhibit the secretion of milk. Some of these glands contain cholin, but we have not found cholin to retard the secretion of milk. As it is neither albumen nor cholin in these extracts which inhibits the action of infundibulin, we must infer that it is the hormones in these glands which inhibit the milk secretion. Now orchitic extract is synergistic to infundibulin, and so is albumen. In this case we acidified the

orchitic extract, boiled, filtered through paper, and neutralized the solution. Then we tried its effect upon the action of infundibulin. As all the other extracts contain albumen and are not synergistic to infundibulin it would be very exceptional if it was the albumen in the orchitic extract which acted synergistically. When, however, all the albumen is removed, orchitic extract still has a synergistic action upon the galactagogue properties of infundibulin. Hence, we can divide the animal extracts as regards their action upon the milk secretion into exciting, inhibitory, and synergistic:

EXCITING	INHIBITORY.	SYNERGISTIC.
Infundibulin, the strongest. Corpus luteum. Pineal gland. Thymus. Mammary (Mackenzie).	Ovary minus corpus luteum. Spleen. Pancreas. Adrenalin. Iodothylin.	Orchitic extract.

We made thirty experiments and we have appended some of them.

Experiment 1.—Goat.

[The Cc. represent the quantity of milk in five minutes.]

P.M.			
2.00	0.11	Cc.	
2.05	4.5	"	Injection of a solution of 0.108 gramme of corpus luteum.
2.10	1.2	"	
2.30	1.8	"	
2.35	2.2	"	Injection of a solution of 0.108 gramme of ovary and a solution of 0.108 gramme of corpus luteum.
2.40	0.8	"	
3.00	0.7	"	
3.05	3	"	Injection of a solution of 0.108 gramme of corpus luteum.

			<i>Experiment 2.—Goat.</i>
P.M.			
2.35	0.8	Cc.	
2.40	11	"	Injection of 0.059 Cc. of infundibulin.
2.45	2	"	
3.09	1.1	"	Injection of a solution of 0.108 gramme of ovary and 0.059 Cc. of infundibulin.
3.45	1.2	"	Injection of 0.059 Cc. of infundibulin.

			<i>Experiment 3.—Goat.</i>
P.M.			
2.30	0.13	Cc.	
2.35	11.2	"	Injection of 0.059 Cc. of infundibulin.
2.40	1.3	"	
3.00	1	"	
3.05	5	"	Injection of a solution of 0.054 gramme of pancreas and of 0.059 Cc. of infundibulin.
3.10	0.6	"	
3.30	0.7	"	
3.35	10	"	Injection of a solution of 0.059 Cc. of infundibulin.

			<i>Experiment 4.—Goat.</i>
P.M.			
3.40	0.8	Cc.	
3.45	4.5	"	Injection of 0.059 Cc. of infundibulin.
3.50	1	"	
4.10	0.9	"	
4.15	8	"	Injection of a solution of 0.108 gramme of orchitic extract and 0.059 Cc. of infundibulin.
4.20	1	"	

			<i>Experiment 5.—Goat.</i>
P.M.			
3.00	0.6	Cc.	
3.05	10	"	Injection of 0.059 Cc. of infundibulin.
3.10	1.6	"	
3.30	1.2	"	
3.35	4.3	"	Injection of 0.059 Cc. of a solution of adrenalin and 0.059 Cc. infundibulin.
3.40	1	"	
3.55	0.4	"	
4.00	5	"	Injection of 0.059 Cc. of a solution of infundibulin.

P.M. *Experiment 6.—Goat.*

3.05	0.6	Cc.	
3.10	4.5	"	Injection of 0.059 Cc. of infundibulin.
3.15	1	"	
3.35	0.6	"	
3.40	2	"	Injection of a solution of 0.108 gramme of iodothyryn and 0.059 Cc. of infundibulin.
4.05	0.6	"	
4.10	4.1	"	Injection of 0.059 Cc. of infundibulin.

P.M. *Experiment 7.—Goat.*

2.00	0.5	Cc.	
2.05	11	"	Injection of 0.059 Cc. of infundibulin.
2.10	2	"	
2.30	0.8	"	
2.35	16	"	Injection of a solution of 0.108 gramme of dried liver.
2.40	2	"	

P.M. *Experiment 8.—Goat.*

1.50	0.8	Cc.	
2.05	0.8	"	Injection of a solution of 0.00128 gramme of cholin.
2.10	0.9	"	
2.20	0.6	"	
2.25	0.5	"	Injection of a solution of 0.0025 gramme of cholin.
2.30	0.7	"	
2.35	0.7	"	
2.40	0.7	"	
2.45	0.8	"	

Experiment 9.—Goat.

[Orchitic extract was acidified with acetic, boiled, filtered through paper, and was free of albumen when injected.]

P.M.			
3.00	0.5	Cc.	
3.05	8.2	"	Injection of 0.108 Cc. of infundibulin.
3.10	2	"	
3.30	0.6	"	
3.35	11.1	"	Injection of a solution of 0.108 gramme of orchitic extract and 0.108 Cc. of infundibulin.
3.40	2.1	"	

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Reprinted from THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL
THERAPEUTICS, VOL. III, No. 6, p. 625, July, 1912.

THE ACTION OF GLANDULAR EXTRACTS UPON THE AMOUNT OF EPINEPHRIN IN THE BLOOD.

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Received for publication, May 8, 1912.

Fraenkel¹ has shown that the unstriated fiber of the uterus can be used to determine an excess of epinephrin in the blood of patients with Basedow's disease and chronic nephritis. He used blood serum. He found that strips of uterine tissue reacted to epinephrin in the dilution of 1 to 20,000,000. The serum of healthy persons usually acted in a dilution of 1 to 5 and 1 to 10, in a few cases in a dilution of 1 to 20 and 1 to 40, and three times in a dilution 1 to 50, but not beyond this dilution. He found the serum in Basedow's disease was active in a dilution of 1 to 400. He estimates the quantity of epinephrin in the blood to be about 12.5 mgs.

One² of us was the first to show that the adrenal extract relaxes the tonus and inhibits the rhythmic contractions of the intestine.

¹ Archiv. für experiment. Pathol. und Pharmakol., Bd., lx, p. 394, 1909.

² Medical Bulletin, xix, p. 376, 1897.

Magnus³ in 1905, showed that suprarenin, 1 to 20,000,000, inhibits the rhythmic contractions of the intestines.

Hoskins⁴ has shown that the rhythmic contractions of the intestine of the rabbit are inhibited by epinephrin, 1 to 400,000,000. We have shown that of the ductless glands there are none which give this peculiar reaction by the intestine to epinephrin.⁵

Cannon and de la Paz⁶ have shown that the adrenals can be excited by emotional impulses, and that the excess of epinephrin in the cat can be detected by the intestinal strip of the same animal. They obtained the blood from the vena cava above the opening of the adrenal veins, by a snip in the femoral vein, through which they passed a catheter. This blood was defibrinated and tested. The normal blood showed no epinephrin reaction, but excited the contractions and tonus of the intestine.

Cannon and Hoskins⁷ have also shown that in cats asphyxia and sciatic irritation increases the amount of epinephrin in the blood. They narcotized the animals with urethane and used the intestine of the rabbit for the test with defibri-

³ Pflüger's Archiv., Bd., cviii, p. 48, 1905.

⁴ Jour. of Pharmacol. and Exper. Therapeutics, iii, no. 1, p. 93.

⁵ American Medicine, March, 1911.

⁶ Amer. Jour. of Physiol., xxviii, p. 64, April, 1911.

⁷ Amer. Jour. of Physiol., xxix, p. 274, 1911.

nated blood before and after asphyxia and sciatic irritation.

Ether, according to Elliot,⁸ causes a centrally excited loss of epinephrin in the medulla of the adrenal.

Delbet, Herrenschmidt and Beauvy,⁹ found that chloroformization causes epinephrin to diminish and to completely disappear from the medulla of the adrenal, to reappear twelve hours after the use of the chloroform. Chloroform also causes considerable changes in the cortex of the adrenals. Kehrer and Fraenkel also noted that etherization materially diminishes the activity of uterine muscle as regards epinephrin.

Hoskins¹⁰ by feeding guinea pigs with dessicated thyroid and weighing the adrenals of their offspring found them depressed in weight by 53 per cent. In thyroidectomized guinea pigs he found that the adrenals of their offspring contained an average hyperplasia of 20 per cent. Normal animals fed on 5 to 15 mgs. of dessicated thyroid had an average hypertrophy in the adrenals of about 25 per cent. He holds that these results support the theory that thyroids normally stimulate the adrenals.

⁸ Jour. of Physiol., xliii, no. 6, p. xxxii.

⁹ La Presse Médicale, no. 19, p. 200, March 6, 1912.

¹⁰ Jour. Amer. Med. Assoc., lv. no. 20, p. 1724, 1910.

TESTS FOR EPINEPHRIN IN THE BLOOD.

Our experiments were made upon cats deeply narcotized with urethane. The rabbits were also deeply narcotized with the same drug. The blood of the cat was obtained from the vena cava according to the method of Cannon, and defibrinated. Then as a rule, the filtrate of 0.1296 grams of the dry powdered extract was injected per jugular. The filter was usually absorbent cotton although a paper filter was also used. After the usual wait of three and one-quarter minutes blood was again drawn from the vena cava, and defibrinated. With the albumens we waited from three and one-quarter to 30 minutes. Then a small segment of the intestine was obtained from the narcotized rabbit, attached by a pin hook to the bottom of the tube and by a pin and thread to Porter's heart lever. Then Ringer's solution was added, and the contractions noted; then normal blood until the contractions were uniform, when the blood, after the injection of the animal extract, was added. The saline and blood were drawn from the glass tube by means of an exit tube at its bottom, and oxygen was bubbling into the glass by means of an inlet tube at the base of the glass tube. In changing from normal blood to the blood affected by the animal extract the lever rises some. We have made over eighty experiments.

Thyroid, iodothylin (fig. 1), parathyroid, thymus, infundibulin (fig. 2), pineal, pancreas, ovary and orchitic extract produced the epinephrin fall of tonus and a temporary inhibition of the rhythmic contractions. The thyroid, in causing an increase of epinephrin in the blood, supports Fraenkel's facts in Basedow's disease and also the results of Eppinger, Falta and Rudinger.

Spleen extract free of albumen was without effect.

The short duration of the epinephrin dip is partly due to the fact that all the above animal extracts except the adrenals, when injected, increase the tonus and often the extent of the rhythmic contraction and counteract in part the effect of the epinephrin.

Dr. Oswald Schwarz,¹¹ found that after the subcutaneous injection of a solution prepared from two fresh hypophyses of a horse into a rabbit the animal had paresis of the posterior extremities, then of the anterior extremities, marked dyspnoea, with evacuation of urine and feces. The animals died in twenty-four to thirty-six hours. When he made the test for the epinephrin present by the rise of the blood pressure none was found in the adrenals. He found horse's pancreas, thyroid and adrenals gave the same result. Muscle and liver were considerably

¹¹ Wien. Klin. Wochenschr., p. 984, 1909.



Fig. 1. Effect of Iodothyron per Jugular upon Amount of Epinephrin in the Blood.

N.B., normal blood; *I.B.*, iodothyron blood.

Time in four seconds.

less toxic, but there was no epinephrin in the adrenals. The injection at intervals of horse serum from one and one-half to two months in a rabbit, in order to obtain a precipitating serum, caused the epinephrin to be absent from the adrenals. He believes his experiments prove that foreign albumen is a poison, and when given in lethal doses by subcutaneous injection influences in a very intense negative way the chromaffine system.

In the case of the thyroid, pineal, thymus, pancreas, ovary, orchitic extract and parathyroid, we boiled them and their solution was filtered through paper whilst hot. Heller's nitric acid ring test showed no albumen in the filtrate. In some cases we added 0.059 cc. of dilute acetic acid with a little sodium chloride, and then boiled the extract and filtered. The first filtrate was taken and contained no albumen when tested by Heller's ring test. Infundibulin does not contain albumen.

The antithyroid serum of Moebius (Merck) when given in doses of 0.177 cc. by the jugular causes an excess of epinephrin in the blood.

Diphtheria antitoxin made chiefly of globulins, in doses of 0.354 cc. by the jugular, caused an epinephrin effect upon the intestine.

Diphtheria antitoxin serum gave, in doses of 0.118 to 0.354 cc. by jugular, a marked epinephrin

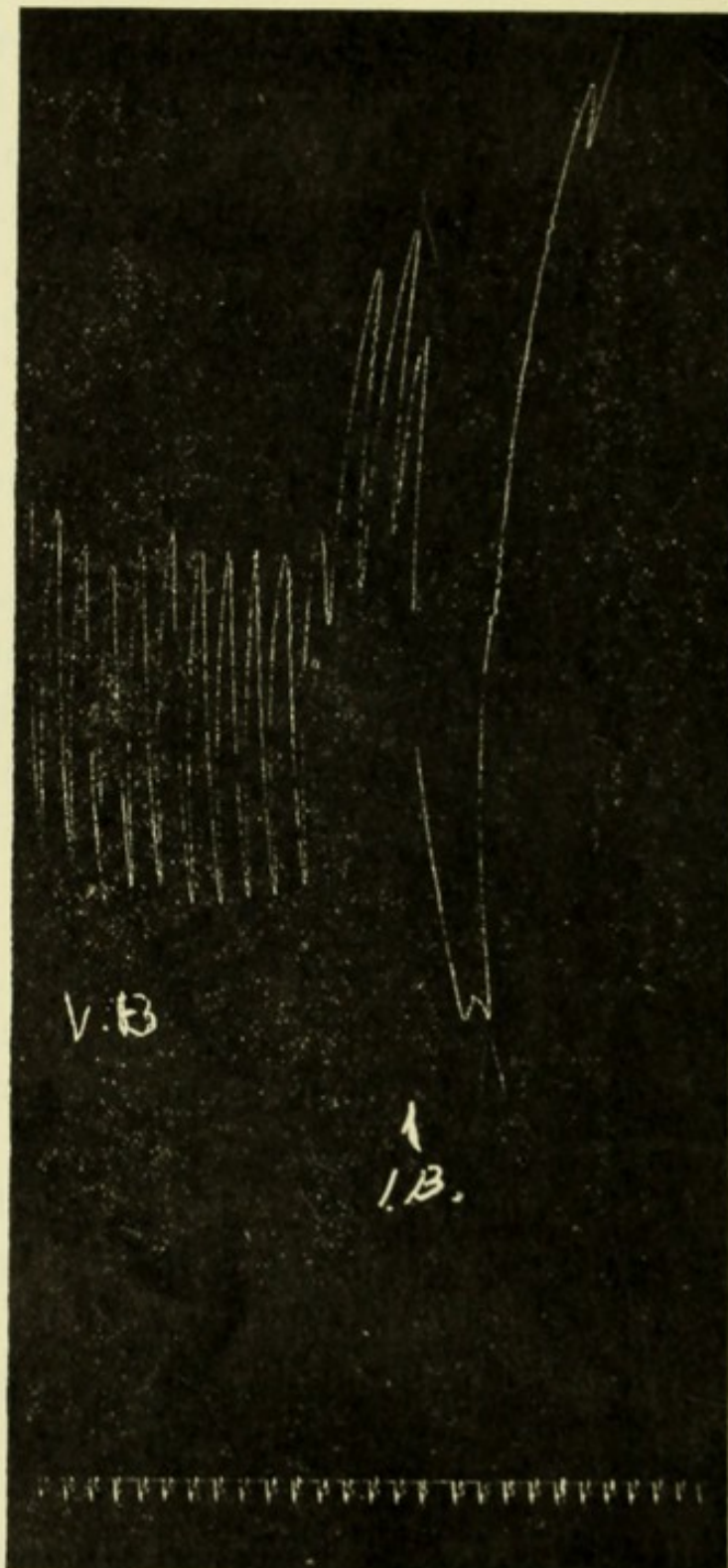


Fig. 2. Effect of Infundibulin (20 per cent. Extract of the Posterior Part of the Pituitary) upon the Amount of Epinephrin in the Blood.

reaction, which persisted for a half-hour afterwards.

We found that 0.118 cc. of egg albumen (fig. 3) by the jugular gave a marked epinephrin reaction. The same was true of peptones (fig. 4). The albumen of muscle extract and liver extract also gave an increase of epinephrin in the blood. Hence we can draw the conclusion that foreign albumens increase the amount of epinephrin in the blood. But our glandular extracts were free of albumen, as far as Heller's ring test goes. Iodothrin and infundibulin being free of albumen, and nearer a state of chemical purity, we can infer that they stimulate the adrenals to increased activity. As to the other extracts we can not state whether it is due to a hormone or to some protein which causes an increase of epinephrin in the blood. We will have to wait until the chemists can produce the hormones in a state of purity. Some of these glands contain cholin, which increases the amount of epinephrin in the blood, according to recent experiments by us.

Pettit and Girard¹² found that, in a horse used in the preparation of antitoxin for diphtheria, the adrenals were in a state of general excessive secretory activity, especially marked at the level of the fasciculate layer and the medulla, with slight fatty degeneration.

¹² *Compt. rend. de la Soc. de Biol.*, p. 272, 1905.

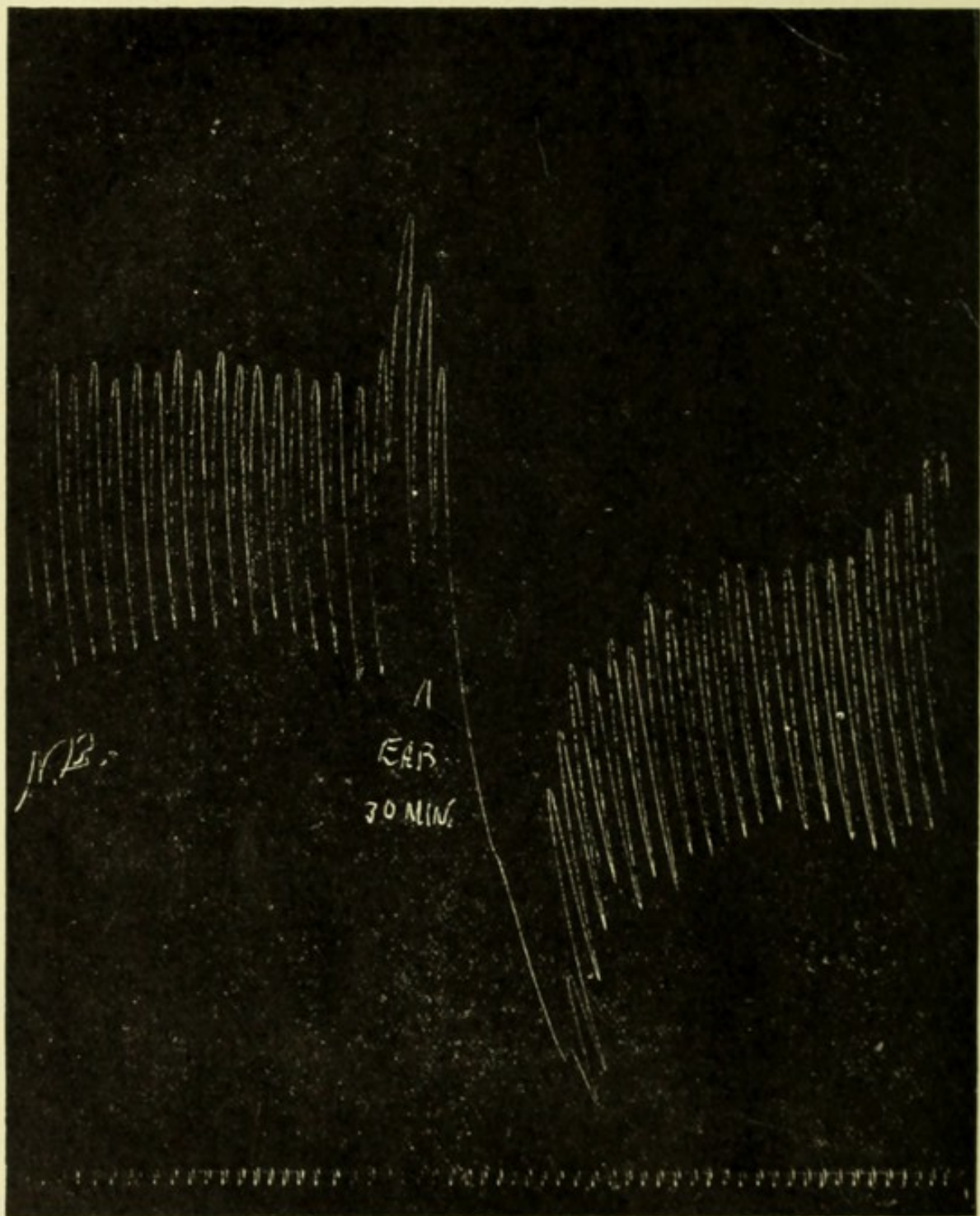


Fig. 3. Effect of 0.118 C.C. of Egg Albumen upon the Amount of Epinephrin in the Blood, Thirty Minutes After the Injection per Jugular.

Pettit and Girard¹² found in the horse who served many years in the production of antidiphtheritic and pest sera the hypophysis was the seat of a slight fatty degeneration with vascular congestion and an active proliferation of cells.

Perrier¹³ also confirms this statement as regards the horse's adrenals in the production of the antitoxin for diphtheria.

That removal of a gland is followed by extensive changes in many other glands has been shown by Ascoli and Legnani,¹⁴ who found, after removal of the hypophysis in dogs, changes in the testicle, which did not develop. There were no spermatozoa, the ovary remained in the state of primitive follicles, the spleen was small, while no Malpighian bodies were seen, the thymus was only one-fifth to one-sixth its normal weight, the lobes had disappeared, the tissue was loose, the lymphoid elements scarce, the separation between the cortex and medulla was lost, the concentric corpuscles were numerous and confluent. The thyroid had no marked microscopic changes, except it was small, atrophic and the epithelium was flattened. The adrenals contained hemorrhages. The cortex of the normal adrenal has the glomerular, fascicular and reticulated zones, whilst in the operated animal there was no differ-

¹² *Compt. rend. de la Soc. de Biol.*, p. 272, 1905.

¹³ Perrier, *Thèse pour le Doctorat en Médecine*, p. 39, 1909.

¹⁴ *Münche. Med. Wochenschr.*, no. 10, p. 518, March 5, 1912.

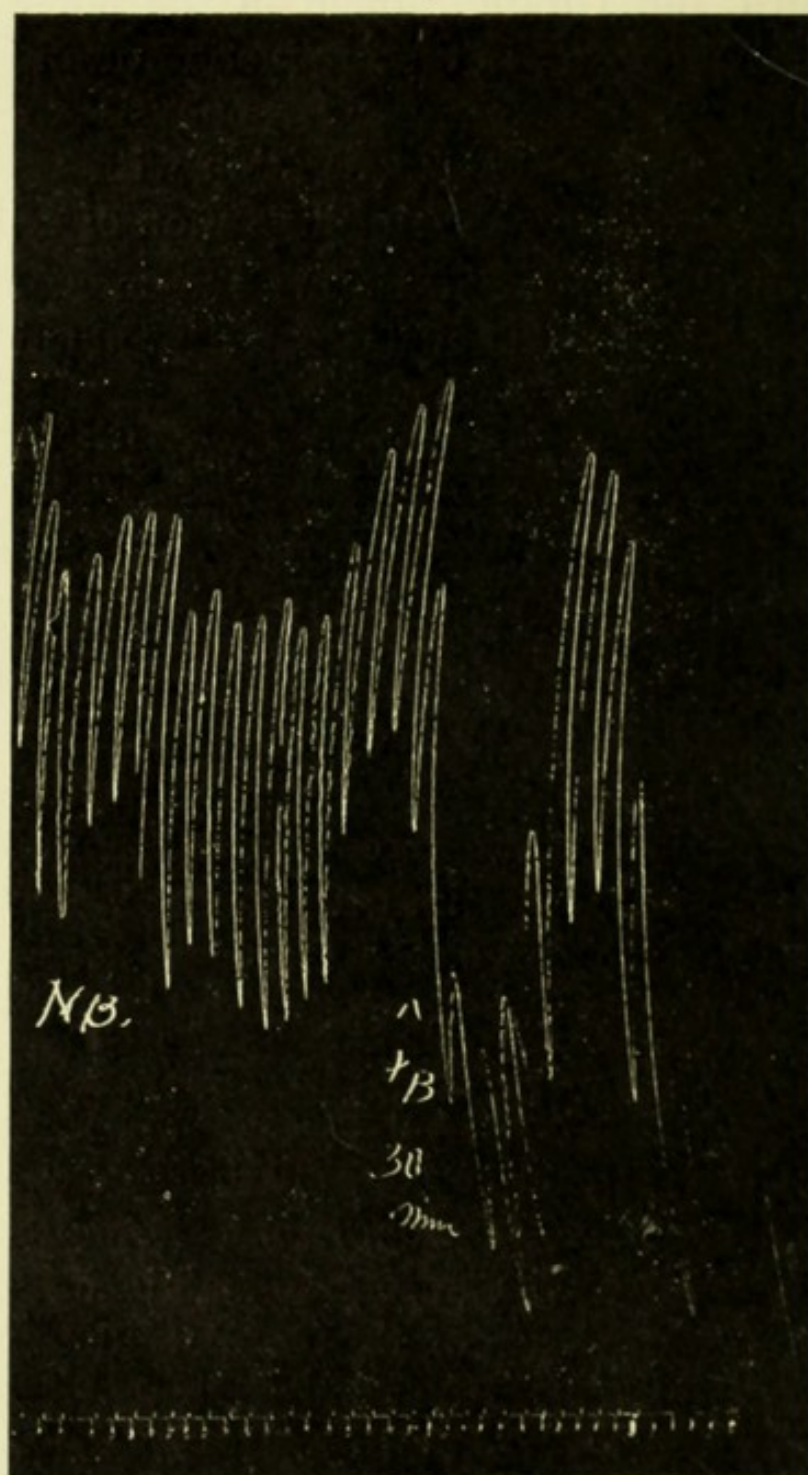


Fig. 4. Effect of 0.0648 Gram of Peptone (Merck) upon the Content of Epinephrin in the Blood.

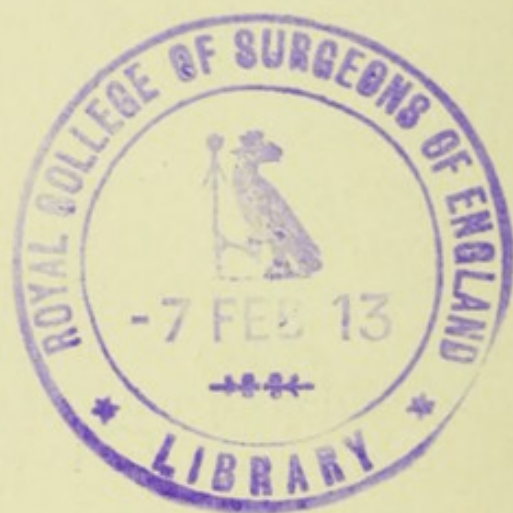
entiation of the two inner zones; they were as one, their cells enlarged and coarse, filled with drops of fat and lipid bodies. Here are five glands affected by the removal of one.

The removal of the hypophysis causes changes in the formation of the lipoids of the adrenal cortex.

It is evident that the glands with an internal secretion are closely interlocked in function and that a diminution or an excess of activity in one is followed by anatomical and functional changes in several others.

That several glands increase a secretion was well illustrated in that of milk, where we have five—infundibulin, thymus, pineal, corpus luteum and mammary. Each one of these greatly augments the secretion of milk when a solution of them is injected per jugular in the goat.¹⁵

¹⁵ Ott and Scott, *Therapeutic Gazette*, October, 1911.





THE ACTION OF SOME SUGARS AND OTHER BODIES UPON THE CONTENT OF EPINEPHRIN IN THE BLOOD.

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Recent researches have accumulated considerable evidence showing a close association between certain ductless glands and the metabolism of sugar. The parathyroids, the adrenals, the pancreas and the posterior part of the pituitary¹ are undoubtedly connected in some way with glycosuria. We must assume that it is the glycogenolytic process upon which the internal secretions of these glands act.

Mayer² found in rabbits after extirpation of both adrenals that puncture of the medulla failed to produce glycosuria. In three dogs he found the same result. Frouin³ obtained similar results. In Addison's disease we have hypoglycemia, according to Porges⁴, and after removal of both adrenals in animals he found a progressive diminution of sugar. The adrenals are under the control of the splanchnic nerve, as was first shown by Dreyer⁵ and confirmed by Tschoboksaroff⁶ and Ascher⁷. Macleod and R. G. Pearce⁸, after a

- (1) Ott and Scott. *The Alienist and Neurologist*, May, 1910.
- (2) *Compt. rend. de la Societe de Biologie*, 1906, LX, p. 1124.
- (3) *Compt. rend. de la Societe de Biologie*, 1910, LXIV, p. 219.
- (4) *Muenchen. Med. Wochenschrift*, LVI, p. 156.
- (5) *Am. Journal of Physiology*, 11, p. 203, 1899.
- (6) *Pflueger's Archiv*. CXXXVII, p. 59, 1910-11.
- (7) *Zeitschrift f. Physiol.* XXIV, p. 928, 1910.
- (8) *American Journal of Physiology*, Vol. XXIX, 1912, p. 419.

number of experiments, concluded that it is only when the adrenal glands are intact that it is possible, by stimulation of the nerves supplying the liver, to excite hyperglycogenolysis. Some influence exercised by the adrenal glands is evidently essential for the functional integrity of the nerves which control the process of glycogenolysis.

R. H. Kahn⁹ found if you extirpated in a rabbit an adrenal, made the piqure, and after the appearance of sugar you extirpated the other adrenal, that, after staining with chrome salts, the medulla of the last adrenal took very little of the chrome salt, that the cells of the medulla are poor in granules and rich in vacuoles, its finer vessels are dilated and its amount of epinephrin very much lessened.

Starkenstein¹⁰ found carbon monoxide and asphyxia glycosuria produced the same results in the adrenal, but that section of the splanchnic going to an adrenal preserved it. Starkenstein found in rabbit after carbon monoxide poisoning ensuing hyperglycaemia, which did not occur in animals who had their adrenals extirpated some months previously. Hence we can infer that the piqure causes a central irritation, which, going by the splanchnics, produces an abnormal secretion of epinephrin from the medulla of the adrenals, and a glycosuria. It is supposed that epinephrin, by its well-known stimulant action upon the sympathetic terminals, makes the irritability of the sympathetic nerves greater, so that piqure and carbon monoxide can act through the

(9) Zuckerstich und Nebennieren, Pflueger's Archiv. Band 140, p. 209, 1911.

(10) Zeitschrift f. exp. pathol. Band 10, p. 78, 1911.

sympathetic on the glycogen; for removal of the adrenals prevents this action.

Starkenstein, however, found that central irritation of the vagus in rabbits without adrenals could produce a hyperglycaemia. Here we must assume that this irritation is powerful enough to stir up a stimulus running down to the sympathetic nerve endings in the liver.

Cannon¹¹ and de la Paz found in cats by psychical action a glycosuria with an increased secretion of adrenalin; and Cannon, Strohl and Wright¹² found in cats that diabetes due to binding the animal down was prevented when the adrenals were previously extirpated.

Kahn¹³ found also in cats that after piqure there was less stain of the adrenal medulla by chrome salts, and that the quantity of epinephrin in the adrenals is much less than before the removal of the adrenals, as shown by the Laewen's preparation—method. By the same method he found in the monkey that the content of epinephrin in the adrenal was very much reduced, the stain of the adrenal by potassium chromate is less, vacuoles are present; there was also glycosuria and hyperglycaemia,—all as the result of asphyxia. He also made experiments upon the amount of epinephrin in the blood of the vena cava of rabbits before and after the piqure, and found the blood to have an increase in its quantity of epinephrin. He used the Laewen preparation.

(11) *Am. Journal of Physiology*, Vol. 28, p. 64, 1911.

(12) *Am. Journal of Physiology*, Vol. 29, p. 280, 1911.

(13) *Pflueger's Archiv*, Band 146, p. 578, 1912.

Elliott¹⁴ measured the quantity of epinephrin in the adrenal by the blood-pressure test. He used cats. He found that in intact animals the residual epinephrin is exactly equal in the right and left glands.

Excitation of the brain by morphia and Beta-tetrahydronaphthylamine exhaust the adrenals by a central action. He found that ether, chloroform and urethane lower the content of epinephrin. Pilocarpin, physostigmine and epinephrin did not affect the adrenals. Irritation of the afferent fibers of the great sciatic or direct injury to the brain causes a loss of epinephrin. The center controlling this is close to the bulbar vaso-motor center. The efferent path is by the splanchnic sympathetic nerves. Their section prevents exhaustion, for then the exhausting agents have no effect on the adrenals.

Faradization of the splanchnic nerves discharges adrenalin into the blood, causing a characteristic drop in the rising curve of blood-pressure and such phenomena as paradoxical pupillo-dilation. He states that it appears probable that the supra renal glands are played upon by the splanchnic nerves in the emotional and vaso-motor reflexes with almost as delicate and ever-changing an adjustment as are the muscles of the peripheral tissues connected with the sympathetic nerves. The glands are capable of automatic excretion, for the decentralized gland suffices to keep the animal alive. If one adrenal be removed and the splanchnic of the other divided, the cat does not die until the second supra renal has been also excised.

(14) Journal of Physiology, Vol. XLIV, Nos. 5 & 6, p. 374.
1912.

Borberg¹⁵ used the method of staining the medulla of the adrenals by chrome salts. He used rabbits, cats and guinea pigs. Inanition causing death produced a marked disappearance of the chromaffine substance, and anemia causes no important weakening of the chrome coloration in the adrenal. Asphyxia in rabbits was followed by a complete loss of chromaffine substance. Fall of blood pressure has little or no action upon the chromaffine substance. Choline produced no real diminution of chrome-affinity, but a physiological vacuolization; hyper-secretion of adrenalin and glycosuria go in parallel lines and hyper-secretion of the chromaffine tissue is an important cause of glycosuria.

He found after extirpation of one adrenal no sign of hyper-secretion in the other adrenal.

Poisoning by urine diminished the quantity of chromaffine substance, which was central in origin. Poisons acting upon the kidneys produces changes in the adrenal medulla. He saw no changes in the adrenal in hyperthyroidism or athyroidism. A peritonitis produced by chemicals causes only a slight disappearance of chromaffine substance, but when combined with infection or intestinal occlusion or phenolic intoxication there was a marked loss of the chromaffine substance. Intestinal occlusion alone causes a loss of the chrome reaction.

Pilocarpin caused no results in two guinea pigs. Short chloroformization is without any marked action, but when continued causes a slight diminution of the affinity for chrome stains. Repeated etherization is without important ac-

(15) Skandinav. Archiv. f. Physiology, p. 91, Band XXVIII.

tion upon the affinity for the stain. Urethane when given for three days per rectum, in a quantity amounting to 8 grams, had no action upon the chrome stains in rabbits. Oil of pennyroyal by repeated injections causes death and is attended with a nearly complete loss of stain by the chrome salts. One per cent. solution of corrosive sublimate subcutaneously caused a distinct weakening of the chrome stain. Phosphorus in olive oil produced the same result. Arsenate of sodium and acetate of lead had no action. Potassium iodide gave a light decrease in the stain.

Protracted poisoning by diphtheria causes a light faded chrome stain. Tetanus poison had no action upon the chrome stain. Nucleinate of soda, causing a fever, produces no marked changes in the affinity for chrome salts.

Now the effect of urethane upon the amount of epinephrin in the blood is affirmed by Elliot to be increased, and by Cannon and Borberg to cause no increment, hence it was necessary to make control experiments as to the effect of urethane by the mouth and of distilled water by the jugular on the epinephrin content in the blood.

Elliot gave a cat 18 c.c. of a 25% solution of urethane subcutaneously and at the end of $1\frac{1}{2}$ hours cut the left splanchnic. At the end of $4\frac{1}{2}$ hours he killed the animal and found the right adrenal contained .07 mgm and the left .13 mgm of adrenalin.

Borberg, in a rabbit and using 8 grams of urethane per rectum, in divided doses, extending over 3 days, found no loss of chrome stain in the adrenal medulla. We gave the cat 4 grams of urethane by the mouth and the experiment was at an end in 2 hours.

The intestinal strip is more sensitive as a test object than the blood pressure test for the presence of epinephrin, as Hoskins¹⁶ has shown.

The activity of urethane in Elliot's experiments by subcutaneous injection is much greater than in ours, where it was given by the mouth.

Our experiments with glucose and other agents were made in the same manner and on similar animals as detailed elsewhere¹⁷. All the agents used except iodine were from Merck's laboratory.

We made seven control experiments but we saw no evidences of the presence of epinephrin in the blood. Whilst O'Connor¹⁸ has pointed out that fresh serum of the rabbit contains even apart from the content of epinephrin, substances which act like epinephrin on plain muscle. We have seen no such results except very rarely in the defibrinated blood of the cat. Our experiences include the testing of the defibrinated blood of the cat on more than 100 intestinal segments. The great inhibition of the intestine by the drugs precludes in our minds any error in the conclusions.

That the sugars, pilocarpin, iodine, indol skatol and phloridzin did not cause the inhibition of the intestine was proved by the addition of a small quantity of each to the defibrinated blood. The intestinal segment was then tested with this blood but no inhibitory arrest ensued.

The tests for epinephrin were made $3\frac{1}{4}$ and 30 minutes after the injection of the drug, dis-

(16) Archives of Internal Medicine, Vol. X, p. 343.

(17) Journal of Pharmacology & Exp. Therapeut., Vol. III, No. 6, p. 626, 1912.

(18) Archiv. f. Experimentelle Pathol. u. Pharmakol. Band, 67, p. 195.

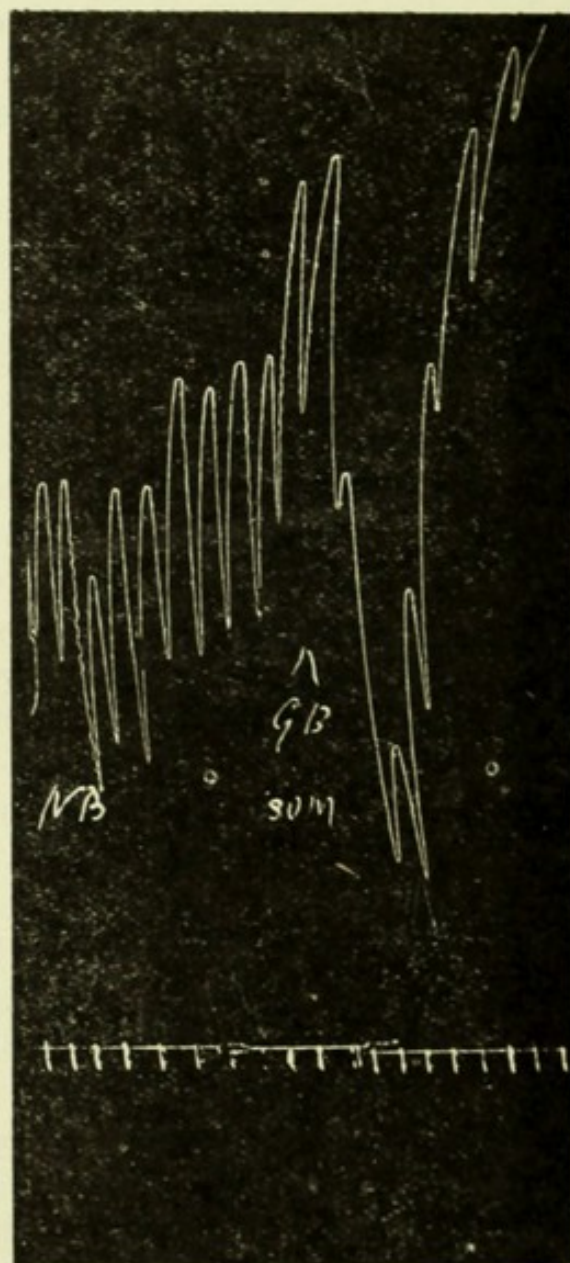


FIG. 1. Effect of 0.01296 gram of glucose upon the amount of epinephrin in the blood 30 minutes after the injection, time in 4 seconds.

solved in 2 c.c. of distilled water by the jugular. We made 50 experiments.

Glucose, 0.01296 gram per jugular.

Whilst glucose caused the reaction of epinephrin on the rabbit's intestine after $3\frac{1}{4}$ minutes, it gave the most marked effect 30 minutes after its injection. (Fig. 1.)

Maltose, 0.01296 gram.

It caused a marked epinephrin reaction at the end of $3\frac{1}{4}$ and also at the end of 30 minutes.

Saccharose, 0.01296 gram.

This body when injected was followed by a decided epinephrin reaction at the end of 30 minutes.

Laevulose, 0.01296 gram.

Laevulose at the end of $3\frac{1}{4}$ minutes caused the blood to give an epinephrin reaction.

Lactose, 0.01296 gram.

Lactose was followed 30 minutes after its injection by a reaction of epinephrin.

Pilocarpin, 0.000648 gram.

At the end of $3\frac{1}{4}$ and of 30 minutes there was an excess of epinephrin in the blood.

Ehrmann¹⁹, Tscheboksaroff²⁰ and Elliot²¹ did not observe any change in the output of epinephrin by the injection of pilocarpin.

Dale and Laidlaw²² found pilocarpine to double the adrenal content of the blood.

Iodine, 0.0056 gram.

This body caused the reaction of epinephrin at the end of $3\frac{1}{4}$ and 30 minutes. Kawashima and Borberg found potassium iodide to diminish the adrenal stain by chrome salts.

(19) Archiv. f. Exper. Path. and Pharm., LXIII, p. 97, 1905.

(20) Pflueger's Archiv., CXXXVII, p. 59, 1911.

(21) Journal of Physiology, XLIII.

(22) Journal of Physiology, XLIV, p. 1, 1912.

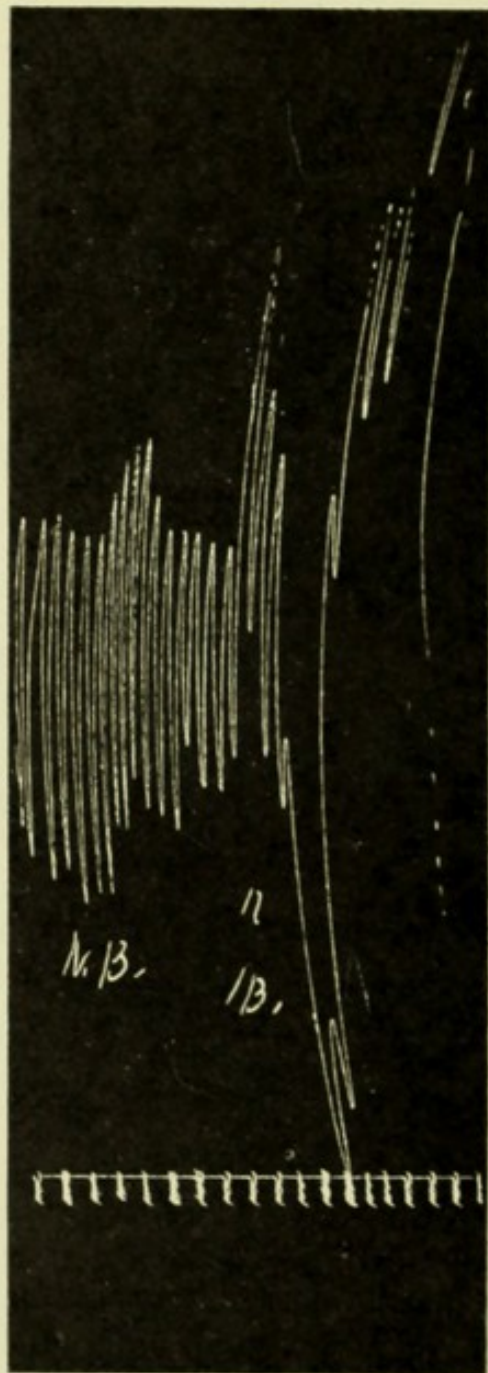


FIG. 2. Effect of 0.0056 gram of iodine upon the amount of epinephrin in the blood $3\frac{1}{4}$ minutes after the injection.

Indol, 0.001396 gram.

Indol caused a weak epinephrin reaction at the end of $3\frac{1}{4}$ and 30 minutes.

Skatol, 0.00648 gram.

Its injection was followed in $3\frac{1}{4}$ and in 30 minutes by a marked epinephrin reaction.

Phloridzin, 0.0054 gram.

This agent caused a marked reaction of epinephrin in 30 minutes after the injection.

It is evident from Borberg's and our experiment that varied agents cause a discharge of epinephrin from the medulla of the adrenals. Whether the above agents act directly upon the adrenals or upon their secretory nerves, the splanchnics, has not been investigated. These organs seem excessively sensitive to substances in the blood and are constantly discharging their contents into the circulation.

The modern theory of experimental diabetes is that a glyco-secretory center is located in the medulla, from which impulses pass down the cord, emerge in the splanchnics, the secretory nerves of the adrenals, and increase the amount of epinephrin, which mobilizes the glycogen of the liver and thus produces a diabetes. It is well known that epinephrin is a stimulant of the sympathetic nerves, hence it is a stimulant of the splanchnics. We have found the injection of glucose per jugular in the cat increases the amount of epinephrin in the blood, as shown by the intestinal strip of the rabbit. Hence we have here a circle: epinephrin stimulates the secretory nerves of the adrenals to produce epinephrin, which via the glycogen of the liver produces more glucose, which in its turn discharges more epinephrin.

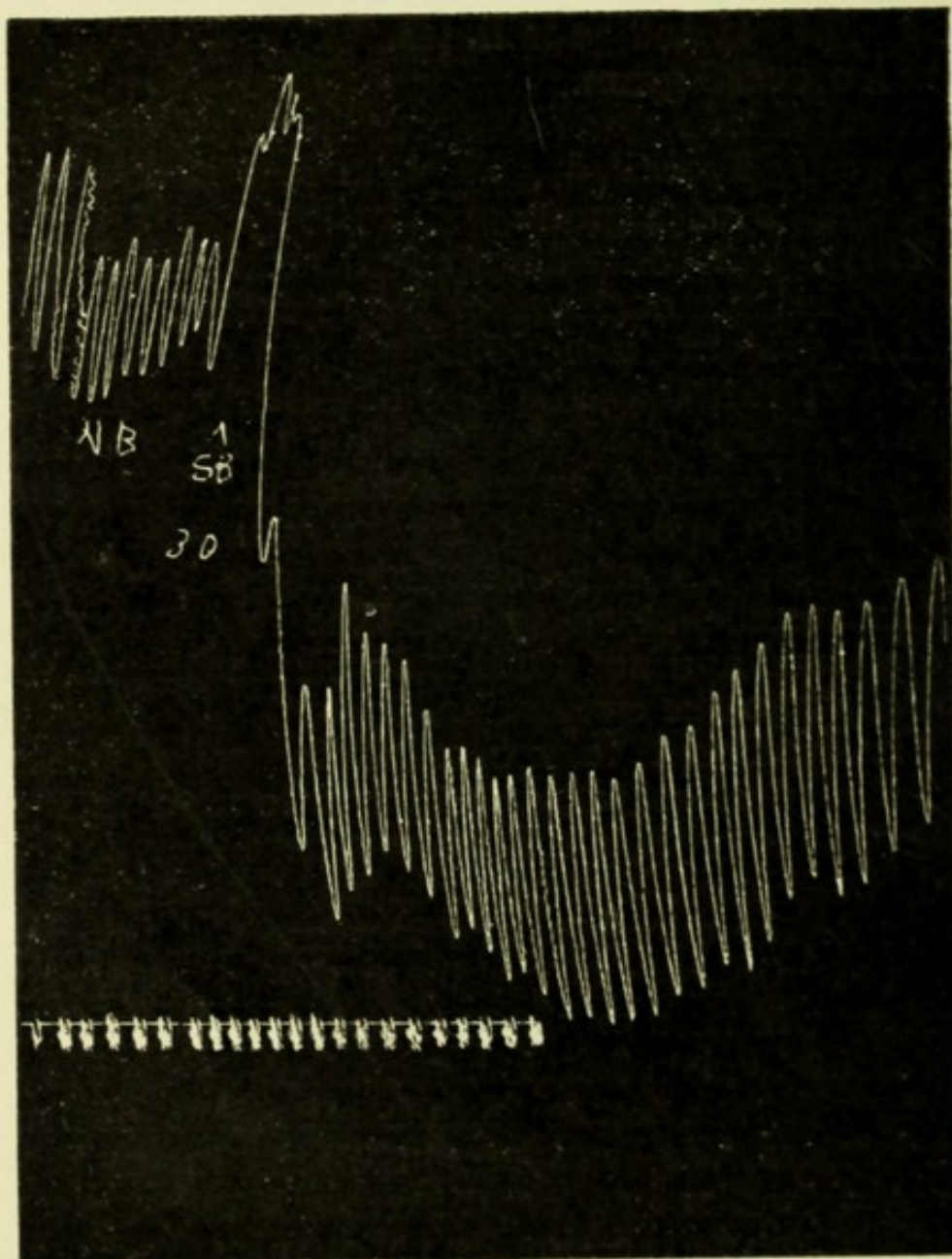


FIG. 3. Effect of skatol 0.00648 gram upon the amount of epinephrin in the blood 30 minutes after the injection.