CCLXVII. BLOOD SUGAR AND BLOOD CHLORIDE CHANGES IN THYROIDECTOMIZED RATS FOLLOWING EXPOSURE TO VARIOUS DAMAGING AGENTS

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Previously described experiments have shown that exposure of animals to non-specific damaging agents, such as toxic doses of drugs, surgical shock, excessive muscular exercise, cold etc., elicits a syndrome with characteristic changes in various organs and in blood chemistry. These changes are largely independent of the specific nature of the damaging agent to which the organism is exposed. However, if an animal is subjected beforehand to a damaging stimulus for a few days, it will no longer respond in this manner to further treatment with the same agent. It was concluded, therefore, that the syndrome represents the somatic expression of the "alarm" of the organism when first confronted with a stimulus to which it is quantitatively or qualitatively not adapted. For this reason, the syndrome has been termed the "alarm reaction" [Selye, 1937, 1, 2; 1938, 1; Harlow & Selye, 1937].

Among the blood chemical changes which characterize the alarm reaction, an initial increase followed by a marked decrease in blood sugar was found to be very constant. With continued treatment this hypoglycaemia disappears within a few days and after resistance to the stimulus is acquired, further treatment will actually increase the blood sugar above the normal level. The blood chlorides show a marked decrease during the alarm reaction and this is followed by an increase after adaptation [Selye, 1938, 2, 3].

It was observed furthermore that removal of endocrine glands which influence the adaptability of the organism may considerably alter this chemical response in the blood. Thus adrenalectomized [Selye, 1938, 4] or hypophysectomized [Selye & Foglia, 1938] animals show no initial hyperglycaemia but a very pronounced hypoglycaemia when exposed to agents capable of eliciting an alarm reaction. The hypoglycaemia is usually most marked in animals which are particularly severely damaged, hence it was not surprising to note an especially marked decrease in the blood sugar in hypophysectomized or adrenalectomized animals, since animals deprived of these glands become unusually sensitive to any damaging agent. It was very unexpected, however, to find in the course of these experiments that removal of the thyroid has an exactly opposite effect, inasmuch as it exaggerates the hyperglycaemic phase of the response. It was noted furthermore that in a group of thyroidectomized rats, the most severely damaged individuals are usually the ones which show the most pronounced hyperglycaemia. In spite of this inverse blood sugar response, the blood chlorides react in the usual manner; in fact, the hypochloraemia is exceptionally pronounced. The purpose of this communication is to report on a series of experiments illustrating these points.

Methods

The blood sugar determinations were carried out by the Shaffer-Hartmann-Somogyi method and the blood chloride determinations by the Van Slyke method. The chlorides were determined in whole blood specimens, not in plasma, because in some cases it was found that a severe alarm reaction may be accompanied by intravital haemolysis. In every case the animals were fasted 24 hr. prior to the determination so as to avoid any change in blood composition resulting from the ingested food. One animal was used for one determination only, so as to avoid changes resulting from repeated fasting and bleeding.

Female "hooded" rats weighing 95–135 g. were used in all the experiments of this series. The alarm reaction was elicited by exposure to cold, formaldehyde treatment or muscular exercise. The animals treated with formaldehyde received 0·2 ml. of a 4% solution subcutaneously three times the first day and once the next morning, 23 hr. after the first injection. They were killed one hour after the last injection. Those exposed to cold were placed in an ice-box at +3° for a period of 24 hr. Those forced to perform muscular exercise were placed in drum cages having a diameter of 12 in. and revolving at a speed of 18 r.p.m. They were forced to make three 15 min. runs in the course of the first day, and one the following morning. They were killed 1 hr. after the beginning of this last exercise period. The total length of treatment was 24 hr. in each case, during which period no food was allowed. This length of treatment was chosen because in normal animals the blood sugar curve usually reaches a low point at about 24 hr. after exposure to an alarm reaction-eliciting agent. 8 normal and 8 thyroidectomized rats were exposed to each of the agents and two similar groups of otherwise untreated rats served as controls. The thyroidectomies were performed 9 days before the beginning of treatment. It should be emphasized that in the rat the two internal parathyroids are enclosed in the thyroid tissue and were consequently removed together with the thyroid. Although no signs of tetany were evident in animals thus operated upon, it is possible that ablation of these parathyroids may have influenced the response. Experiments are now in progress in this laboratory in which only the parathyroids are removed. These may throw some light on this aspect of the problem.

Results

Table I summarizes the results of these experiments. The numbers in parentheses represent extreme variations.

Table I

	Blood sugar, mg. per 100 ml.		Blood chlorides, mg. per 100 ml.	
Damaging agent	Normal	Thyroidectomized	Normal	Thyroidectomized
Formaldehyde	**76** (70–85)	**111** (81–144)	**386** (363–421)	**356** (339–374)
Exercise	**70** (56–80)	**78** (65–82)	**463** (456–479)	**407** (385–410)
Cold	**74** (55–80)	**91** (70–112)	**407** (386–433)	**384** (362–395)
Controls	**85** (81–92)	**70** (60–80)	**435** (421–456)	**423** (410–433)

It is quite obvious that exposure to the various damaging agents used in this experimental series led to a marked fall in the blood sugar of the normal animals, while in the thyroidectomized rats exposure to these same stimuli not only failed to produce such an effect but actually caused hyperglycaemia. This is particularly interesting in the case of animals exposed to cold or performing muscular exercise, since these stimuli call for increased combustion of carbohydrate

reserves. It should also be emphasized that following a 24 hr. fasting period, the blood sugar of thyroidectomized rats is 15 mg. per 100 ml. below that of the normals, a fact which we have confirmed in the course of many experiments performed in connexion with other problems. In spite of this lower initial value, the blood sugar of the damaged thyroidectomized rat is far above that of the normal. The blood sugar concentration was usually highest in those rats which appeared to be most severely damaged. The blood chlorides of the thyroidectomized rats, on the other hand, decrease even more markedly than those of the normals. A particularly interesting point in this connexion is the behaviour of the blood chlorides in the exercised group. Previous experiments have shown that whilst an alarm reaction produced by any damaging stimulus so far examined causes hypochloraemia, that elicited by excessive muscular exercise results in a pronounced rise in blood chlorides [Selye, 1938, 3]. It was found, however, that the same amount of exercise which increases the blood chlorides in the normal rat causes hypochloraemia in the adrenalectomized animal [Selye, 1938, 4]. A similar change in the response was also observed in the thyroidectomized rats of the present series, as will be seen from the data in Table I; the blood chlorides of the normals rose while those of the thyroidectomized rats fell under the influence of the same amount of muscular exercise.

Since prolonged fasting also elicits typical signs of the alarm reaction (hyperplasia of the adrenal cortex, loss of adrenaline from the medulla, atrophy of the thymus, lymph glands and spleen etc.), it seemed of interest to examine the effect of this stimulus on the blood sugar of thyroidectomized rats. 24 normal and 24 thyroidectomized rats comparable in every respect with those in the above-mentioned experiments were used to elucidate this point, one-third of them having been fasted for 24, another third for 48 and the remainder for 72 hr. The results of the blood sugar determinations in these groups are summarized in Table II and Fig. 1.

Table II

Fasting period hr.	Blood sugar, mg. per 100 ml. Normal	Thyroidectomized
24	**85** (80–91)	**70** (61–79)
48	**76** (69–81)	**94** (83–112)
72	**62** (46–69)	**65** (55–76)

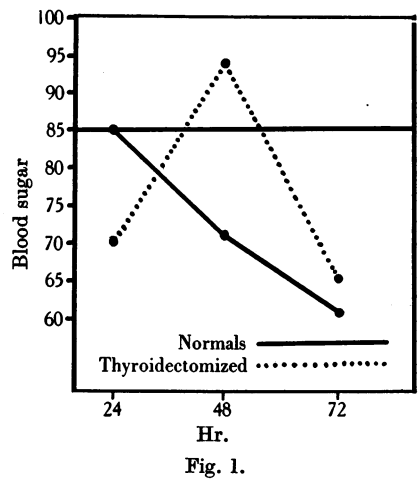

Fig. 1.

It will be seen, in conformity with what we said above, that after 24 hr. fasting, the blood sugar of the thyroidectomized animal is considerably below that of normal controls fasted for the same length of time. Yet after 48 hr. fasting, when morphological signs of the alarm reaction become evident, the blood sugar rises, not only above that of normal controls fasted for the same period, but even above that of normal animals fasted for 24 hr. only. At the end of 72 hr., however, the blood sugar values of both groups are very low and not significantly different from each other. We do not wish to speculate concerning

the fundamental disturbances in the carbohydrate metabolism caused by thyroidectomy on the basis of mere blood sugar determinations, since much more detailed metabolic studies would be required before one could discuss this question to advantage. Yet it seems obvious that the rise in blood sugar is elicited by the non-specific damage inflicted upon the animal and not by the specific action of any of the agents employed; otherwise we should not have obtained the same result with such different agents as formaldehyde, cold, muscular exercise and even fasting.

It is hardly within the scope of this communication to review the existing rather voluminous and contradictory literature on blood sugar changes following thyroidectomy. It is evident however that since a short period of fasting decreases, while a longer period of fasting or exposure to any other damaging agent increases, the blood sugar of the thyroidectomized animal, all experiments designed to study the specific effect of a certain agent on the blood sugar of a thyroidectomized animal necessarily had to be complicated by this particular change in the response to the non-specific harmful stimulus.

Summary

Thyroidectomized rats respond with hyperglycaemia to non-specific damaging agents which decrease the blood sugar of the normal rat.

While a 24 hr. fasting period causes more pronounced hypoglycaemia in thyroidectomized than in normal rats, 48 hr. of fasting actually increase the blood sugar of the thyroidectomized rat while in the normal it causes a further decline in blood sugar concentration.

Thyroidectomized rats exposed to non-specific damaging agents respond with a more pronounced decrease in blood chloride than normal animals. They show hypochloraemia even under the influence of excessive muscular exercise which raises the blood chloride of the normal rat.

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