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Blood Sugar and Chloride Changes in Adrenalectomized Rats During Adaptation to Various Stimuli.

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Previous experiments have shown that if rats are continuously exposed to a uniform damaging stimulus (a drug, exposure to cold, excessive muscular exercise, etc.) they first display the symptoms of the alarm reaction,[1-5] then they become resistant to this stimulus, but finally their acquired resistance is lost again. Since this reaction and all its accompanying symptoms are almost identical in every case, and relatively independent of the specific nature of the agent to which adaptation occurs, it has been regarded as the somatic expression of adaptation as such, irrespective of the type of adaptation which is acquired. The 3 stages of this "general adaptation syndrome" have been termed: 1. The acute stage, or stage of the alarm reaction. 2. The stage of resistance. 3. The stage of exhaustion.[6-8] As a working hypothesis, it has been assumed that every organism possesses a certain limited amount of adaptability or "adaptation energy." During the alarm reaction, this would be mobilized in some way and during the stage of resistance, it would be specifically directed against the damaging agent to which the organism is exposed. The final stage of exhaustion could then be regarded as due to the depletion of the available adaptation energy.

It has been found that during the alarm reaction, the blood sugar decreases, following a transitory rise, so that marked hypoglycemia ensues. During the resistant stage, the blood sugar increases above normal, while during the stage of exhaustion, a second period of hypoglycemia ensues. The total blood chlorides decrease during

1 Harlow, C. M., and Selye, H., PROC. SOC. EXP. BIOL. AND MED., 1937, **36**, 141.

2 Selye, Hans, *Brit. J. Exp. Path.*, 1936, **17**, 234.

3 Selye, H., Harlow, C. M., and Collip, J. B., *Endokrinologie*, 1936, **18**, 81.

4 Selye, Hans, *Lancet*, 1936, 1210.

5 Schacher, Josephine, Browne, J. S. L., and Selye, H., PROC. SOC. EXP. BIOL. AND MED., 1937, **36**, 488.

6 Selye, Hans, *Endocrinology*, 1937, **21**, 169.

7 Selye, Hans, *Nature*, 1938, **141**, 926.

8 Selye, Hans, *Nature*, 1936, **138**, 32.

the alarm reaction, rise above normal in the resistant stage and tend to decrease again during the stage of exhaustion.[9, 10]

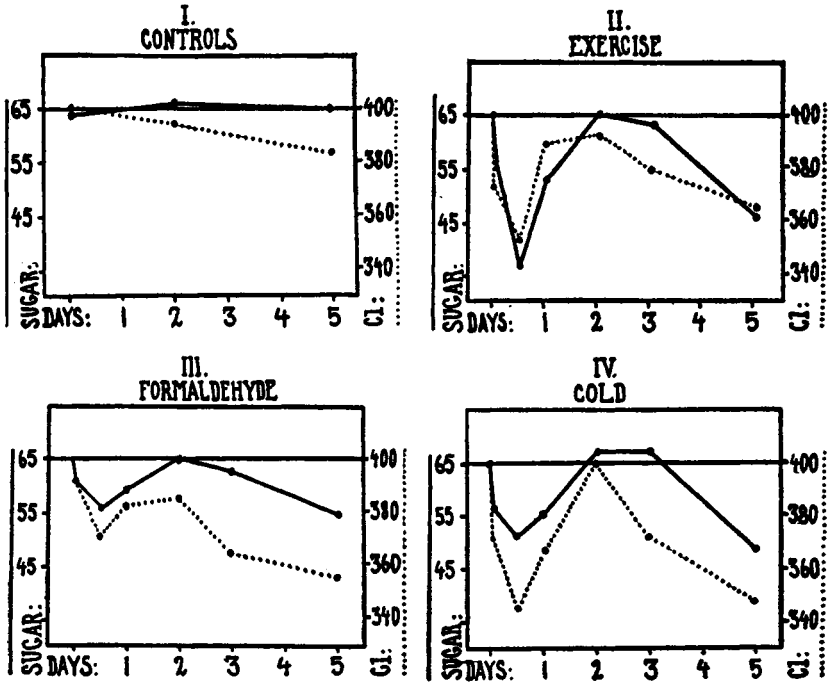
Since the adrenal glands show marked signs of increased activity during the alarm reaction and the stage of exhaustion, but not during the stage of resistance, and since the hypoglycemia and hypochloremia characteristic of the first and third stage of the adaptation syndrome are typical of adrenal insufficiency, it was felt that a condition of relative adrenal insufficiency exists during these two stages. It seemed of interest, therefore, to study the blood chemical changes during the adaptation syndrome in adrenalectomized animals.

Female hooded rats weighing between 125 and 140 g were used. Accessory adrenals are extremely rare in our colony and adrenalectomy is almost invariably fatal within a few weeks. The animals were fed a uniform purina diet and given tap water without the addition of NaCl throughout the experiment but food was withdrawn 24 hours before the determination. In every case, the animals were given a rest of 24 hours following adrenalectomy as it was found that the blood sugar reaches a constant level at this time and stays constant until insufficiency symptoms appear. Treatment was begun in all our experiments 24 hours after the operation, so that the first day of the experiment (day 1 on the graphs) corresponds to the second day after adrenalectomy. Graph I shows the average blood sugar (continuous line) and blood chloride (dotted line) values in 3 groups of rats, each consisting of 6 animals. The initial point corresponds to the beginning of treatment in the subsequent series, that is, it represents the values 24 hours after the operation. The second point is a control corresponding to the experimental animals on the second day and the last point on the fifth day of treatment. Since the average blood sugar (Shaffer, Hartmann and Somogyi method) was 64 in the first, 66 in the second and 65 mg/100 cc in the third group, it is obvious that no significant change occurs in untreated adrenalectomized rats between the first and the sixth day after the operation. The blood chlorides (Van Slyke method), on the other hand, showed a slight linear decrease from 401 to 384 mg %. Whole blood chlorides were determined in preference to plasma chlorides as signs of intravital hemolysis have occasionally been observed during the adaptation syndrome. The possible objection that whole blood chlorides are entirely dependent on the red cell volume can be refuted, since we

[9] Selye, Hans, Congress of Am. Physiol. Soc., Baltimore, March, 1938.

[10] Selye, Hans, *J. Gen. Physiol.*, 1938, in press.

found that although high hematocrit values are usually observed in animals in which the blood chlorides are low, there is no close correlation between these two values.



Our results are summarized in Graphs II, III, and IV. In order to avoid complicating our experiments with repeated fasting and bleeding, each rat was used for one determination only. The animals were bled in groups of 6 at 1, 12, and 24 hours and 2, 3, and 5 days respectively in each experiment. Each point on the graphs represents the average of 6 individual determinations on 6 rats. In the case of the first experiment (Graph II), the animals were adapted to muscular exercise, inasmuch as they were forced to run 3 times daily for a period of 15 minutes in revolving cages, having a diameter of 12 inches and turning at a speed of 15 revolutions per minute. In the second series, the animals were given 3 daily subcutaneous injections of 0.1 cc of a 2% formaldehyde solution, and in the third series they were exposed 3 times daily to a temperature of +1°C for one hour each time.

As can be seen from the graphs, the blood sugar and blood chloride curves run approximately parallel in all these experiments, reaching a first minimum level after 12 hours' treatment, a maxi-

mum after 48 hours, and a second minimum on the fifth day. It should also be mentioned that the appearance of the animals ran closely parallel with these blood chemical findings, inasmuch as the general condition was particularly bad during the first day, almost normal, in spite of continued treatment, on the second and third day, while on the fifth day, they appeared even more seriously damaged than on the first day.

Although no accurate blood volume determinations were made, it became obvious from the amount of blood obtained by cutting the carotid that the blood volume likewise parallels the blood sugar and chloride values and so does the volume of the spleen.

Both the experiments described in the literature and the present findings, we feel, are in agreement with the conception[11, 12] that the adrenals play an important rôle in the process of adaptation. Although adaptation is possible in the complete absence of adrenal tissue, it cannot be maintained for a prolonged period, that is to say, the stage of resistance of the general adaptation syndrome is particularly short. The simplest explanation of these phenomena would be that the organism uses so much of its "adaptation energy" for adaptation to life without the adrenals that little is left for resistance against damaging agents. As a result of this, the appearance of the signs of the alarm reaction and the stage of exhaustion (decrease in blood sugar, blood chlorides, blood volume, thermoregulating ability, muscular efficiency, general resistance, etc.), all of which are also known as characteristic signs of adrenal deprivation, may readily be accelerated in adrenalectomized rats by exposure to damaging agents.

Recently an increase in blood potassium has frequently been regarded as the primary change in adrenal insufficiency. Kendall and Ingle[13] showed, however, that while not pretreated adrenalectomized animals are extremely sensitive to potassium, they can acquire an adaptation to it if they are pretreated with gradually increasing doses. In this case, they will withstand large amounts of potassium although their blood potassium rises to a very high level. It is evident from these findings that the mere presence of large amounts of potassium in the blood cannot in itself be the cause of the adrenal insufficiency symptoms, but potassium intoxication, like any other condition of stress, is not tolerated well by adrenalectomized animals unless they have previously been adapted to it.

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11 Selye, Hans, *Science*, 1937, **85**, 247.

12 Selye, Hans, *Arch. Internat. de Pharm.-dynamie et de Thér.*, 1937, **55**, 431.

13 Kendall, E. C., and Ingle, D. J., *Science*, 1937, **86**, 18.

Summary and Conclusions. Experiments in the rat show that continuous exposure to non-specific damaging agents elicits a characteristic 3-stage general adaptation syndrome which is of considerably shorter duration in the adrenalectomized animal than in the normal. During the first stage, the blood chlorides and blood sugar are decreased; during the second stage, both these values return to normal in spite of continued treatment and the general condition of the animals is considerably improved. During the final third stage of exhaustion, hypoglycemia and hypochloremia reappear and general resistance decreases again. These experiments are in agreement with the conception that the primary cause of the adrenal insufficiency syndrome is a disturbance in the mechanism of adaptation and more particularly a decrease in the ability to maintain adaptation once it is acquired. The decrease in blood sugar, blood chlorides, blood volume, thermoregulating ability, muscular efficiency, etc., as well as the increase in blood potassium, are probably all simply the consequences of this primary disability.

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In vitro and *In vivo* Effect of Sulfanilamide on *Brucella abortus* and *Brucella suis.*

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In vitro Experiments. Various concentrations of para-aminobenzene sulfonamide* were added to dextrose broth, veal-infusion broth, and 10% serum-veal-infusion broth. The effect of the chemical on the growth-rates of *Br. abortus* and *Br. suis* was relatively the same regardless of the medium used.

The strains used had been under artificial cultivation for over 2 years but were still pathogenic for guinea pigs. The cultures grew quite well on veal-infusion agar and in the various liquid media mentioned above after incubation for 48 hours at 37°C under ordinary atmospheric conditions.

One-tenth cubic centimeter of a 1:100 dilution of a 48-hour broth culture was seeded into flasks containing 100 cc of broth; sterile

* The para-aminobenzene sulfonamide (prontylin) was kindly supplied by the Winthrop Chemical Co., New York.