FUNCTIONS OF THE ADRENAL CORTEX.[1]

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Recent work carried out in our own and other laboratories has indicated certain functions of the adrenal cortex. We propose to briefly review some of these functions.

It has been known for over three-quarters of a century that the adrenal glands are essential for life; but not until 1916 did Wheeler and Vincent demonstrate that it was the cortex of these glands which was so vital.

ADDISON'S DISEASE.

The first really important contribution to the understanding of the function of the adrenal was the work of Thomas Addison, an English physician, who described the effects of disease in these organs. We now know that an absence of certain functions on the part of the cortex is responsible for these changes. Let us examine the picture from the earliest symptoms to the extreme prostration in late disease.

Asthenia.—Asthenia is the first to appear. This is so insidious that the patient may be unable to date its first appearance. He recognizes it only as an inability to perform accustomed tasks without fatigue, a condition which might be accounted for in many ways. Therefore, until the disease becomes farther advanced, it is usually ignored.

The asthenia involves the nervous system as indicated by the easy fatigue of the mental processes and the intolerance to stimuli. In the later stages general debility reduces activity to a minimum and a profound inertia develops, finally ending in prostration or coma. Other evidences of the involvement of the nervous system are insomnia, mental depression, failure of memory, poor judgment, lack of co-operation. Later there may be heightened motor activity and finally twitching and convulsions. If one administers an extract containing cortin, the vital hormone of the adrenal cortex, a patient in the late stages of Addison's disease responds with a disappearance of

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the symptoms in the reverse order. Coma is replaced by increased motor activity, twitching and marked myotatic response to stimuli. With the return of consciousness, there may be disorientation, mental irritability and lack of co-operation. Later a state of calm is reached in which the heightened irritability disappears, pain is relieved and the patient becomes more rational and sleeps much. Finally the stage of recovery is reached in which mental alertness returns and asthenia is reduced. The patient sleeps well and not abnormally long as before. He becomes co-operative and takes an interest in his surroundings. These improvements begin to appear usually within a few hours after injections start, and recovery is reached within two or three days.

Experiments with animals have proven conclusively the widespread involvement of the nervous system in the asthenia of cortin insufficiency. By using a reflex preparation of the rat, we have been able to show that cortin will prevent to a large extent the fatigue which develops after the removal of the adrenal glands. This fatigue or asthenia is found in the reflexes, the myoneural junction and the muscle.

The subjective evidence from patients, as already stated, indicated that cortin played a role in the function of the higher centers. Anderson, Liddell and Hartman have shown objectively that cortin can influence the higher centers. They found that sheep made neurotic by attempting to develop a fine discrimination in the conditioned reflexes were improved by the injection of cortin. Under its influence, spontaneous movement almost disappeared while the response to the conditioned stimulus more nearly approached the magnitude of that in normal sheep.

Hartman, Beck and Thorn have shown that cortin has a pharmacological effect on the nervous system. Cases in which fatigue was the outstanding complaint have sometimes shown improvement in the nervous symptoms with cortin injections. Mental irritability was decreased, sleep improved and resistance to fatigue, both mental and muscular, was increased.

Cortin affects the nervous system in a normal individual under certain conditions; namely, when he is below par from over-work or from an infection. Improvement may be reflected in better sleep, and an increased sense of well-being sometimes to the point of euphoria. There is no proof, however, that in these subjects there was a cortin insufficiency. It might be

explained as a pharmacological action—merely the effect of added cortin to that normally poured into the blood stream.

As already stated, muscle as well as the nervous system is involved in the asthenia of cortical insufficiency. A number of workers have observed that the metabolic activity of the muscle itself is greatly reduced.

Asthenia also involves the circulatory system. According to many authorities, however, this is not the first system to be affected. In the later stages the heart action may be feeble. This may be similar in origin to the weakness found in muscle. The blood vessels themselves may be at fault. The poor compensation to change in posture indicates as much. A subject in advanced Addison's disease not only may have a blood pressure lower than normal but when he changes from a reclining to a sitting or standing position the pressure may fall. This may be due to failure of the reflex mechanism. In the later stages, the fluid may be lost to the tissues and the blood may become concentrated. A number of workers as far back as 1927 have suggested that the function of the adrenal was to regulate the proportion of plasma. Viale and Bruno attributed the increase of permeability to the nervous system and to changes in the composition of the blood. We have found that removal of the adrenals causes an increase in the water content of many of the tissues, such as skin and liver. When adrenalectomized animals are exposed to heat, water shifts less readily from the reservoirs into the blood. Such animals suffer from heat more readily than animals treated with cortin.

Kidney.—The kidney becomes involved in adrenal insufficiency. In the late stages particularly this is true, and it seems to appear before the blood pressure is sufficiently low to account for the reduced function. In late stages of adrenal insufficiency the blood urea may become quite high.

Gastrointestinal instability.—Gastrointestinal instability is an outstanding symptom of Addison's disease. In some patients, it may occur quite early; in others, later. This may be accounted for in part by changes in the nervous system. In the later stages the circulation may be a factor. Not only the more sluggish circulation associated with hypotension but hemorrhages and ulcers which develop indicate as much. Cortin stops the nausea and vomiting, and brings about recovery of appetite. It likewise stops the hemorrhages which sometimes occur from the alimentary canal in late insufficiency in animals.

You perhaps begin to realize that the vital hormone seems to be essential for all the tissues.

Metabolism.—It was shown in 1922 by Aub, Forman, and Bright that removal of both adrenals in an animal reduced the metabolism. In 1928 we were able to show that metabolism could be maintained within normal limits with small amounts of cortin. On the other hand, it has been impossible to raise the metabolism above normal either in animals or in normal human beings by the injection of large amounts of cortin.

Effect of cold.—The need for cortin under stress is very well demonstrated on exposure to cold. Adrenalectomized rats divided into two groups, one injected with salt solution and the other with cortin, at first show no difference on exposure to cold, but very soon the animals without cortin begin to be seriously effected. A study of the heat production has shown us that although both those treated with cortin and those only injected with saline at first produce the extra heat required, later those without cortin are not only unable to produce the extra heat required, but they produce less than they did normally at ordinary temperatures. Thus, we find a marked fall in their body temperature and some of them even die. The failure to produce the heat may be accounted for by the fatigue of the reflexes which are involved in response to cold, and the failure of the muscle itself to carry on the increased activity in the long run.

Growth.—Cortin is essential for growth whether it be the natural development of young animals or the renewal of tissue in the healing of wounds. In adrenal insufficiency growth or the healing of wounds may stop. Upon the administration of adequate amounts of cortin, growth is resumed.

Resistance to toxins.—In adrenal insufficiency there is a lowered resistance to various toxins. That resistance can be raised by the injection of cortin.

RELATION TO VITAMINS.

Cortin appears to bear some relation to the utilization of vitamins B_1 and C. The use of extracts containing cortin was suggested by the well-known changes which occur in the cortex of the adrenal gland in deficiencies of these vitamins. These changes indicated a possibility of extra demand on the gland. When an extract containing cortin was given to guinea pigs on vitamin C deficient diets the onset of scurvy was delayed.

The extract was prepared in such a way that none of the vitamin which itself prevents scurvy could have been present. Injection of this extract also delayed the onset of nervous symptoms due to a deficiency of vitamin B_1 in the diet.

CHEMICAL CHANGES.

The various chemical changes which appear in adrenal insufficiency have been followed by different investigators with an attempt to find a change which is a key to the disturbance in function without success. The evidence seems to accumulate that cortin is a general tissue hormone.

CORTILACTIN.

We have been able to separate from cortical extract a substance which is necessary for lactation. Adrenalectomized mother rats treated with amounts of cortin much more adequate than that required to maintain weight and health does not enable them to raise litters of young. A second substance must be added. Young rats nursed by adrenalectomized mothers receiving only cortin begin to die off a few days after birth, with 10 per cent or less reaching the stage of weaning. Adrenalectomized mothers, however, furnished with this new hormone in addition to cortin are able to raise a considerable portion of their litters. This new hormone which is essential for lactation has been named cortilactin.

We may say in conclusion that there is now positive evidence that the adrenal cortex produces two hormones: one, cortin, the vital hormone which seems to serve as a general tissue hormone; and, two, cortilactin, which is necessary for milk production.

Psychology, Genetics, and Intelligence.

This volume is an attempt to gather within a single cover the voluminous material on mental testing, and the relation of intelligence to its twin causes, heredity and environment. The book appears to be a very complete summary of the literature, including a considerable number of references with which the casual student would be unfamiliar, and some which even the specialist might readily have missed. The most valuable inclusions in the book, however, are the critical comments on the abstracted material, which are keenly analytical and are constructively presented. No more timely book in the field of human biology could well be imagined.—L. H. S.

Heredity and Environment, by Gladys C. Schwesinger. ix+484 pp. New York, The Macmillan Company, 1933.

The adrenal cortex, as a component of the hypothalamic-pituitary-adrenal (HPA) axis, secretes steroid hormones important for the regulation of the long-term stress response, blood pressure and blood volume, nutrient uptake and storage, fluid and electrolyte balance, and inflammation. The HPA axis involves the stimulation of hormone release of adrenocorticotropic hormone (ACTH) from the pituitary by the hypothalamus. ACTH then stimulates the adrenal cortex to produce the hormone cortisol.Â One of the major functions of the adrenal gland is to respond to stress. Stress can be either physical or psychological or both. Physical stresses include exposing the body to injury, walking outside in cold and wet conditions without a coat on, or malnutrition. The functions are: 1. Adrenal Cortex 2. Adrenal Androgens 3. Aldosterone 4. Endocrine Function of Adrenal Medulla. Function # 1. Adrenal Cortex: It is divisible into three different layers, from outwards within will be: i. Zona glomerulosa.Â This brings about the depression of the hypothalamopituitary-adrenal axis function. If Cortisol is withdrawn suddenly, the axis cannot get revived immediately and patient may develop a crisis. If Cortisol is withdrawn slowly and steadily (tapering dose), more time is provided for the regaining of the activity of the hypothalamopituitary-adrenal axis and the restoration of the endogenous secretion of Cortisol can start once again (Fig. 6.24). Aminoglutethimide is a potent inhibitor of desmolase reaction and thereby decreases all adrenal steroid synthesis.