engaging and interesting manner the theme "Science and Higher Learning." Following Dr. Caldwell's pleasing address, came the event of the evening, namely, the presidential address, on the topic, "Modern Medicine—the Crossroads of the Social and Physical Sciences," by President Charles A. Doan. This address is, we believe, a noteworthy contribution to scientific literature and should receive wide-spread publication.

One must be impressed by the wide range and variety of scientific subjects covered by the 159 papers presented in the several sectional meetings on Friday afternoon and on Saturday; the meeting of three sections, namely, Zoology (A), Medical Sciences (D) and Chemistry (H), ran into Saturday afternoon owing to the large number of papers.

WILLIAM H. ALEXANDER,
Secretary

SPECIAL ARTICLES

THE SIGNIFICANCE OF THE ADRENALS FOR ADAPTATION TO MINERAL METABOLISM

RECENTLY Selye[1] has discussed the significance of the adrenals for adaptation. Briefly stated, he found that the removal of the adrenals increased the severity of the reaction produced in rats after exposure to variable surrounding temperature, excessive muscular exercise and toxic doses of various drugs. He found that rats became adapted to these stimuli, and after subsequent removal of the adrenals a severe reaction did not occur as a result of such treatment or exposure. Selye was of the opinion that the essential changes take place in the peripheral tissues and that the adrenal gland is involved merely in increasing resistance.

He assumed that "the symptoms of the alarm reaction are mainly due to the liberation from the tissue of some toxic metabolite (possibly histamine or some physiologically similar compound)," and finally pointed out that the changes which have been noted after adrenalectomy, such as circulatory disturbances, hypoglycemia, changes in concentration of sodium and potassium in the blood serum, deficiency in phosphorylation or increase in nonprotein nitrogen, all of which have been considered to be primary changes, are, in fact, symptoms of, rather than the cause of, adrenal insufficiency.

We have studied the changes which occur after adrenalectomy and agree with the conclusions of Selye in so far as they pertain to the ability of the adrenalectomized animal to acquire a tolerance to withstand toxic agents which throw stress on the organism.

Somewhat more than a year ago we[2] reported the effect of potassium when administered to adrenalectomized dogs which were maintained without the use of cortin on a diet which contained large amounts of sodium chloride and sodium citrate. It was found that if a diet which contained only traces of potassium was given for several months the adrenalectomized dog became extraordinarily sensitive to potassium in the daily ration. As little as 500 mg would bring about a severe prostration closely simulating acute adrenal deficiency. This experiment has been repeated in many dogs, but we have found that if the amount of potassium in the daily food is slowly increased the animal acquires the ability to tolerate it and much larger amounts of potassium are required to bring about a toxic effect.

Similar results were obtained by sudden shifts in the content of sodium chloride in a diet which also contained small amounts of potassium. If the sodium chloride was suddenly reduced to a minimum, profound collapse would occur and death would follow within forty-eight hours.

During stimulation of muscles in adrenalectomized rats it has been observed over a period of two years that there was an increase of potassium in the blood serum and as failure approached the concentration of potassium would rise to between 30 and 40 mg per cent. The administration of thyroxine improved the efficiency of the muscle, but failure was brought about more promptly and in each case it was found that the increase in potassium was more precipitous in the presence of thyroxine.

The concentration of potassium in the serum of some adrenalectomized rats is between 40 and 50 mg per cent. These animals may be apparently in good condition. Other adrenalectomized rats have died with typical symptoms of insufficiency with a concentration of potassium in the blood serum which was 10 to 15 mg per cent. lower. The important factor appears to be whether the animal has been able to acquire a tolerance which will withstand these increased concentrations of potassium. If sufficient time is given adaptation can occur.

Evidence that the adrenal gland is directly involved in the defense reaction against thyroxine but only in a transient way is shown by the following experiment: A series of rats after unilateral enucleation of the adrenal were treated daily with 0.1 mg of thyroxine. There was a prompt and marked enlargement of the remaining adrenal gland. The increase in weight was more than 200 per cent. However, after six weeks a regression in the size of the gland occurred and even-

[1] Hans Selye, SCIENCE, 85: 247–248, March 5, 1937.
[2] W. D. Allers, H. W. Nilson and E. C. Kendall, *Proc. Staff Meet. Mayo Clinic*, 11: 283–288, April 29, 1936.

tually the weight returned to about normal, even though the administration of the same amount of thyroxine was continued. We interpret this as evidence that until the peripheral tissues could acquire a tolerance to the changes induced by thyroxine the adrenal gland was stimulated. After adaptation by the tissues the stimulus to the adrenal was removed.

We agree with Selye that the several changes observed after adrenalectomy are all symptoms of, rather than the primary cause of, the condition of insufficiency, but we do not agree that the primary change is an increase in histamine or similar substance. Rather it is the inability to resist sudden violent changes in the concentration or distribution of electrolytes, and we feel that potassium should be included as at least one of the "toxic metabolites" postulated by Selye.

Brief comment may be made on two points of Selye's note. Although he stressed the emergency action of the adrenal cortex it is now known that the cortex is essential for life with or without a stress on the animal. There is only one known treatment by which a normal condition can be maintained in an adrenalectomized animal without the use of cortin. This treatment is the use of an enormously high intake of sodium chloride with sodium citrate or bicarbonate and a minimal intake of potassium. It has not been shown that such treatment modifies in any way the detoxification of histamine or like substances.

In all the conditions given by Selye as suitable to produce the "alarm reaction" there is a rise in the concentration of potassium in the serum. Adaptation may not prevent a rise in the concentration of potassium, but it does permit the animal organism to withstand the effects of such an increase.

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THE DISAPPEARANCE OF INJECTED EPINEPHRINE IN THE ANIMAL BODY[1]

ALTHOUGH several hypotheses have been advanced by various authors to explain the rapid disappearance of epinephrine from the blood after injection, none of these theories have been proved adequate. The general belief held was that destruction occurred mainly in the liver. From the present work it appears that the liver can not assume the major rôle in the destruction of epinephrine, since ligation of the blood supply to that organ does not alter the pressor effect of the active principle. Similar experiments with the spleen and kidney indicated that these organs also play unimportant rôles. These findings are substantiated by the fact that nephrectomy does not retard the disappearance of the active principle from the blood.[2] Other theories have been advanced that the nerve endings in the walls of the blood vessels lose their sensitiveness under the influence of epinephrine and relax. However, the pressor effect may be maintained for a long time by a continuous flow of dilute epinephrine solution into the jugular vein. The blood can not actively destroy epinephrine during the short duration of the pressor effect, since it was found by the present workers that freshly drawn blood or a phosphate buffer (pH 7.3) containing 0.5 per cent. H_2O_2 oxidized only 25 per cent. of a solution of epinephrine (1:1000) when allowed to remain in contact for a period approximating the normal duration of physiological activity. Oxidized epinephrine has no effect on blood pressure.[3]

The period of existence of ephinephrine in the circulation has been studied by several investigators. It was believed that at least 75 per cent. of intravenously injected epinephrine disappeared within 15 seconds after injection and, when hypertension subsided, no trace of the drug could be further demonstrated.[4] Weiss and Harris[5] believed that epinephrine is still left in the circulation after the blood pressure returns to normal. These investigators showed this by allowing blood, from which epinephrine seemed to have disappeared, to flow into an artery which had been previously ligatured; a constriction was observed. This observation has been confirmed by the present workers in the following way: Several samples of blood were removed from the circulation of an anesthetized cat at various intervals during epinephrine hypertension, and the presence of the hormone tested on a contracting gut preparation. It was observed that epinephrine remained in the circulation in small quantities for three minutes after the blood pressure returned to normal.

A few experiments on the products of destruction of epinephrine in the animal body have been reported by other investigators. The results which were obtained could not be interpreted. Embden and Von Furth[6] fed epinephrine to a rabbit orally after sewing up the rectum, and afterwards isolated from its urine a yellow product. They were unable, however, to determine its structure or suggest any possible relation to the epinephrine molecule. In the present experiments,

[1] From the Departments of Chemistry and Physiology, University of Saskatchewan.

[2] M. A. Goldzieher, "The Adrenals." The Macmillan Company, 1929.

[3] S. S. Weinstein and R. J. Manning, *Proc. Soc. Exp. Biol. and Med.*, 32: 1096, 1935.

[4] M. A. Goldzieher, *loc. cit.*

[5] O. Weiss and J. Harris, *Pfluger's Archives*, 103: 510, 1904.

[6] E. Embden and O. Von Furth, *Beitr. Zeits. Chem. Physiol. Path.*, 421, 1904.