fasted animals can only be due to some obscure refractory state against the metabolic effect of the extract, but apparently not against its growth-promoting effect.

Preliminary efforts to detect an inhibitory effect in the serum in chronically treated normal animals have been unsuccessful. However, in confirmation of Black,[4] it has been found that such chronically treated normal rats became resistant to the ketogenic effects of crude anterior lobe extracts. A group of 7 rats during a 72-hour fasting period, while receiving 1.5 cc. per day of extract, excreted an average of 43 mg. of urinary ketone bodies; after one month's daily injection, this fell to 4.6 mg. for the same fasting period while receiving a like amount of extract. An untreated control group of rats excreted 5.3 mg. of ketone bodies during a 72-hour fast.

Summary. Crude anterior lobe extracts are able to maintain the fasting muscle glycogen levels of hypophysectomized rats in an acute test, but are unable to do so when injected chronically. Continued treatment of normal rats with such extracts abolishes their ketogenic effect.

9443 P

Effects of Hypophysectomy and of Anterior Pituitary Extracts on Disposition of Fed Carbohydrate in Rats.*

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Rapid disappearance of body carbohydrate and correspondingly high rates of carbohydrate oxidation were observed in fasted hypophysectomized rats, and anterior pituitary extracts were found to restore to these animals the ability to maintain their carbohydrate levels.[1, 2, 3] In order to determine whether hypophysectomized rats differed from the normal in their carbohydrate metabolism in the fed state as well as when fasted, and to determine whether anterior lobe

4 Black, P. T., *J. Physiol.*, 1935, **84**, 15.

*Aided by the Presnell Fund for the study of the metabolic relations of the anterior hypophysis, contributed by Robert R. Presnell, Frank Tuttle, Arthur Stebbins, and Mrs. Gordon Kahn, of Los Angeles.

†Porter Fellow, 1937-38.

1 Russell, J. A., and Bennett, L. L., *Am. J. Physiol.*, 1937, **118**, 196.

2 Fisher, R. E., Russell, J. A., and Cori, C. F., *J. Biol. Chem.*, 1936, **115**, 627.

3 Russell, J. A., and Bennett, L. L., PROC. SOC. EXP. BIOL. AND MED., 1936, **34**, 406.

extracts acted also under these conditions, the following experiments were performed:

Normal and hypophysectomized rats were fasted, then fed known amounts of glucose. The oxygen consumption, respiratory quotients and N excretion were determined during the next 4 hours. Then the animals were killed and the levels of blood glucose and of liver and muscle glycogen were determined, as were also the amounts of glucose remaining in the alimentary tracts. Identical experiments were performed at the same time on both normal and hypophysectomized rats which had been treated for various lengths of time with standard alkaline extracts of anterior pituitary. Respiratory data and carbohydrate levels were also determined in normal unfed rats, with and without A. P. injections.

It was found in the hypophysectomized rats that 74% of the absorbed glucose was oxidized, as compared to 53% in the normal animals. The hypophysectomized rats stored less carbohydrate than did the normal rats, the difference being accounted for approximately by the increase in the proportion of carbohydrate oxidized. The actual amounts of carbohydrate apparently oxidized were about the same in the 2 series, in spite of the fact that the total oxygen consumption, and the rate of absorption of the fed glucose were much smaller in the hypophysectomized rats. Therefore, as also found previously by others,[4] the proportion of total calories obtained from carbohydrate was higher in the operated animals. Evidently, under the conditions of these experiments, a factor was operating in the normal but not in the hypophysectomized rats which depressed the proportion of carbohydrate being oxidized, even when there was a plethora of carbohydrate available.

The injection of the anterior lobe extracts caused an immediate fall in the apparent rate of oxidation of carbohydrate in both hypophysectomized and normal rats, in the former to levels below the normal. The amount of carbohydrate oxidized was 44% and 31% of the amount absorbed in the hypophysectomized and normal rats respectively, and carbohydrate oxidation accounted for only 39% and 25% of the total calories under these conditions. Much more carbohydrate was stored as glycogen by the normal rats injected with A. P. than in those not treated. This change was not marked in the treated hypophysectomized animals, but the blood sugar levels rose rather higher in the operated than in the normal rats under these conditions.

[4] Fisher, R. E., and Pencharz, R. I., PROC. SOC. EXP. BIOL. AND MED., 1936, **34**, 106.

In the normal unfed rats, no action of the A. P. extracts was demonstrable, except a slight increase in the muscle glycogen level. The average R. Q. was 0.722, compared to 0.724 in uninjected rats. Since carbohydrate oxidation was already at such a low level under these conditions, the absence of a further decrease was not surprising.

9444 P

Production of Refractoriness to Action of Anterior Pituitary Extracts in Depressing Oxidation of Fed Carbohydrate.*

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In the previous paper, it was reported that anterior lobe extracts caused a fall in the apparent rate of oxidation of fed carbohydrate in both hypophysectomized and normal rats. The decrease, judged by the R. Q. and the glycogen deposition after feeding glucose, occurred within a few hours after the injection of standard alkaline extracts, and was also evident when injections had been made over several days preceding the experimental periods. It was found recently in this laboratory by Mr. L. L. Bennett[1] that after chronic treatment with A. P. extracts, hypophysectomized rats become refractory to the action of these extracts in maintaining fasting muscle glycogen levels. In view of this finding, it seemed advisable to try chronic treatment in conjunction with the experiments described above.

A group of normal rats was therefore injected daily for 20 days with one cc. of the standard alkaline extract. They were then fasted 24 hours, fed glucose, and determinations of the disposition of the carbohydrate were made in the same manner as in the groups described in the previous paper. After this pre-treatment final injections of the A. P. extract, given 2 hours before the glucose was fed, had absolutely no effect on the respiratory quotients or on the deposition of the fed carbohydrate. Evidently, in these normal rats, after prolonged treatment with a beef anterior extract, a refractory state

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† Porter Fellow, 1937-38.

[1] Bennett, L. L., PROC. SOC. EXP. BIOL. AND MED. In press.