in castrated rats. The times for continuation of muscular contractions and the values for total work for both normal and castrated rats were much smaller in their experiment than in the present one. Heron, Hales, and Ingle[2] have discussed some of the important differences between the methods used by Gans and Hoskins and the method described by themselves, which I have used in this experiment.

10154

Blood Sugar Changes in Hypophysectomized Rats During Adaptation to Various Stimuli.

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Recent experiments have shown that the blood sugar of fasting adrenalectomized animals decreases rapidly under the influence of exposure to any damaging agent capable of producing an "alarm reaction". Such a decrease, however, is not seen in animals which have been pretreated for a few days with the same dose of the same damaging agent and are consequently in the "resistant phase" of the general adaptation syndrome. It seems, therefore, that the hypoglycemia is simply part of the alarm reaction, and consequently cannot be elicited at a time when the nocuous agent has lost its "alarming" effect. After further continued treatment, however, during the "stage of exhaustion", these animals again responded with hypoglycemia which in this latter case proved to be fatal.[1]

Since hypophysectomy elicits disturbances in carbohydrate metabolism which in certain respects are very similar to those caused by adrenalectomy, it seemed of interest to perform similar experiments in the hypophysectomized animal. Female hooded rats weighing between 95-130 g were used for all experiments reported in this communication. In every case, a rest of 8 days was allowed following hypophysectomy as it was found that the blood sugar reaches a constant level at this time and stays fairly constant for as long as the animals are in good condition. In order to avoid complicating our experiments with repeated fasting and bleeding, each rat was

2 Heron, W. T., Hales, W. M., and Ingle, D. J., *Am. J. Physiol.*, 1934, **110**, 357.

1 Selye, Hans, Proc. Soc. Exp. Biol. and Med., 1938, **38**, 728.

used for one determination only. The animals were bled in groups of 6 at 1, 12, and 24 hours, and 2, 3, 5, and 6 days after initiation of treatment in each experiment. Each point on the graph represents the average of 6 individual determinations on 6 rats. In the first experiment (full line on the graph), the animals were adapted to cold by placing them in an ice-box at a temperature of +1°C for a period of one hour, 3 times a day. In the second group (dotted line), the animals were adapted to muscular exercise by forcing them to run 3 times daily for a period of 15 minutes in revolving cages having a diameter of 12 inches and running at a speed of 15 revolutions per minute. All blood sugar determinations (Shaffer, Hartmann and Somogyi method) were performed after a 24-hour fasting period. The base line has been placed at 60, since the average blood sugar of 6 control rats fasted during 24 hours on the 8th day after hypophysectomy was 60 mg %. That without treatment,

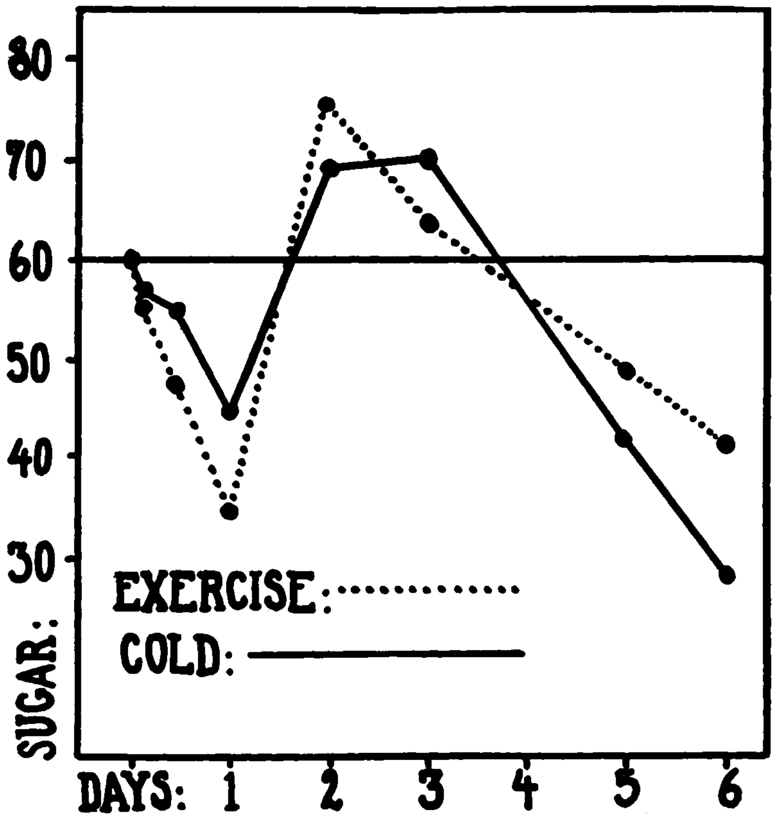

Fig. 1.

Blood sugar variations in hypophysectomized rats during adaptation to exercise and cold.

this blood sugar level would not change materially during the 6 days of our experiments was shown by the fact that a second group of 6 rats fasted during 24 hours on the 14th day following hypophysectomy had an average blood sugar of 58 mg %.

The graph shows that exposure either to cold or to muscular exercise causes an initial decrease in the blood sugar concentration, which is followed by an increase above the base line on the second and third day (that is to say, at a time when the animal acquired adaptation to these stimuli). After this, however, the blood sugar decreases again and death occurs in hypoglycemia. It appears that during the process of adaptation, the blood sugar variations in hypophysectomized rats are very similar to those of adrenalectomized animals. The fact that the adaptation acquired during the first few days is lost at a later stage gives further support to the conception that adaptive functions are not performed merely at the expense of the caloric energy supplied by food but that some special "adaptation energy" is used during the process of adaptation and that the available stores of this adaptation energy become exhausted during the process of adaptation even though unlimited amounts of food are available.

Since the blood sugar level of fed hypophysectomized animals is not significantly below normal while prolonged fasting causes particularly marked and often fatal hypoglycemia in such animals, it is held that the essential disturbance in the carbohydrate metabolism of the hypophysectomized animal is an inability to regenerate blood sugar from endogenous sources. The present experimental series is not in agreement with this interpretation, since it shows that although exposure to cold or performance of muscular exercise caused marked hypoglycemia in not pretreated fasting hypophysectomized animals, this effect is not seen after adaptation occurred; in fact, in the adapted animal, the response may be reversed so that the same stimuli elicit an increase in blood sugar. In view of these findings, it would seem more likely that hypophysectomized (like adrenalectomized) animals suffer from a disturbance in their adaptability, which makes them particularly sensitive to agents to which they are not adapted. Consequently in such animals, these agents will cause a very severe alarm reaction with the characteristic accompanying hypoglycemia. This would also explain why after a few days of pretreatment when the damaging agent lost its ability to elicit symptoms of the alarm reaction, it also ceases to cause hypoglycemia. However, the hypophysectomized, like the adrenalectomized, animal cannot maintain acquired resistance for a long time, and the final stage of exhaustion, with its characteristic fatal hypoglycemia, follows after a relatively short stage of resistance; in intact animals, the resistant stage would last for several weeks. The fact that prolonged fasting in itself may elicit severe hypoglycemia in hypophysectomized animals offers no difficulty of interpretation in terms of this theory since prolonged withdrawal of food also causes characteristic symptoms of an alarm reaction with hyperplasia of the adrenal cortex, atrophy of the lymphatic organs, decrease in blood volume, etc., even in animals not exposed to any other nocuous agent.

It should be emphasized that the general condition of our hypophysectomized rats was particularly bad during the first and the last 2 days of the experiment, while they seemed to stand treatment without visible signs of damage during the third and fourth day. In this respect, their general condition ran roughly parallel with their blood sugar. A similar parallelism existed between blood sugar and blood volume.

Unlike in our previous experiments in normal[2] and adrenalectomized rats, we were unable to make continuous blood chloride curves in this experimental series, since the blood volume was so low in many cases that we could not obtain a sufficiently large amount for an accurate determination. Yet individual chloride determinations show that in hypophysectomized, though not in adrenalectomized rats, the blood chlorides (Van Slyke method) are often very high during the terminal stage of hypoglycemia. In one such case, the chlorides were as high as 505 mg per 100 cc of whole blood although the blood sugar fell to 28 mg per 100 cc.

Summary. Experiments on hypophysectomized rats show that exposure to nocuous agents (cold, excessive muscular exercise) induces marked hypoglycemia in the animal before adaptation, but following a few days of pretreatment during the resistant stage, these same agents elicit an inverse reaction and actually increase the blood sugar above the normal level. In the absence of the hypophysis, this acquired adaptation cannot be long maintained, however, and under the influence of continued treatment the animals soon enter into the stage of exhaustion, during which fatal hypoglycemia ensues. In this respect, the response of the hypophysectomized is very similar to that of the adrenalectomized animal. These experiments are not in accord with the assumption that the characteristic disturbance in the carbohydrate metabolism of the hypophysectomized animal is an inability to regenerate blood sugar from endogenous sources,

2 Selye, Hans, *Arch. Internat. de Pharm. et de Ther.*, 1938, in press.

since following adaptation the fasting hypophysectomized animal learns to maintain its blood sugar at the normal, or even above the normal level, although it is exposed to such stimuli (cold, muscular exercise) as cause severe hypoglycemia in the unadapted organism.