THE ADRENAL CORTEX ITS SUPPOSED FUNCTIONS AND SUGGESTED USES OF CORTICAL EXTRACTS*

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The adrenal gland has been the object of intensive research since Thomas Addison, in 1855, first disclosed its relation to a comparatively uncommon disease, to which his name has been attached. The massive volume of literature on this relatively small paired gland is scarcely commensurate with our factual knowledge of its function in normal physiological processes (Grollman, 1936). In spite of its smallness the adrenal gland must exert a vital influence in the organism, for the surgical removal of both glands soon leads to a complete breakdown of normal function in most of the organs and tissues of the body, rapidly terminating in death.

Each adrenal is situated in the posterior part of the abdomen, overriding the upper pole of the kidney like a "triangular cocked hat with rounded corners." The mammalian adrenal is a compound organ formed by the union of two originally separate tissues—namely, the cortex and the medulla. The cortex, which anatomically and physiologically constitutes the chief part of the gland, is usually of a deep yellow colour, due to the presence of lipids, while the medulla is small and pulpy and of a dark reddish colour due to the presence of blood.

In man and the anthropoid apes the medulla is a post-natal development, being represented at birth by a small strip of undifferentiated tissue only. The cortex, on the contrary, is the whole pre-natal adrenal, which at birth is one-third the size of the kidney. Shortly after birth the foetal adrenal cortex begins to involute, being gradually replaced (the process is not complete until the end of the third year of life) by a permanent cortex and medulla. (In my opinion this period of the "switch over" from the old cortex to the new is a potentially dangerous period in the life of the human infant: a too rapid involution of the foetal cortex and a too slow development of the "permanent" cortex may constitute a hiatus in adequate cortical function which leads to severe symptoms or death.)

Although some variation exists in the cellular arrangement of the cortex in different species, a more or less general pattern is present according to which the cortex is divided into three zones: the glomerulosa, the fasciculata, and the reticularis. The first-named is the layer immediately beneath the capsule. Time will not permit a more detailed description of the anatomy and histology of the adrenal gland.

The Medulla

The function of the adrenal medulla has been the subject of much study and speculation since Oliver and Schafer first directed attention in 1894 to the remarkable rise in blood pressure which follows the subcutaneous injection of a medullary extract. To-day the pharmacodynamic effects of adrenaline are well known, but little has been definitely proved in regard to the medulla's normal physiological function. Whatever that function may be it certainly is not an indispensable factor in animal biochemistry, because the adrenalectomized animal can be maintained indefinitely in good health with a normal func-

tion provided an optimum amount of a potent cortical extract be daily injected or ingested. At post-mortem examination there is seldom any hypertrophy of accessory chromaffin bodies if such be present.

The Cortex

Since investigators have failed to demonstrate any essential function of the adrenal medulla interest has gradually shifted to the cortex, as it appears to be the really important and essential part of the adrenal gland. The indispensability of the cortex in the maintenance of the functional integrity of the organism has been conclusively and absolutely proved in oft-repeated adrenalectomies in animals and by clinical experience in cases of Addison's disease and established cases of adrenal haemorrhage. There cannot now be any doubt that the cortical cells of the adrenal gland elaborate a secretion, or secretions, of vital necessity to the continuity of life.

The mechanism by which this hormone exerts its effect is still unproved. However, a great advance in the study of cortical function has been made by the discovery of methods of extraction of the hormone, or hormones, in sufficiently pure and potent form to permit their application to experimental and clinical research. Research into the effects of adrenalectomy on laboratory animals has done much to suggest rational hypotheses in answer to the question of cortico-adrenal function.

Chronic Adrenal Insufficiency

As early as 1856 Brown-Séquard, inspired by Addison's classical description of the clinical picture of chronic adrenal insufficiency (Addison's disease), attempted to reproduce the Addisonian syndrome in animals. The rapidly fatal outcome, the animals surviving only a matter of hours, led him to conclude that the adrenals were indispensable to life. In recent years it has been frequently demonstrated that, with good surgical technique and an operation in two stages, complete adrenalectomy can be performed on all the common laboratory animals with recovery from the usually immediate lethal effects of the operation. However, in two, three, or four days dogs show the early signs of cortical insufficiency, and unless they are supplied with potent cortical hormone (cortin) they die in six or seven days. Recently it has been shown that the ingestion of large quantities of sodium chloride will prolong the life of the adrenalectomized animal.

When a two-stage adrenalectomy has been completed on a dog and the animal recovers from the effects of the anaesthetic and the surgical procedure, one notices few or no abnormal signs for several days, the length of this symptom-free period varying to a considerable extent with the animal's diet. Such an adrenalectomized animal, like Dragstedt's thyroparathyroidectomized dogs (Dragstedt, 1923), is very vulnerable to a meat diet, and its post-operative life can be markedly shortened by such a meat-rich diet.

The first unusual signs seen in the adrenalectomized dog are anorexia and listlessness. The animal becomes more apathetic and vomits a great deal. Usually diarrhoea is present, which soon is very bloody. Muscular movements become slow and uncertain, and weakness of the hind legs may cause the gait to be very unsteady. Eventually the animal lies prostrate. As insufficiency progresses the body temperature falls in warm-blooded animals, and the skin becomes cold and the mucosae turn pale. Muscular twitches or convulsions may appear. Respiration is first rapid and then slow. There is a terminal anuria. Death

* Read before a meeting of the Osler Society.

occurs in coma, usually with respiratory failure while the heart is still feebly beating (Grollman, 1936). These objective signs of acute cortico-adrenal insufficiency are summarized graphically in Fig. 1.

Marked anhydraemia is a constant and striking feature of these adrenalectomized animals, and is due to the great loss of water and sodium chloride by way of the kidneys, owing possibly to impaired powers of resorption in the kidney tubules. This loss of water and electrolytes from the tissues and blood is such a marked feature of acute cortical insufficiency that some observers consider that the

FIG. 1.

FIG. 2.

prime function of the adrenal cortex is the maintenance of salt and water balance. It is certainly true that the quantity of cortin necessary to maintain life in an adrenalectomized animal or in a person with Addison's disease can be materially decreased by simply increasing the sodium chloride intake. In acute cortical insufficiency there is inevitably a pronounced and constant change in blood chemistry. A rise in non-protein nitrogen occurs early. Later there is a rise in cholesterol and potassium* and a fall in chlorides, sodium, and glucose. The pH is that of a severe acidosis. These outstanding features of the blood chemistry are graphically represented in Fig. 2.

* Recent work by Zwemer would indicate that inefficient potassium elimination is a potent factor in the origin of the classical signs of acute cortico-adrenal insufficiency.

Anatomical Changes Found Post Mortem

In comparison with the severity of the *in vivo* signs of acute cortico-adrenal insufficiency few anatomical changes are found on post-mortem examination. The most constant of these findings are (Banting and Gairns, 1926): (1) an enlarged thymus gland; (2) enlarged mesenteric lymphatic glands; (3) degeneration and necrosis of the liver; (4) degenerative changes in the kidneys; (5) congestion and ulceration of the gastro-intestinal tract. When a chronic or partial cortico-adrenal insufficiency is produced in dogs after the method of Crowe and Wislowski (1914) only the following findings were noted after the accidental or deliberate death of the dogs: (1) enlargement of the thymus gland; (2) enlargement of the mesenteric lymphatic glands; (3) hypertrophy of Peyer's patches; (4) visible tonsils (a rarity in a dog).

(It surely must be more than a coincidence that the above findings are the most constant and diagnostic found in infants in Vancouver who have died suddenly and for no apparent reason. In these cases—and there is on the average one a month in this city—the pathologist's diagnosis is invariably "status lymphaticus.")

Function of the Adrenal Cortex

The question naturally arises, What is the function of the adrenal cortex? While many aspects of cortical function are still obscure, experimental research during the past decade has thrown much light on this vital and hitherto little understood endocrine gland. The cortex constitutes the whole adrenal gland in foetal life. The fact that at birth it is one-third the size of the kidney (the adult cortex being one-fortieth) is an indication of its importance in the pre-natal development of the child. Just what that role is we can at present only surmise. At birth the foetal type of cortex (and it is histologically different from the post-natal cortex) begins to involute and the new cortex and medulla to develop. The post-natal development of the cortex is not complete until the end of the third year, according to Grollman. The question of the function of the "permanent" adrenal cortex is now our immediate concern.

Out of the extensive experimentation of the past decade there emerges evidence which suggests that the chief functions of the adrenal cortex are threefold.

1. To maintain normal blood volume by control of excretion and resorption (in the kidney tubules) of electrolytes and water.
2. To act as a general tissue and cell catalyst, particularly in regard to hepatic function.
3. To play an important part in carbohydrate metabolism, particularly in respect to glycconeogenesis.

There is also considerable evidence to indicate that the adrenal cortex is closely related to urea formation, to vitamin C storage, to cholesterol metabolism, and to resistance to infection and toxæmia. Some observers believe that it is a factor in the normal healing of wounds and callus formation. Possibly it increases the production of leucocytes and heightens their phagocytic activity.

From the mere point of view of mathematical probability it is entirely reasonable to assume that many clinical syndromes whose aetiology is at present unknown are due to cortico-adrenal dysfunction or may be influenced favourably by increased cortico-adrenal function or the presence of cortin in increased quantities. In view of the freely admitted limitations of post-mortem study of the adrenals (due to rapid autolysis) it would seem that the

effective elucidation and recognition of new clinical forms of cortico-adrenal hypofunction must be initiated and controlled by open-minded clinicians imbued with the spirit of clinical research so well exemplified by the distinguished career of the late Sir James Mackenzie and so well described by Sir Thomas Lewis (1930).

Subjects for Research

In this spirit of clinical research may I suggest that the members of the Osler Society give their open-minded and earnest consideration to the following entities as worthy of the clinical trial of cortico-adrenal therapy:

- I. The so-called "thymic syndrome" (status lymphaticus).
- II. Cyclic vomiting.
- III. Infantile diarrhoea of uncertain aetiology.
- IV. The vomiting of pregnancy.
- V. Severe infections.
- VI. Severe burns.

I. The "Thymic Syndrome"

Paediatricians practising in the Pacific North-West are well aware of the existence of a real clinical syndrome of uncertain aetiology which, like the Angel of Death, may cause the death of apparently healthy infants as they lie in their cribs presumably asleep. Post-mortem examination in these cases (I quote from the data available from a series of forty-seven such unexpected fatalities in Vancouver in the eight-year period from January, 1925, to October, 1932) reveals little anatomical pathology. Usually the thymus gland is enlarged to a varying degree (assuming the normal maximum weight of this gland in Vancouver children to be similar to that found by Anderson and Cameron (1927) in Glasgow—namely, 15 grammes). The mesenteric lymphatic glands are almost invariably enlarged (tuberculosis being excluded). Petechial haemorrhages are often seen in the serous membranes of the heart and lungs. Peyer's patches are usually enlarged. In such cases the diagnosis of our pathologists (Drs. A. W. Hunter and H. H. Pitts) is invariably "status lymphaticus."

In 1931, before the International Congress of Anaesthetists in New York, and a year or so later before the Vancouver Medical Association, 1933, I presented data in support of the hypothesis that these infants die because of an acute exacerbation of a temporary cortico-adrenal insufficiency, possibly predisposed by thyroid hypofunction. Time will not permit even a summary of these data here. Suffice it to say that the passage of time and the clinical trials of this therapy by my colleague Dr. R. P. Kinsman have made me still more confident of the soundness of the original hypothesis. In brief, I believe that time and repeated therapeutic trials will eventually demonstrate that status lymphaticus and the so-called "thymic syndrome" are essentially the same, being an endocrinopathy primarily involving the adrenal cortex. The final proof (or disproof) of this hypothesis (or some other yet to be formulated) is the responsibility of paediatricians, who from time to time are called to treat patients for "attacks" of this mysterious and often fatal syndrome. The "attacks" referred to are often termed "breath-holding spells," and are generally accepted as evidence of the presence of the "thymic syndrome." In my opinion these syndromes are clinical manifestations of status lymphaticus, differing only in degree from the tragic cases of sudden death referred to in the opening paragraph. These little patients should be given, both for clinical research and for therapeutic purposes, cortical extract in appropriate dosage. Dr. R. P. Kinsman has found $1\frac{1}{2}$ grains of Armour's desiccated extract an effective daily dose. Certainly one need have

no fear of giving too much. If, as I hopefully expect, this therapy proves valuable, then real progress will have been made in the elucidation of one of the most tragic and puzzling problems of Pacific North-West medicine. Inasmuch as status lymphaticus snuffs out life in its early stages it is possibly of greater importance than the more widely published problems of tuberculosis and carcinoma.

II. Cyclic Vomiting

I am indebted to Dr. Frederic Fenger of Chicago for the suggestion that cyclic vomiting may possibly be related to adrenal cortical function. The usual teaching in regard to this well-known clinical paediatric problem has been to the effect that the causative factor is ketonaemia due to incomplete oxidation of the fatty elements in the child's diet. The praiseworthy clinical researches of Dods (1935) have definitely shown that ketonaemia and ketonuria are concomitant phenomena and not aetiological factors in cyclic vomiting. The real cause still remains obscure. However, the prodromal symptoms of languor (even prostration), headache, and pallor which precede the vomiting attack, and the vomiting itself which features the syndrome, all indicate a severe metabolic disturbance that suggests cortico-adrenal insufficiency as the most likely basic endocrinopathy. The adequate therapeutic use of a potent liquid extract of the adrenal cortex would do no harm and might prove valuable.

III. Infantile Diarrhoea of Uncertain Aetiology

Severe diarrhoea is an invariable sequel of complete adrenalectomy in dogs. May it not be possible that in some cases of diarrhoea in infants insufficiency of cortico-adrenal function may be the aetiological factor?

IV. The Vomiting of Pregnancy

In suggesting the use of adrenal cortex therapy for this universally common clinical entity, so common that some consider it "physiological," I feel that here at least I am on firm ground. With the co-operation of Vancouver colleagues, in general practice and specializing in obstetrics, I recently (1934) reviewed 200 consecutive cases of hyperemesis gravidarum that had been treated with adrenal cortex, with undoubted success in 85 per cent. of cases. This series is of interest also for the reason that it shows that the oral use of adrenal cortex is effective.

V. Severe Infections

As Grollman (1936a) points out, in patients who have died as a result of a severe acute bacterial toxæmia focal necroses have often been observed in the adrenal cortices. Cloudy swelling and oedema of the cortical cells, congestion, and small focal haemorrhages are also common findings. The question arises, To what extent are the symptoms of asthenia, anorexia, vomiting, etc., that characterize the course of the clinical condition, and which we account for by "toxæmia," the results of the coexisting cortical insufficiency? It is well known that adrenalectomized animals are much more vulnerable to toxins of all kinds than are their litter-mate controls. Accordingly it is reasonable to postulate for purposes of clinical research that the fatal outcome in cases of severe bacterial infection is probably due, in part at least, to acute adrenal insufficiency caused by the bacterial toxæmia.

VI. Severe Burns

According to Grollman (1936b), in uncomplicated cases of superficial burns characteristic changes occur in the

adrenals. They become swollen and deep red. On section extensive haemorrhages may be found. The cells are pale and swollen, and are in a process of hydropic degeneration. While it is now generally supposed that the absorption of toxins from the injured skin (histamine shock) is the prime factor in the fatal outcome, the marked pathological changes found in the adrenal cortices suggest that acute cortico-adrenal insufficiency (secondary to the above-mentioned pathological changes in the cortex) plays a prominent part in these deaths. It is quite within the bounds of reason to expect that the generous administration of cortin in such cases would prevent an otherwise inevitable fatality.

Summary

In summary may I recall to you that we have briefly reviewed the probable functions of the adrenal cortex (it being the "vital" part of the adrenal gland), and have suggested the use of a potent cortical extract in certain clinical entities, including the so-called "thymic syndrome," cyclic vomiting, certain cases of infantile diarrhoea, the vomiting of pregnancy, severe infections, and severe burns. May I suggest in conclusion that it is only by applying clinically the findings of the experimental physiologist that real progress can be made in the solution of our medical problems. Such experimental clinical research can readily be made compatible with the best interests of the patient.

**** An account of the discussion on this paper will be found at page 1221.**

[Figs. 1 and 2 are reproduced from *The Adrenals*, by A. Grollman (The Williams and Wilkins Company, Baltimore, 1936).]

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A congress of the International Union for the Study of Population Problems will be held in Paris from July 28 to 31 under the presidency of Professor Adolphe Landry. A large number of papers will be read upon a diversity of populational, biometric, and demographic subjects. A 50 per cent. reduction on the French railways to and from Paris will be accorded to members attending and their families, with free entrance to the Paris Exhibition during the Congress. The British National Committee of the Union is the British Population Society, founded in 1928 to develop in Great Britain and Northern Ireland scientific studies pertaining to problems of population. Membership of this society is open to all those whose scientific or other special qualification will enable them to forward the objects of the society, and carries with it membership of the International Population Union with the right to attend and speak at meetings of the Union and to contribute papers upon populational subjects. Associate membership is open to all interested in populational problems, and includes the right to attend the International Congress. The official journal of the Union is *Population*. Full particulars of the British Population Society may be obtained from the hon. secretary, Dr. C. Conyers Morrell, D.P.H., Mudeford House, Mudeford, Christchurch, Hants.

CHRONIC AGRANULOCYTOSIS SUCCESSFULLY TREATED WITH LIVER

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A pastrycook aged 25 was admitted to St. Bartholomew's Hospital on May 22, 1936, for dimness of vision. He was quite well and healthy, with normal eyesight, till five years before, when his eyes became inflamed and his vision impaired. He was partially relieved of symptoms for the time being by hospital treatment, but attacks recurred and alternated with intervals of relief. Both eyes were affected by chronic iridocyclitis, of which investigation failed to reveal the cause. In the course of these investigations he was found to have a very low white blood count. It was naturally wondered whether the leucopenia was in any way connected with the iridocyclitis, its origin or its treatment, and whether restoration of the white count to normal would improve the condition of the eyes.

Case History

Apart from the iridocyclitis the only abnormality was a shallow ulcer on the inner aspect of the cheek. The ulcer was first noticed by the patient about nine months before, and it appeared and disappeared at irregular intervals without any treatment. The family and personal history were good, and there was no history of allergy in the patient or his relatives. Nine months ago he took a proprietary tonic which then contained amidopyrine, of which he probably had some 30 grains in all. About the same time he had one or more injections of gold for the eyes without any benefit.

The blood count on May 20, 1936, was: red cells, 6,140,000 per c.mm.; haemoglobin, 102 per cent.; platelets, 250,000; white cells, 3,600, of which 1,188 were polymorphonuclear cells. Two days later the white blood count was 2,800, of which 812 were polymorphonuclear cells. The differential count on the bone marrow obtained by sternal puncture on June 4, 1936, was as follows:

Myeloblasts	3%	Eosinophils	2%
Premyelocytes	3%	Lymphocytes	4%
Myelocytes	32%	Monocytes	0.5%
Metamyelocytes	10%	Reticulum cells	0.5%
Staff neutrophils	13%	Macroblasts	11%
Segmented neutrophils	1%	Erythroblasts	20%
Basophils	0%		

The most notable feature of the marrow smear is the excessive proportion of myelocytes, apparently due to a failure in their development into polymorphonuclear cells. Maturation has been arrested, though at a later stage than in a previous case, in which the cells had not advanced beyond the myeloblast level (Witts, 1936). The myeloid cells, especially the myelocytes, seemed more fragile and more easily "smudged" than in health; their granulation was scanty and often lacked uniformity. The nucleated red cells were less mature than in the normal marrow smear and there were few pyknotic nuclei. In view of the changes in the erythropoietic tissue and of the subsequent response to liver, it is interesting that the fractional test meal revealed achlorhydria; unfortunately the effect of histamine was not observed.

Failure with Nucleotide Therapy

It was concluded that the patient was suffering from a chronic form of agranulocytosis, possibly the effect of