ENDOCRINES IN THEORY AND PRACTICE

This article is one of a series on Endocrinology contributed by invitation

PHYSIOLOGY OF THE ADRENAL GLAND

BY

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The adrenal glands consist of two components, an outer cortex and an inner medulla, the former being derived from the mesoblastic urogenital ridge and the latter from the neural ectoderm in common with the sympathetic neurones. The main nerve supply is from the splanchnics, and the neural impulse is transmitted (somewhat paradoxically) by liberation of acetylcholine at the terminal ganglia (Feldberg and others). In the elasmobranch fishes—for example, shark—the cortex (interrenal body), and medulla (para-aortic chromaffin bodies) are quite separate; in reptiles they are in more intimate association; but it is only in the mammals that the cortex surrounds the enclosed medulla.

From without inwards the cortex consists of three zones—glomerulosa, fasciculata, and reticulosa. The inner portion of the latter is known as the pigment zone, the cells having an affinity for osmic acid. This may represent the involuted androgenic zone, which is concerned with sex and is very large in the foetus. The cortex is rich in lipoid-containing double refractile crystals. It secretes a hormone, cortin, which is essential for life. The cells of the medulla, as those of the para-aortic chromaffin bodies, have an affinity for chromic acid. The medulla secretes adrenaline, but is not essential for life.

Adrenaline

The essential secretory product of the medulla has the formula $C_9H_{13}O_3N$, dioxyphenylethanolmethylamine, and is related to tyrosine and the intermediate product dioxyphenylalanine (dopa). It is prepared by extraction of the mixed glands with dilute acids, removal of proteins by alcohol precipitation, evaporation of the alcohol, and precipitation of the free base by ammonia. It can also be obtained from the aortic preganglion of the foetus (Elliott) and from the para-aortic accessory chromophil tissue of dogs, guinea-pigs, and rats (Vincent and others). Nevertheless these tissues do not hypertrophy after adrenalectomy.

Adrenaline can be assayed colorimetrically (Folin, Cannon, and Denis) by its power to reduce tungstic acid to the blue oxide. The following biological methods are more sensitive and more specific, and are dependent upon the sympathomimetic action of adrenaline: (1) inhibition of an intestinal strip suspended in saline; (2) inhibition of a muscle strip of the uterus of non-pregnant cat; (3) vasopressor response in a spinal animal; (4) dilatation of denervated iris; (5) acceleration of denervated heart, etc. The rate of secretion of adrenaline was found by Stewart and Rogoff to be 0.00025 mg. per kilo of body weight per minute, using the "cava-pocket" method: veins entering the vena cava, excepting the adrenal veins, are clamped, so that a pocket can be formed by occluding the cava beneath the diaphragm and below the entrance of the adrenal veins. To obviate the influence of general anaesthesia Satake and others produced anaesthesia by cutting the dorsal roots T9 to L3, and some months later took specimens of blood by syringe directly

from the adrenal vein; biological assay then showed the output to be only 0.00007 mg. per kilo of body weight per minute.

Adrenaline acts after section of the sympathetic nerves but not after paralysis of the terminal fibres by apocodeine or ergotoxine. Its site of action is therefore the myo-neural junction (Langley). Previous nerve section, novocain, and thyroxine augment the sympathomimetic action of adrenaline. Ergotoxine paralyzes vasoconstrictor fibres, and after its use adrenaline has a vasodilator and vasodepressor action instead of the normal vasoconstrictor and vasopressor action. Adrenaline produces acceleration and irregularity (with extrasystoles) of the heart with fatal dilatation. Particularly after chloroform is there a tendency to ventricular fibrillation. In moderate doses there is an increase in pulse rate, blood pressure, and cardiac output. The cerebral and pulmonary arteries may be slightly constricted but the coronaries are dilated. Respiration tends to become shallow and irregular, with periods of apnoea. The bronchioles are dilated, especially if previously in a state of spasm. The movements of the stomach are inhibited by injections of adrenaline, but when given by mouth jejunal colic occurs. Movements of the human pregnant uterus are inhibited (Bourne and Burn), but the cat's uterus is contracted if pregnant, relaxed if not. In the guinea-pig dilatation of the pupil and exophthalmos may result from adrenaline, but this effect is much more marked with ephedrine. This is also true of the pilomotor action. Sweating may be obscured by the accompanying vasoconstriction. The temperature and basal metabolic rate are increased. Coagulation time is diminished. Adrenaline produces contraction of smooth muscle—for example, spleen—and has an important influence on haemopoietic centres or depots. Thus an injection is followed by increase in the number of red cells, lymphocytes, leucocytes, and platelets.

Adrenaline and Carbohydrate Metabolism

Adrenaline accelerates glycogenolysis in both liver and muscle, thus increasing the blood sugar and the blood lactic acid. After hepatectomy only the lactic acid is increased. The hyperglycaemia and glycosuria that result from puncture of the floor of the fourth ventricle (Claude Bernard) are partly due to the release of adrenaline and partly to direct nervous transmission of the impulse to the liver. Denervation of the adrenals or cauterization of the medulla will diminish the severity of diabetes mellitus resulting from pancreatectomy. By cross-circulation experiments, acceleration of the denervated heart, increase of erythrocytes and leucocytes, and other methods, it can be proved that adrenaline is secreted during insulin hypoglycaemia. That there is normally an antagonism or balance between adrenaline and insulin secretion is further suggested by Cori's observation that the adrenaline effects on carbohydrate metabolism could all be obtained if adrenaline was injected at a rate and concentration no greater than that at which it is secreted in the anaesthetized animal.

Adrenaline and Cannon's Emergency Theory

Cannon has produced evidence (not undisputed) that "afferent stimulation, asphyxia, and emotional excitement cause a quick and abundant secretion of adrenaline." This would aid the organism in an emergency by in-

creasing the cardiac output, increasing metabolism, raising the blood-sugar concentration, diminishing fatigability of muscles, raising the oxygen-carrying power of the blood by increasing haemoglobin and red cells, and by diminishing the coagulation time of the blood. Such reactions might aid the primitive animal in flight or combat. Cannon and collaborators also showed, however, that neither the medulla nor the sympathetic nervous system was essential to life. Animals deprived of them were sensitive to cold, and their rage was not associated with hyperglycaemia or erection of hair.

Adrenalectomy

Since unilateral adrenalectomy, with destruction of the medulla of the remaining gland, has little or no effect on the health of the animal, a study of the results of bilateral adrenalectomy should give some indication of the function of the cortex. This supposition is further supported by the fact that adrenaline injections cannot influence the fatal outcome of the latter operation, whereas cortical extract can.

In some species, such as the cat and the dog, the operation is almost invariably fatal and usually within a week. In others, such as the rat, accessory suprarenals may prolong survival, sometimes indefinitely. With correct technique, including the removal of the periadrenal fat, there is nevertheless a 100 per cent. mortality in most strains if young rats weighing less than 100 grammes are used. The results are the same for one-stage or two-stage operations, but the latter may minimize acute fatalities from surgical trauma.

In the case of rats recovery from the operation may appear complete within one or two days, and superficially the operated rats may appear no different from the controls; nevertheless sudden collapse and death may take place within a few hours. Where the survival period is more prolonged, either spontaneously or with minute doses of cortical extract, the more definite results of cortical insufficiency can be studied. A loss of appetite and failure to gain weight adequately are early signs. If control rats are given daily an amount of food equal to that eaten by their paired adrenalectomized litter mates it is seen that with the latter there is also a deficient gain of weight per gramme of food intake (Levy Simpson, Dennison, and Korenchevsky). The animals are inert and apathetic, but hyperexcitable when interfered with. Their muscle tone is poor, and they are unable to climb the observer's hand when suspended. The fur is ruffled, dry, and lustreless. Infection of the eye and eyelids may be present. Diarrhoea and bloody stools occasionally occur, but are rare features except in the terminal phases. In the absence of cortin there is a susceptibility to nasal and respiratory affections. The rectal temperature is often subnormal, and even when normal falls very rapidly on exposure to cold, which the animals are unable to withstand. At necropsy there is a striking absence of abdominal fat, a hyperplasia of the thymus and lymphatic nodes, congestion of the viscera, haemorrhagic erosions of the gastro-intestinal tract, and other changes. The blood is thick and coagulation time diminished. In more chronic insufficiency in cats and dogs there may be a slaty-grey pigmentation of the skin and a chocolate-brown coloration of subcutaneous fat.

The Cortex and Carbohydrate Metabolism

The blood sugar after adrenalectomy falls acutely just before death and hypoglycaemic convulsions may occur. Apart from this terminal drop it may or may not be low, according to the species of animal. There is, how-

ever, a profound disturbance of carbohydrate metabolism, as shown by a decrease in muscle and liver glycogen, the latter being especially severe. Probably for this reason excitement, fright, or adrenaline will not produce the rise of blood sugar that occurs in normal animals. The adrenalectomized animals are also unable to synthesize glucose or lactic acid into hepatic glycogen. There is a high concentration of lactic acid in the blood. All these changes are corrected by a cortical extract. Britton and Silvette think that the regulation of carbohydrate metabolism is the most important function of the adrenal cortex.

The Cortex and Sex

There is strong clinical evidence in support of an association between the cortex and sex. Experimentally, hyperplasia occurs after castration in rats, during pregnancy in guinea-pigs, oestrus in frogs, and ovulation in pigeons. Adrenalectomy is followed by suppression or by irregular appearance of the oestrous cycle, and by degeneration and atrophy of the testis. It is not certain how far this is due to the general metabolic changes and poor condition of the animal, rather than to a specific influence. If the animals are kept in a more chronic state of insufficiency there is at first a hyperplasia (? compensatory) of the interstitial cells of ovary and testis, without any degeneration, but later on a gradual atrophy follows. The latter would appear to be an indirect effect through the pituitary, since adrenalectomy results in a diminished gonadotropic potency of the pituitary and a decrease in the proportion of its basophil cells. Pregnancy prolongs the survival period after adrenalectomy.

Injections of cortical extracts have given discordant results. Atwell produced enlargement of the ovaries in hypophysectomized frogs, and Corey and Britton precocious sexual maturity in young rats. The majority of experimenters have obtained negative results with an extract which was quite potent in preserving the life of adrenalectomized animals. Reichstein, however, has isolated from the adrenal gland a crystalline steroid, adrenosterone, with male-hormone properties. In adrenal virilism comb-growth hormone may be present in excess, and in adrenal feminization oestrogenic hormone may be present in excess. Callow and Parkes have obtained adrenal extracts that show oestrone-like and progesterone-like activity.

It is important to remember that in the adrenal of the human foetus and of some young animals there exists a large zone between the cortex and medulla which is called the androgenic zone, because of a probable relation to the gonads. Thus in the mouse this zone disappears at puberty and in the male adult mouse hypertrophies after castration (Howard, Deanesly). It also involutes in the female mouse during pregnancy. The presence of this zone has not been observed in the dog, cat, rabbit, or cow. In man it involutes rapidly after birth, and it is postulated (Grollman) that the cells of the rudimentary androgenic zone are the ones that undergo hyperplasia in virilism and pseudohermaphroditism.

The Cortex and Mineral Metabolism

An important function of the adrenal cortex is the regulation of the balance and excretion of sodium and chloride. Adrenalectomy results in an increased excretion of these two elements and a fall in their serum values. There may be an initial diuresis and subsequent oliguria, but the water excretion is insufficient to account for the degree of haemo-concentration as manifested by a rise in total solids, haemoglobin, and plasma proteins.

Evidence is in favour of an increase in the extracellular fluid of the body (and to a less extent even intracellular fluid), and the liver and muscles have been found to be hydrated. In more severe adrenal insufficiency there is a rise in the serum potassium. This appears to be a direct result of the abnormal loss of sodium, since the administration of this element will cause a fall of serum potassium to normal. All these changes in mineral and water metabolism, in the adrenalectomized animal, can be prevented or remedied by the administration of adequate amounts of cortical extract. Swingle and others found that "sodium chloride and water cannot be regarded as an effective substitute for the cortical hormone in the bilaterally adrenalectomized dog, since it was necessary to inject cortical extract in order to save the animals when they sooner or later developed severe symptoms." Harrop and others, however, have kept adrenalectomized dogs alive for 150 days with mixtures of sodium chloride, bicarbonate, lactate, etc.

The rise of blood urea and non-protein nitrogen and the negative nitrogen balance that occurs after adrenalectomy are partly, if not entirely, secondary to the disturbance of electrolytic balance and diminished osmotic pressure, since these changes tend to be abolished by the administration of sodium chloride in adequate dosage. McCance produced similar changes in man, as well as many features of Addison's disease, by experimental salt deprivation, but there was no rise in serum potassium. A diet low in potassium will prolong the survival of adrenalectomized animals, and, conversely, a high potassium diet will precipitate death or necessitate a higher dosage of salt and/or cortical extract.

That the disturbance of sodium balance is not the essential feature in all species is suggested by the observations of Silvette and Britton on the adrenalectomized marmot, in which a fatal outcome was associated with the characteristic disturbance of carbohydrate metabolism but a serum sodium above normal level. Jimenez-Diaz believes that the changes in mineral metabolism are secondary to the acidosis resulting from diminished ammonia formation by a poorly functioning kidney.

Other Changes following Adrenalectomy

Apart from the relative polycythaemia (anhydraemia) there are other important changes in the blood picture—namely, a considerable reduction in the percentage of polymorphonuclear cells as well as a diminution in the total leucocyte count. Analogy with agranulocytosis has been suggested. The blood pressure may be maintained at normal level until the terminal crisis, but in some species a subnormal pressure characterizes more chronic adrenal insufficiency.

The rise in blood urea and inorganic sulphate may be partly due to disturbed mineral balance and partly to circulatory disturbance, but changes in the kidneys have also been recorded. Banting and Gains observed nephritic changes in dogs, and Levy Simpson and Korenchevsky recorded tubular degeneration in rats killed during chronic adrenal insufficiency. Marshall and Davis found a failure of renal function in cats before other symptoms occurred, and postulated a suprarenal hormone regulating renal function. The basal metabolism is usually normal until the terminal phase, when there is an acute fall. There may be an impairment of absorption of fat from the intestine. The blood cholesterol may be raised in some species after adrenalectomy. There is a hypersensitivity to foreign proteins (allergy), histamine, narcotics and other drugs, toxins, and bacterial infection. Gonadotropic hor-

none may stimulate the sex organs and pituitary growth hormone may increase the deficient rate of growth, but neither prolongs survival.

Adrenal Glands and Infection

Elliott showed that the cortical lipoid vanishes with great rapidity in all acute febrile conditions. Haemorrhage and necrosis of the adrenal cortex is characteristic of experimental infection, especially with *B. diphtheriae*. Cortical extract combined with ascorbic acid is said to protect a guinea-pig from what would otherwise be a fatal dose of a broth culture of *B. diphtheriae*. Caldarera found that the bactericidal power of the blood of the rabbit against several organisms is increased by cortical extract. The medulla may play some part since there is an increased output of adrenaline during infection, and a virulent culture of pneumococci can be rendered avirulent by treatment with adrenaline. Adrenalectomized animals are susceptible to infection and toxins.

Adrenals and Vitamin C

The adrenal gland has a high content of ascorbic acid (vitamin C), the cortex having about thrice, and the medulla about twice, the potency of fresh orange juice. This vitamin is also present in large quantities in the pituitary gland and the liver. Pure preparations of cortical extract, potent in maintaining adrenalectomized animals, do not contain vitamin C, and, conversely, this hormone cannot prolong survival after adrenalectomy. Some animal experiments suggest that the addition of vitamin C to cortical extract increases its protective action against *B. diphtheriae*. Hypertrophy and degeneration of the cortex results from experimental vitamin deficiency (A, B, and C). *In vitro* ascorbic acid inhibits the formation of melanoid pigment from adrenaline or dioxy-phenylalanine.

Preparation and Standardization of Cortical Extract

According to Swingle and Pfiffner "the suprarenal glands (beef) packed in ice are received from the slaughterhouse within twenty-four hours after the death of the animals, and the cortex dissected as free as possible from extraneous fat and medullary tissue, ground, and extracted with 95 per cent. and 80 per cent. ethyl alcohol for three or four days. Extract with benzene. Remove benzene *in vacuo*. Then distribute between 70 per cent. ethyl alcohol and petroleum ether. Latter removed by distillation. Wash, concentrate *in vacuo*; add water to desired volume." Grollman uses a method based on the adsorption of the cortical hormone by charcoal from neutral aqueous solution. Prepared in this latter way cortical extract is said to be active even when given by mouth. As usually prepared, however, it is administered parenterally and loses the greater part of its activity if given orally.

The following methods have been used for assay of cortical extract and are all based on its influence after adrenalectomy: (1) survival of dogs, cats, or rats; (2) growth rate of rats; (3) response of rat gastrocnemius muscle to electrical stimulus; (4) resistance to histamine or narcotic drugs; and (5) maintenance of normal blood urea in dogs. The "dog unit" is defined as the minimum daily dose of an extract per kilogram of body weight necessary to prevent an increase in blood urea after adrenalectomy. No one method gives constant results, and different methods are not strictly comparable. Extracts are therefore usually labelled "30 grammes of cortex per 1 c.cm. of extract." It is hoped that the isolation and synthesis of a crystalline product will be found possible and thus constitute a basis for standardization.

Kendall has prepared a crystalline product, and de Fremery, Laqueur, Reichstein, Spanhoff, and Nyldert have just announced the separation of very active crystals.

The maintenance dose of cortical extract, as usually prepared, for different species is approximately: rats 1/2 to 1 c.cm.; dogs 1 to 2 c.cm.; cats 2 to 3 c.cm.; and monkeys 6 to 12 c.cm.

BIBLIOGRAPHY

- Britton, S. W., and Silvette, H. (1932). *Amer. J. Physiol.*, **100**, 693 and 701.
 — (1934). *Ibid.*, **107**, 190.
 Callow, R. K., and Parkes, A. S. (1936). *J. Physiol.*, **87**, 28.
 Corey, E. L., and Britton, S. W. (1931). *Amer. J. Physiol.*, **99**, 33.
 De Fremery and others (1937). *Nature*, **139**, 26.
 Gaunt, R., and Parkins, W. M. (1933). *Amer. J. Physiol.*, **103**, 511.
 Grollman, A. (1936). *The Adrenals* (Baillière, Tindall and Cox, London).
 Harrop, G. A. (1936). *Johns Hopk. Hosp. Bull.*, **59**, 11.
 Loeb, R. F., Atchley, D. W., and Stahl, J. (1935). *J. Amer. med. Ass.*, **104**, 2149.
 McCance, R. A. (1936). *Lancet*, **1**, 823.
 Reichstein, T. (1936). *Helv. chim. Acta*, **19**, 223.
 Simpson, S. Levy, Dennison, M., and Korenchevsky, V. (1934). *J. Path. Bact.*, **39**, 569.
 — and Korenchevsky, V. (1935). *Ibid.*, **40**, 483.
 Stewart, G. M., and Rogoff, J. M. (1923). *Amer. J. Physiol.*, **56**, 235.
 Swingle, W. W., Phffner, J. J., Vars, H. M., and Parkins, W. M. (1934). *Ibid.*, **108**, 159.
 — (1930). *Science*, **71**, 321.

Nova et Vetera

MEDICAL HISTORY OF LIVERPOOL

The late Mr. Thomas H. Bickerton was well qualified to write the medical history of Liverpool. He had an ancestral connexion with the city and was one of its leading ophthalmic surgeons. As early as March 3, 1904, he read a paper on the Liverpool Medical Institution, and on October 7, 1909, he gave an inaugural address on Dr. John Rutter. During the rest of his life he continued to collect data for a more general medical history of Liverpool. The results were reduced to book form by Miss May McKisack, B.Litt. It is now issued after revision by Dr. R. M. B. Mackenna, who is in charge of the dermatological department of the Southern Hospital. The resulting volume¹ would have gladdened the heart of Mr. Bickerton could he have lived to see the outcome of his work—a stately quarto of 313 pages, well printed on good paper, lavishly illustrated with maps, plans, and portraits, and at the moderate price of twenty-one shillings.

The story begins with the building of the Infirmary in 1749 and is continued until 1920. It tells of the formation of the dispensary (1778), the Hospital for the Blind (1796), the fever hospital (1801), the Northern Hospital (1833), and the Royal Southern Hospital in 1841. A noble record of voluntary charity in a city growing in size and in wealth. At first every medical man practised every branch of his profession, but specialism crept in, eyes and ears first, then throats, skins, children, and finally x rays, which seem to have attracted attention in Liverpool within a few months of their discovery.

Some Outstanding Names

Many names of the physicians and surgeons are well known: Thomas Robinson, said to be an M.D. of Oxford, but of whom there is only the bare university record that he matriculated from Brasenose, at the age of 20, on May 2, 1741; Park and Manson, surgeons in advance of their time; Rutter and Bostock; the Bickersteths; T. H. Waters; Richard Caton, physician, archaeologist, and lord mayor; Mitchell Banks, Reginald Harrison, and

F. T. Paul, great surgeons. The Thomases, father and son, and Sir Robert Jones all added lustre in their day to the medical circles in Liverpool. From the beginning the Liverpool physicians took an active interest in furthering the interests of the profession through the British Medical Association. We read that in 1832, when the Provincial Medical and Surgical Association—the precursor of the British Medical Association—was formed, four distinguished medical men were on the Council, and no fewer than sixteen essays and cases were contributed to the first volume of *Transactions* by Liverpool practitioners. The Association itself has held four of its Annual Meetings in the city, and the names of Dr. A. T. K. Waters and Sir James Barr will long be remembered as those who did yeoman service in its interests.

Medical Education in Liverpool

The teaching of medicine has always been a strong point at Liverpool: clinical material has been abundant, because it is a seaport with a large migratory population. Long before the School of Medicine was opened in 1834 there were two Schools of Anatomy, with an attendance of about forty medical students, sculptors, and artists. Subjects appear to have been so plentiful that in October, 1826, three casks labelled "Bitter salts" consigned to a firm in Edinburgh were found to contain eleven dead bodies partially salted and pickled. The private schools of medicine were absorbed by the School of Medicine attached to the Infirmary. This became a faculty, first of University College, then of the Victoria University, and finally of the University of Liverpool. Side by side with it was the University School of Hygiene and the much-needed School of Tropical Medicine, which has done magnificent work in connexion with our Dominions in the Tropics.

There is an interesting chapter on the development of nursing from the time when it was proposed to secure the services of a better type of nurse at the Infirmary by raising the salary from £10 to £16 a year. The matron reported that she only had four nurses whom she could trust not to celebrate such a rise in prosperity by getting drunk on quarter day. There is, too, a terrible picture of the sanitary condition of the city even as late as 1871, when Professor Parkes of Netley and Professor J. Burdon-Sanderson of University College, London, reported that every cellar dwelling should have at least a window and access to a water supply and sanitary conveniences. As lately as 1895 some 26,000 people were still living in cellars.

A Forgotten Classic

Dr. David Waldie, we read, was a native of Linlithgow, and obtained the diploma of the Royal College of Surgeons of Edinburgh in 1831. He practised for a time in Liverpool as a surgeon and apothecary, but, being interested in chemistry, gave up medicine, became chemist to the Liverpool Apothecaries' Hall, and later settled in India, where he established a chemical works in Calcutta, and died in 1889. His claim to remembrance is that he introduced (Sir) James Y. Simpson to chloroform as an anaesthetic, having already tried its effects upon himself and his friend Dr. Abraham. His paper is a classic, and has long been hidden, for it was read on November 19, 1847, at a meeting of the Literary and Philosophical Society of Liverpool.

The book ends with serviceable tables of names and dates, and there is a sufficient index. It may be looked upon as a valuable contribution to medical history, and so far as can be tested it is accurate.

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¹ *A Medical History of Liverpool from the Earliest Days to the Year 1920*. From the data collected by the late Thomas H. Bickerton, Ch.M., F.R.C.S. London: John Murray. (21s.)

A report of Mr. Walter Howarth's Semon lecture on "Some Tumours and Ulcers of the Palate and Fauces" appeared in our issue of November 14, 1936 (p. 988). The full text of the lecture, with illustrations (many of them reproduced in colour), is published in the January issue of the *Journal of Laryngology and Otology*.