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Diabetogenic Principle of the Anterior Pituitary.

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In this laboratory we have been engaged in the preparation of potent extracts of the anterior pituitary for isolation of the lactation principle. While studying the effects of these extracts on the normal dog, the development of a severe lipemia was noted to occur some 24 to 48 hours after the first injection. Further investigation revealed that these extracts contained the diabetogenic principle of the anterior pituitary.

The writer communicated his findings to Dr. A. J. Carlson March 26, 1933, for criticism. Further, Dr. B. O. Barnes reported to the Physiological Society, Cincinnati meeting, April 11, 1933, that an acid extract of the anterior lobe produced glycosuria in 3 normal dogs. At that time, neither Dr. Barnes nor myself were aware of Houssay's report of the same nature. Thus, it seems that this observation was made independently in 3 laboratories, although admittedly earlier by Houssay.[1]

The summary of the author's evidence that a diabetic syndrome of varying intensity can be established in normal dogs by the subcutaneous administration of alkaline extracts of the anterior lobe follows. To date 12 dogs have been studied.

Lipemia: Within 24 to 48 hours after the first injection, a marked lipemia developed in 6 of the 12 dogs. In general, this lipemia did not persist beyond the fifth day. It may be that this lipemia is caused by a sudden unloading of the fat stores of the body into the blood stream.

Polydipsia: Within 24 to 36 hours, polydipsia develops, all dogs drinking about 1900 cc. per day. It was distinctly observed that the polydipsia preceded the polyuria.

Polyuria: Polyuria is not marked until the fifth day, the urine output averaging then about 1500 to 2300 cc. In most cases, the specific gravity of the urine would indicate a diabetes insipidus (about 1.006): in 5 dogs the urine sp. gr. rose to between 1.035 and 1.045.

[1] Houssay, B. A., Biassotti, A., and Rietti, C. T., *Revista de la Soc. Argent. de Biol.*, 1932, **8**, 469.

Glycosuria: In 7 dogs, glycosuria was evident on the fifth day (mild). In 3 dogs, the glycosuria was marked. The D/N ratio was not determined. The presence of sugar in the urine follows rather closely the blood sugar level and does not appear until the blood sugar is about 145 mg. %.

Hyperglycemia: The fasting blood sugar (Shaffer and Hartman) in these dogs was about 93-113 mg. % before injection; it rises 48 hours after the first injection to 145-425 mg. %. This high sugar level persists for about a week (injections being continued) and then some compensation takes place, the blood sugar level falling to a sub-normal level (70-90 mg. %). In some dogs this apparent hypoglycemia persists for at least a month after the injections have been stopped. There is a distinct vagatonia during the initial hyperglycemic period but after the injections have been discontinued the dogs exhibit a fairly marked polyphagia.

Glucose tolerance test (Killian): Before the injections the dogs gave normal glucose tolerance curves. After injections, the curves indicate diabetes, the first hour sample showing a rise to 250-280 mg. %. Even after the fasting blood sugar has returned to normal, the glucose tolerance curves are abnormal. No opportunity has yet been afforded to simultaneously determine the R.Q. values during a test period.

Acidosis: In 3 dogs specifically studied, the pH (quinhydrone electrode 20°C.) dropped from a normal of 7.55-7.60 to 7.35, 7.41 and 7.42. In 2 cases the pH drop was accompanied by a lowering of the alkali reserve from a normal of 55 vol. % CO_2 to 35.2 and 41 vol. % respectively. These dogs went into coma which was partly relieved by insulin. The alkaline reserve was not restored to normal until bicarbonate was administered.

Attempts have been made to separate the diabetogenic principle from the lactation principle, so far with no success. It is evident, however, that the diuretic action of these extracts is probably not due to the "foreign protein" injected. Injection of the globulin fractions of the extract in comparable doses produced no increase in urine output of normal dogs.