1939

Addison's disease : special reference to etiology

James B. Blair
University of Nebraska Medical Center

ADDISON'S DISEASE

SPECIAL REFERENCE TO ETIOLOGY

BY

JAMES B. BLAIR

SENIOR THESIS

UNIVERSITY OF NEBRASKA COLLEGE OF MEDICINE

OMAHA 1939

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INTRODUCTION

The recognition of the functions of the various endocrine glands and of the importance of the hormones which they produce is one of the recent developments in medicine. The adrenal glands, for example, were described by Eustachius in 1563, but nearly 300 years elapsed before there was any real insight into their physiologic activity. In 1855 Addison pointed out the constitutional effects of diseases of these glands and established the clinical syndrome which bears his name.

There are few rare disorders which have attracted as much attention as Addison's disease. Because of the striking nature of the condition and because of the fact that our knowledge of it is so intimately connected with the study of the physiology of the suprarenal glands, the disease has been studied with great thoroughness by physiologists, pathologists, and clinicians since the time of Addison's original description. This work has been largely unrewarded until recently. With the isolation of the cortical hormone and the demonstration of the relation of this substance to the metabolism of salt, a new impetus has been given to the study of the disease. The advances

in diagnosis and methods of treatment which has been made in the last few years are sufficiently promising to warrant an optimistic view for the future, and perhaps this originally fatal condition may be brought under control.

In this paper special reference is made to the etiological agents producing Addison's disease with their respective incidence and pathology.

ANATOMY

"The suprarenal glands are composite products of the chromaffin and cortical systems. Each consists of a relatively thick cortex enclosing a medulla of chromaffin tissue. Typically, there are two suprarenal blands, a right and left, placed in the epigastric region, one on each side of the vertebral column. They lie in the same plane as, and in intimate relation to, the supero-medial aspects of the kidneys." (21)

STRUCTURE

"The suprarenal gland consists of a highly vascular central mass of chromaffin tissue, the medulla, enclosed within a thick parenchymatous capsule of cortical substance, the cortex, which in turn is enveloped in a capsule of fibrous tissue, tunica fibrosa. From the deep aspect of the tunic fibrous tissue trabeculae pass inwards to support the glandular parenchyma. In the superficial part of the cortex the trabeculae interlace freely so as to enclose a series of small rounded clusters of cortical cells, thus forming the zona blomerulosa; in the deeper intermediate region of the cortical cells, run vertically to the surface, forming a zona fasciculata; in the deepest part of the cortex the cell columns are more irregularly arranged and form

a reticulum zona reticulata.

The cortical parenchyma consists of large polyhedral cells arranged in the interstices of the fibrous trabeculae. The cells contain more or less granular lipoid material and pigment giving a yellow color to the cortex as a whole.

The medulla is formed of a spongework of cell columns separated by anastomosing venous sinusoids. The cells are large and granular and exhibit the characteristic chromaffin reaction. In a fresh gland the medulla is of a dark red color owing to the presence of blood in its sinusoidal spaces.

From the main blood-vessels smaller vessels enter at numerous points in the fibrous capsule and run in the trabeculae, forming a close network around and between the cell masses and columns of the zona glomerulosa and zona fasciculata. In the zone reticulata the blood vessels open up to form a venous plexus, which is continuous with the sinusoidal plexus in the medulla, and thus with the central efferent vein of the medulla which emerges at the hilum of the organ as the suprarenal vein." (21)

In man 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 prenatal adrenal which at birth is one-third the size of the kidney. Shortly after birth the fetal adrenal cortex begins to involute, being gradually replaced by a permanent cortex and medulla. (91)

Zwemer (95) states that the morphology of the adrenal cortex seems to reflect the demands imposed by body needs. An excess of hormone over normal requirements is shown by an increase in the number of storage cells. An acute demand discharges the mature cells but does not immediately affect the accumulative cell types. Prolonged demands stimulate new cell formation which may or may not be able to counteract the cell utilization of the discharging phase.

BLOOD AND LYMPH VESSELS

The suprarenal glands are said to have a more abundant blood supply than that of any other organ in the body. Each gland receives an artery direct from the aorta, one from the inferior phrenic, and one from the renal artery. The glands are drained by one vein, which emerges at the hilum, the right to join the inferior vena cava and the left to join the left renal vein. Many lumph vessels pass from the suprarenal glands to the lateral aortic lymph glands. (21)

NERVES

The suprarenal glands has a very rich nerve supply. The suprarenal plexus consists of two groups of filaments, one from the great splanchnic nerve, and the second comes from the coeliac plexus and ganglion. Through these nerves the glands are in connection with the vagus and phrenic nerves. (21)

PHYSIOLOGY

The first evidence of the importance of the adrenal glands to life was supplied by Thomas Addison in 1855 in his description of the condition now known as Addison's disease. His report stimulated physiological investigation of the adrenal glands and led to extirpation experiments on animals.

The pressor properties of the gland, demonstrated by Oliver and Shafer (59) in 1894 focused attention upon the medulla for some two decades. Accumulated evidence clearly showed that death followed complete removal of the adrenal glands in all species examined. (22)

There has been considerable dispute among observers as to the relative importance of the cortex and medulla as to the cause of death following the removal of the adrenal glands. Following the work of Oliver and Shafer (59) who showed that the medulla of the suprarenals contained adrenalin, it was assumed that the fatal results of the extirpation of the suprarenals and the symptoms of Addison's disease were due to a lack of adrenalin. It was believed up until recent years that the cortex contained no substance with any recognizable action. It is only in recent years that it has been realized that the cortex is after all of great importance

(14). Numerous investigators have now shown that it is the absence of the cortex and not the medulla which is responsible for the death of adrenalectomized animals.

Many attempts have been made to determine the relative role of disturbances in the function of the cortical and of the medullary portion of the adrenal glands producing the symptoms of Addison's disease. Greene (34) has suggested that hypotension, hypoglycemia, and pigmentation are associated with disturbance of medullary function. He states that the variability of the symptoms is best explained if one considers the chemical compounds which have been isolated from the adrenals and which are supposedly specific products - epinephrine, cevitamic acid, and finally extracts containing the so called cortical hormone which have been prepared.

Blood changes following abnormalities in adrenal function have given us the most valuable information regarding their physiology. Britton (15) states that the outstanding blood changes in animals dying of adrenal insufficiency were: a marked rise in non protein nitrogen, lesser increases in potassium, magnesium, calcium, phosphorus, and sulphate; abnormally low values for alkaline reserve, sodium, chlorine, and, occasionally,

sugar, and a loss of water from the blood. (22)

MEDULLA

The pharmacodynamic effects of adrenaline are well known, but little has been proved in regard to the medulla's normal physiological function. Kemp (48) states that whatever the function of the medulla may be it is not an indespensable factor in animal biochemistry, because the adrenalectomized animal can be maintained indefinitely in good health with a normal function provided an optimum amount of a potent cortical extract be daily injected or ingested. Snell (71) states that this dispensability of the medulla cannot be proved since there is so much chromaffin tissue with presumably similar function in the organism.

Some evidence exists which seems to indicate that the suprarenal medulla is connected in some way with the formation of pigment, carbohydrate metabolism, and circulatory efficiency. (71)

CORTEX

The failure of investigators to demonstrate any essential function of the adrenal medulla has resulted in a gradual shift of interest to the cortex. The cortex appears to be the really important and essential

part of the adrenal gland. Kemp (48) states that the indispensability of the cortex in the maintenance of the functional integrity of the organism has been conclusively proved by often repeated adrenalectomies in animals, and by clinical experience in cases of Addison's disease, and that there is now no doubt that the cortical cells of the adrenal glands elaborate a secretion, or secretions, of vital necessity to the continuity of life. Just how this hormone works however is still unproved. Most investigators believe that the prime function of the cortex is the maintainance of salt and water balance.

Hartman (42) came to the conclusion that although there may be a number of hormones in the cortex, there is probably only one vital hormone. This hormone is commonly known as cortin or interrenalin.

Since 1930, when evidence for the presence of the cortical hormone was obtained, active investigation of the physiologic effect of the extract has been carried out in many laboratories. Quoting from Kendall (49) the results may be summarized by the statement of four theories: Hartman (43) has suggested the function in general terms; that the hormone is an essential cellular agent which is used throughout all the tissues.

Britton (16) has suggested that the function of the adrenal cortex is involved principally in carbohydrate metabolism. Swingle, Pfiffner and others (77) have suggested that all the symptoms of adrenal deficiency are produced by a decrease in the volume of the blood and that the function of the cortical hormone is to maintain a normal blood volume.

Kemp (48) states that the cortex constitutes the whole adrenal gland in foetal life, and the fact that at birth it is one third the size of the kidney is an indication of its importance in the pre-natal development of the child. He concludes after a review of the extensive experimentation of the past decade that there is evidence which suggests that the chief functions of the adrenal cortex are three fold. First, to maintain normal blood volume by control of the excretion and resorption (in kidney tubules) of electrolytes and water. Second, to act as a general tissue and cell catalyst, particularly in regard to hepatic function. Third, to play an important part in carbohydrate metabolism, particularly in repsect to glyconeogenesis. He states that there is also considerable evidence to indicate that the adrenal cortex is closely related to urea formation, to vit. c. storage, to cholesterol

metabolism, and to resistance to infection and toxaemia, and that some observers believe that it is a factor in the normal healing of wounds and callus formation.

Harrop (38), Swingle, Parkins (78) and numerous other investigators, have shown that the cortical hormone plays an important part in distribution of body water. Harrop(38) believes that the blood concentration noted in adrenal insufficiency is due to three factors, (a) movement of extracellular fluid into the tissue cells, (b) drainage of plasma water into the extracellular fluid outside the vascular system, and, (c) augmented excretion of urine. Of these factors, he believes that the first is the most important.

Winter (93) quoting from Hartman (42) states that cortin plays an important part in the maintenance of plasma volume, and that the volume reduction in the absence of the hormone is explained neither by loss of fluid through the kidneys nor by decreased intake, because the same results in water balance can be obtained by gradually reducing the food intake in normal animals without producing symptoms.

Hartman (42) states that there must be a redistribution of water in the body of cortin insufficient animals. How this is produced is unknown, but it is known that sodium and chloride escape in abnormal amounts

through the kidneys. This leads to a shift of electrolytes in the body.

Following hormone injection in adrenal insufficiency there is a mobilization and redistribution of body fluids. Parkins, Taylor, and Swingle writing in the American Journal of Physiology in 1937 (79) state that this redistribution of body fluids is associated with a redistribution of electrolytes, and that the increases in serum sodium and chloride during recovery are, to a large extent, masked by a simultaneous expansion in volume of the extracellular fluid.

Zwemer and Truszkowski (96) in drawing conclusions from cortin injection in adrenalectomized cats state that the adrenal cortex has a positive action on potassium metabolism. They showed that in adrenal insufficiency a normal intake of potassium cannot be properly handled but that upon injection of adrenal cortex extract there is a lowering of the blood potassium. They state that the syndromes of potassium poisoning and adrenal insufficiency are remarkably similar.

Richter (67) and other investigators (62) upon observing results produced by adrenalectomy on rats, reached the conclusion that activity was dependent

on secretions of the cortex. Richter (67) stated that there is no evidence as yet to indicate that the medullary secretion plays any part in the control of activity.

Many other functions have been suggested for the adrenal cortex, for example Evans (25) came to the conclusions from experimental work done on albino rats that the adrenal cortex is concerned in the conversion of protein to carbohydrate. Harman (42) drawing conclusions from experiments on female rats stated that the adrenal cortex is important in the abolition of fatigue. They state that in adrenal insufficiency glycogen is very slowly regenerated after severe fatigue, and in the late stages of insufficiency the liver and muscle glycogen are much depleted and the blood sugar usually falls.

In conclusion, I believe that the following statement made by Swingle and Pfiffner in 1932 and which is still valid, sums up the status of the present knowledge of the adrenal cortex: "The real functional significance of the cortical hormone is unknown. All of the changes reported as occurring in the organism following bilateral adrenalectomy, we regard as secondary to some at present unknown, underlying derangement of the animal. The literature is filled

with theories and hypothesis of adrenal function. No one has yet succeeded in presenting definite, clear cut, unequivocal evidence of cortical function. The function of the adrenal cortex is an intriguing one, but the solution is not yet at hand." (50)

ADDISON'S DISEASE

In 1855 Addison described the disease which now bears his name. Addison (2) quoting from Kipler (46) in his original description described a disease with the characteristic symptoms of "anemia, general languor or debility, remarkable feebleness of the heart action, irritability of the stomach and a peculiar change in color of the skin."

Claude Bernard (7) quoting from Kipler (46) excised the adrenal glands of animals and produced the fatal symptoms which he though resembled those of Addison's disease. In subsequent years the observations of both men were confirmed repeatedly, but little advance of any importance was made in the diagnosis or treatment of Addison's disease for 75 years. During these years it was definitely established that tuberculosis or atrophy of the adrenal glands accounted for most cases of Addison's disease, that the morbidity of the disease was largely the result of distruction of the cortex and that the medulla with its hormone epinephrine were of secondary importance.

SYMPTOMS

It is now known that Addison's disease presents two characteristic sets of symptoms and signs. Those of the state of chronicity and those of the stage of crisis.

Shirey (81) states that the onset of thee disease is insidious, the chief characteristics being the progressive muscular weakness, mausea and vomiting, increased pigmentation of the skin and mucous membranes and hypotension. Asthenia is the earliest and most characteristic symptom. Loss of appetite, with nausea and vomiting are frequent. There may be diarrhea accompanied by cramplike pains of abdomen and legs, but obstinate constipation is more common, especially in the terminal stages. The outstanding circulatory disturbances is the low blood pressure, the systolic pressure may be as low as 50-40 mm. of hg. The pigmentation of the skin is of varying intensity and appears first on exposed parts and where there is pressure from clothning and irritation (81).

Root (63) states that the most serious symptoms are those of crisis. These consist of anorexia, nausea, vomiting, diarrhea, and circulatory collapse and are intimately related to the distruction of the cortex of the gland and to the loss of the cortical hormone.

DIAGNOSIS

The diagnosis of adrenocortical insufficiency in man is in many cases a difficult problem. Newbold (56) states that the complete syndrome described by Addison is not difficult to recognize, but the pigmentation is inconspicuous or absent in some cases of frank insufficiency, and the other symptoms and signs are frequently met in other diseases so that it is risky to base a diagnosis on them alone.

In many cases of Addison's disease the presence of calcification of the glands is quite helpful if found. This tends to point to tuberculosis of the adrenal glands. It may be misleading however in that the presence of calcium in lymph nodes in the vicinity of the glands, or in the cartilages of adjacent ribs may be misinterpreted. (91)

Zwemer and Truszkouski (96) have suggested a diagnostic procedure, which consisted in the administration of 10-20 mg. of potassium per pound of body weight, and examining the effects of this on the level of potassium in the plasm. They state that subjects without adrenal insufficiency revealed only a slight rise in this value, with early return to normal; whereas in cases of Addison's disease the rise was two

or three times as great and the return somewhat retarded. The response however is uncertain.

Newbold (56) states insulin has been suggested as a diagnostic procedure as patients with adreno cortical insufficiency are hypersensitive to insulin. The method is of no value however, due to the many other conditions associated with hypersensitivity to insulin.

One of the more reliable diagnostic procedures has to do with the excretion of chloride and other electrolytes in the urine of patients with Addison's disease. Wilder, Power and Catler (93) report that in eight out of nine cases of proved Addison's disease the concentration of the urinary chloride exceeded 225 mg %. In 28 control subjects the highest value was 141, the others under 125. They state however that before confidence can be placed in the reliability of this diagnostic procedure, further experience is necessary (93).

The positive effect of cortin on the sodium and chloride balance is useful in the diagnosis of early Addison's disease. The negative sodium and chloride balance in patients with Addison's disease is changed to a positive balance by cortin. (29)

Deprivation of salt has been suggested by Wilder

(93) and Harrop (38) as diagnostically important in Addison's disease. The chief disadvantage to this however is the state of collapse into which the patient may pass before the values for the electrolytes in the plasma have changed enough to be diagnostic. Another disadvantage is that the test requires six days for completion, and that the final interpretation depends on examination of the blood for sodium and potassium.

Pigmentation is perhaps the most important diagnostic method in Addison's disease in the chronic stage. Root (63) states that while the pigmentation varies greatly in different cases, there are certain characteristics which are almost diagnostic. He states that the color of the skin is most frequently a dirty grayish brown, the discoloration being most pronounced on exposed surfaces. The pigmentation is diffuse, but skin blemishes are darker as scars and bony prominences. The genitalia, anus, axillae, nipples, and lips may be strikingly discolored. Pigmentation of the mucous membranes is especially characteristic. On the oral mucous membranes, especially the buccal surfaces, tongue and gums, are brownish or purplish patches.

INCIDENCE - SEX - AGE

Incidence

From 300-400 cases are recorded annually in the registration area of the United States. The death rate is remarkably constant, about 0.4 in each 100,000 of population. (69)

Sex

Practically all investigators agree that males are more frequently affected than females (20). Snell (71) states that males are affected about twice as often as females. Snell and Roundtree (69) reported 103 cases of Addison's disease at Mayo clinic between 1912 and 1928; there were 66 men and 37 women in the series.

Age

Addison's disease is a disease of middle life, occurring most commonly in the fourth or fifth decade. During childhood Addison's disease is very rare. Monte (29), quoting from Friedman (30) found among 200 cases of Addison's disease, only six children under the age of 13 years. Greenhow's (30) figures show only 4 of 330 cases to have occurred during childhood, or a ratio of 1 to 62. Guttman (32) in a review of 566 cases of Addison's disease found that about 3.45% of all cases are in children under 10.

CLINICAL COURSE

Greene, Rountree, Swingle, and Pfiffner (34) state that in the usual case of Addison's disease the clinical course may be divided into three periods as follows: (a) The period of initial destruction of the adrenal glands or latent adrenal insufficiency. Clinically recognizable signs of adrenal insufficiency do not appear until the functional reserve of the adrenal glands is seriously impaired or four-fifths of gland destroyed. (19) (b) Period of partial adrenal insufficiency. In this period the characteristic clinical symptoms of Addison's disease appear. (c) The terminal perod of crisis or total adrenal insufficiency. A variety of causes may lower the already low resistance of patients with Addison's disease and thus initiate an acute condition resembling shock or a period of crisis. This period is characterized by severe gastro intestinal disturbances, nausea, vomiting, dehydration, pain, nervous irritability, circulatory collapse, low blood pressure, cold extremities, reduction in the out put of urine and lowered body temperature. The condition resembles the condition seen in laboratory animals after complete adrenalectomy.

TUBERCULOSIS

Tuberculosis is considered by most authorities to be the principal factor in the production of Addison's disease. This relationship is however, not as readily proved as might be expected. In the 103 cases reported at Mayo clinic between 1912-1928, only about a third had clinical evidence of tuberculosis. The disease is extremely uncommon in patients in sanitariums, many sanitarium directors stating that they have seen only 1 or 2 cases in their entire experience. (69)

Considering that tuberculosis of the adrenals is responsible for from 80 to 90% of cases of Addison's disease, it is difficult to explain the unusually low incidence of this disease in tuberculosis sanatoria. Minor (13) did not observe a single case in a period of 35 years, while Brown (13) records 3 cases in 2,570 deaths of former patients at Trudeau Sanatorium. To explain this low reported incidence a number of factors must be considered. Extensive bilateral tuberculosis of the adrenals is usually seen in cases with minimal or healed primary tuberculosis of the lung and only rarely in extensive bilateral pulmonary tuberculosis.

Extensive disease of the adrenals often develops long after the patient has been dismissed from a sanatoria. Moreover, in extensive pulmonary tuberculosis symptoms of adrenal insufficiency may be obscured by symptoms of the primary lesions which may simulate those closely of Addison's disease. (13)

If tuberculosis is the chief cause of Addison's disease one would naturally expect that the disease would be more frequently met with in regions where the anticedent infection is most common. In Colorado Springs, Colorado there is an unusually large percentage of the population who have tuberculosis or who have been exposed to it. Reviewing the census statistics for the 10 years 1912 to 1922 inclusive we find that the death rate from Addison's disease remained almost constantly 0.4 per 100,000 population for the registration area of the United States. During that same period the death rate from Addison's disease in Colorado Springs averaged 1.2 per 100,000 population or about three times the rate in the country at large. This finding is one we should naturally expect in a community devoted extensively to the treatment of tubercolosis. (74)

Quoting from Cecil the type of lesion varies between "a very proliferative type with many tubercules many fibroblasts and connective tissue cells, and only a small area of necrosis, and a type in which the gland was a mass of necrosis surrounded by a fibrous capsule in which there were only a few tubercles and a small number of lymphocytes. The lesions were situated rather consistently in two placed; either at some distance from the main suprarenal vein in the medulla or deep layers of the cortex, or else midway in the cortex between the medulla and the outer surface. The larger lesions seem to be spread centrifugally until they extended through practically the full thickness of the gland. As a rule the glands are found to be definitely enlarged, sometimes weighing from 20 to 30 Gm." (19)

Records of 12,000 consecutive post-mortem examinations at the Leeds General Infirmary (1910-1930) with regard to the occurence of tuberculosis of the suprarenal glands, with particular reference to cases giving rise to Addison's disease gave the following figures:

Total Cases of Gross Tuberculous Lesions

Right Adrenal	3.
Left Adrenal	5.
Bilateral	16.

Diffuse Fibrocaseous Lesions

Right Adrenal	2.
Left Adrenal	3.
Bilateral	9.

Nodular Lesions

Right Adrenal	0.
Left Adrenal	2.
Bilateral	7.

Sites of Primary Lesions in Above

Lungs and bronchial glands	14.
Mesenteric glands	3.
Genito urinary tract	5.
Primary in adrenals	1.
Knee Joint	1.

As seen in the above table and also pointed out by most authorities the primary site of the tuberculous infection is in the majority of cases in the lungs. Kipler (46) Gsell and Nehlinger (31) in a recent study on tuberculosis of the adrenal glands reported 35 cases of bilateral total tuberculosis and 37 of unilateral or

bilateral incomplete tuberculosis. These writers concluded that the infection is hematogenous and originates in a primary or post primary tuberculous focus. In a third of their cases the only active tuberculous process was in the adrenal glands. They state that the infection probably gegins during or after puberty and has a long period of development, during which the disease proceeds intermittently, the symptoms of Addison's disease beginning after the period of glandular insufficiency. (31)

Most investigators believe that when a tuberculous infection is said to be primary in the adrenals that there is a primary hidden focus elsewhere in the body and is actually not primary in the adrenals.

Kipler (46) states that tuberculosis of the adrenal glands accounts for from 80 to 90% of the cases of Addison's disease. He states however that the ratio seems to be changing, and as there is no good reason to presume that the adrenal glands are now being attacked by tuberculosis less frequently than in former years it would appear that treatment is either more effective in prolonging life in the group of patients whose condition is caused by adrenal tuberculosis or that these patients may be protected to some extent by the survival of fragments of cortical tissue and cortical

adenomas.

Feinblatt reported seven verified cases of tuberculosis of the suprarenal glands and stated that all seven were free from pulmonary tuberculosis. Five had no tuberculous lesions elsewhere, one had tuberculosis of the pituitary, and one tuberculosis of the vertebrae.

Harbitz (40) reports twenty two cases of Addison's disease treated in Guy's Hospital between 1904 and 1923 showed 22, or 76% to be due to tuberculosis of the suprarenals, with a fibrocaseous condition of the glands. Six showed an active tuberculous process elsewhere. (33)

Snell (72) in a statistical study of Addison's disease states that tuberculosis of the adrenal glands is present in 80% of the cases, and that from 30 to 40% of these cases are associated with tuberculous lesion elsewhere in the body.

Barker (6) reporting on the pathologic anatomy of the suprarenal glands in 28 cases in which the clinical syndrome of Addison's disease had been present, that 25 of these 89% the lesion was tuberculosis.

Guttman (32) surveyed the literature in 1930, and found 69.72% of cases of Addison's disease were caused by bilateral tuberculosis. He states that tubercle

bacilli are found in almost one half the specimens stained for their demonstration.

Nolan (55) in a statistical study of 1,250 autopsies found tuberculosis of the adrenal glands in 22, or 3.2% of these cases.

Colton (20) reported 14 cases of Addison's disease, five of which were due to tuberculosis of the adrenals.

ATROPHY

Next to tuberculosis, atrophy of the suprarenals is probably the most frequent etiological factor in the production of Addison's disease. Many theories have been advanced as to the nature of the process, but as yet no definite conclusion has been reached.

Wells (89) states that in approximately 10% of the cases with Addison's disease there is marked decrease in the size of both suprarenals, which are usually affected about alike, and that this atrophy depends on an extensive, sometimes an almost complete distruction of the epithelium of the cortex, with less or practically no distruction of the medullary substance.

The etiology of this atrophic condition without corresponding damage to any other tissue in the body is as yet entirely unknown. Wells (89) believes that the bilateral character of the condition would indicate that it is hematogenous in origin. He suggests that the resemblance both of the tissue damage and the regenerative changes in the surviving cortical epithelium to the process seen in diffuse toxic necrosis of the liver suggests that the suprarenal condition also

is the result of a toxic necrosis by some poison selectively injuring the epithelium of the suprarenal cortex.

In reviewing the literature one gains the impression that there are apparently several different types of atrophy of the suprarenals leading to end stages which are very similar. Kovacs (47) differentiated between changes purely inflammatory in nature and primary degenerative changes leading to necrosis and disappearance of cortical cells. Other investigators make no differentiation but call the condition either inflammatory or atrophic in nature. (14)

Locally contracted suprarenals is the term used when the condition is thought to be due to local causes and not brought about by a systemic disease acting on the suprarenals. Kovacs (47) states that when these primary degenerative changes occur, they involve the cortical parenchyma only and lead to necrosis of cortical cells. He states that this necrosis is accompanied by a lymphatic infiltration but without apparent scar formation.

Another type of adrenal atrophy is spoken of as "cytotoxic contraction of the adrenals". This condition is also spoken of as "selective adrenal

atrophy". Kovacs (47) believes that the cortical cells are destroyed by a specific toxin, a cytotoxin in his opinion, whose nature is obscure but which may be liberated by abnormal metabolism rather than an infectious disease. (75) It is the opinion of Saphir and Benswanger (75) that the toxin is carried to the suprarenals by the blood stream leading to mandatory involvement of both suprarenals. They state that the progressive nature of the disease which is shown by the degenerative remnants of regenerated cortical cells and by the final death of the patient indicates that the cytotoxin is liberated either continuously or at intervals over a rather long period of time.

Marine (52) thinks that the atrophic changes might signify a state of exhaustion of the suprarenal cortex which must have been preceded by a state of overactivity.

Brenner (14) suggests three possibilities as to the nature of the process. First, that it is a congenital hypoplasis of the glands, especially of the chromaffin system, and associated with status thymico lymphaticus. This possibility may be disregarded, however, as the process first attacks the cortex not the medulla or the chromaffin system.

The second suggestion is that it is due to chronic inflammation with tuberculosis as the cause, and that the tuberculous process may heal so completely that it is impossible to find the cause of the fibrosis. Seldom, however, is tuberculosis elsewhere in the body found in cases of suprarenal atrophy. Brenner (14) states that this does not disprove entirely the tuberculous origin of the condition since in many cases of frank tuberculosis of the adrenals there may be no obvious primary focus elsewhere in the body. Syphilis is also suggested as a possible factor. Brenner (14) suggests that the process is possibly a chronic simple inflammation of the suprarenal but as such changes are confined to the surface with thickening of the capsule and fibrosis of the cortex it is improbable that the process is a chronic simple inflammation.

The third possibility is that the process is a simple atrophy of the cortex with attempts at regeneration. It is suggested that this necrosis of cortical cells is caused by some unknown toxin which has a special affinity for them. This is followed by focal regeneration with the production of hyperplastic islands of hypertrophied cells, which are then attacked

by the same process. The few cortical cells left after the primary damage are probably over worked, and it is possible that part of the subsequent degeneration is due to this.

Although Brenner arrived at no conclusion as to the nature of the process, he favored the last view. Snelling (73) thinks that such a possible etiology is worthy of consideration. He states that Aschoff (4) pointed out the suprarenal cortex may show a loss of lipoid in such acute infections as diphtheria, and scarlet fever, while the medulla remains practically intact. He believes therefore that it seems probable that toxins such as result from these acute infections may be the cause of the initial lesion in certain cases. There is no proof of this, however.

Wahl (89) in a case of adrenal atrophy interpreted small round cells as embryonic neurocytes and pointed out that they bore a certain resemblance to the small round cells seen in malignant tumors of the adrenal medulla, the neuroblastoma. Wahl supported the theory of Bloch (12) that "the condition is not one of true atrophy, but is rather the result of a perversion of the normal process of development of the suprarenal medulla during fetal life." Snelling (73) states that

normally the embryonic neurocytes migrate from the medulla through the cortex but with the increase in size of the medulla there is a corresponding atrophy of the inner zone of the cortex with a simultaneous regeneration of the glomerular zone. According to Bloch (12) if the process of atrophy of the inner zone of the cortex is prolonged into early childhood or later life, the bulk of the cortex may eventually disappear having been replaced by embryonic neurocytes. This theory has however received little acceptance. (73)

Wells (90) "Selective necrosis of the adrenal cortex seems to have become an increasingly common cause of Addison's disease in recent years. The similarity of the changes seen in these adrenals to the changes in toxic necrosis of the liver with resulting 'acute yellow atrophy', which is so often produced by cinchophen, and to the selective distruction of marrow elements by amino pyrene and other drugs, leading to agranulo cytosis, suggests the probability that necrosis of the adrenal cortex may likewise have become more frequent of late because of the action of some drug or chemical in persons with a particular idiosyncrasy." He supported his theory with a case of a woman who had been treated with "germanin" and died with almost

complete selective necrosis of the adrenal cortex. As shown by animal experimentation this drug will produce a distruction of the adrenal cortex. Although the data at present concerning the role played by drugs and chemicals in the production of this condition is not very comprehensive, it may be that they are responsible for many if not all the cases of Addison's disease of this type.(90)

Barnard (7) reported 23 cases of Addison's disease out of a total of 5915 necropsies. Seven of these were reported as atrophy. He states that in these seven cases all showed the same macroscopic trace of medulla. On microscopic examination there was found necrosis of cortical cells, more less chronic inflammation infiltration and recognizable medulla. He believes that the similarity in the type of necrosis and of cell infiltration in all cases leaves little doubt that it constitutes a definite disease and is not a chronic inflammation which happens to be in the cortex.

In a review of the records of 12,000 consecutive post mortem examinations at the Leeds General Infirmary (1910-1930) with regard to the occurrence of atrophy of the suprarenal glands, with particular reference to

cases giving rise to Addisons disease; 3 cases of atrophy of the adrenals were found in definite cases of Addison's disease. (39) In the three cases no evidence was available as to the causation, though in one there was an old tuberculosis scar at the apex of the lung. The following table lists the cases of adrenal atrophy in the 12,000 cases and the sites of their occurrence.

Atrophy of Adrenals

Right	1.
Left	7.
Bilateral	4.

Doubtful Cases

Right	1.
Bilateral	3.

Snell (70) reports a case of suprarenal atrophy and Addison's disease, resulting in a case of adrenal denervation in a case of diabetes mellitus. He also tells of a similar case reported by Rogoff. (60)

Atrophy of the suprarenal glands is responsible for about 10% of all cases of Addison's disease, in 13 or 19% of which atrophy of the suprarenal glands was responsible. There are many series of cases of Addison's disease, however, that have been reported and include no example of this atrophic condition, so

that 10% is probably not far from the actual proportion.

Susman (76) in a review of the literature concluded that atrophy of the adrenals has a high incidence, especially in England. He states that the incidence of such cases in the available necropsy series varied from 0.025 to 0.29 per cent. The female incidence was appreciably higher than the male, and the highest frequency was between 35-45 years of age. He believes that a female sex factor appears to be prominent, in some cases.

Guttman (32) has attempted to contrast the duration of life when the etiological factors of Addison's disease is tuberculosis and when it is due to atrophy. He states that the duration of the disease in man has an average of 34 months when due to atrophy of the suprarenals, and 13.3 months when due to tuberculosis of the suprarenals.

Guttman (32) in a review of the literature found that 19.48% of all cases of Addison's disease were due to adrenal atrophy.

Barker (6) found three cases of advanced bilateral suprarenal atrophy among 28 cases of Addison's disease observed in Mayo clinic.

Harbitz (40) stated that among twenty two cases of Addison's disease examined by him, two showed atrophy of the suprarenal glands.

Snell (68) states, quoting from Kipler (46) that a search of the literature revealed that in 17 of the thirty recently reported necropsies, in cases of Addison's disease which had been treated, atrophy of the suprarenal glands was present. According to these figures atrophy of the suprarenal glands accounted for 57% of the cases in which patients died and came to necropsy.

Rountree and Ball (66) have also made clinical comparisons between Addison's disease caused by tuberculosis and Addison's disease caused by atrophy. They state that the cases of atrophy and tuberculosis run almost identical courses, but that pigmentation is more uniformly present in cases of suprarenal atrophy than in those in which the underlying factor is tuberculosis. He agrees with Guttman (32) that the average length of life is longer in cases of atrophy than in those due to tuberculosis.

AMYLOIDOSIS

This condition of amyloidosis although often called amyloid degeneration is actually an amyloid infiltration. The material is not found in the same place where it is set free, but is deposited in other organs, being an infiltered change of material from the outside.

Amyloid degeneration generally occurs in conditions of long standing long continued destructive diseases, especially those involving the long bones of the body and cartilage. The following etiological factors have been given:

1. Prolonged suppuration of bone and cartilage (destruction)
2. Tuberculosis, especially with secondary infection, or involving bronchi of lungs.
3. Neglected cases of syphilis.
4. Actinomycosis.
5. Rarely in chchexia, malnutrition.
6. Late stages of cancer, or malaria.
7. Some diseases of the blood forming organs, especially destruction of the bone marrow.

In amyloid infiltration, there is a deposit of protein or similar material resembling the nucleo-proteins. When the destructive process involves certain locations in the body, such as the bones or cartilage, there is a destruction of the protein elements of the carilage with a setting free of chondroitin-sulfuric acid which is a normal constituent of bone, cartilage and probably of lung tissue. When it is decomposed the result is a gummy substance, chondroitin, and sulfuric acid. Decomposition generally occurs after the chondroitin sulfuric acid leaves the blood stream.

In appearance, amyloid material shows only a hyaline character. It is stained by acid stains, taking a peculiar rose color with methyl violet. It gives a blue color with iodine and sulfuric acid.

An affected organ is hard and board like in character and a cut surface shows glistening, white areas, like bacon fat so called "Lardaceous disease".

The condition is irreversible, and once reached cannot be repaired. The chief danger from extensive amyloid infiltration is that it forms an impervious wall between a vessel and the region supplied by it. It may also, if in a large area, be the cause of pressure atrophy. It always interferes with the

function of the organ which it involves if it is at all extensive. (24)

Hunter and Rush (41) state that in generalized amyloidosis careful study of the suprarenals not infrequently discloses amyloid in these glands as well as in the commoner sites such as the spleen, liver and kidneys. Frequently it is not abundant and may readily escape detection or be mistaken for hyaline changes unless a careful study is made and specific stains for its recognition employed. Usually the quantity is small, histological structure and pattern well preserved, and adrenal insufficiency due to its presence does not develop.

The microscopic picture is also quite uniform and shows a peculiar localization of the amyloid in the inner two zones of the cortex. No adequate explanation is offered for the marked localization in the zona fasciculata and reticulosa and for its relative scarcity elsewhere. As the amyloid increases atrophy of parenchymatous cells follows due probably both to pressure and diminution in blood supply. Eventually then if the individual survives long enough and the process responsible for amyloid formation continues sufficient parenchyma may be destroyed so that

symptoms of adrenal insufficiency develop. (41)

Cases of Addison's disease due to amyloidosis of the adrenals are apparently rare. Survey of the literature by Hunter and Rush (41) in 1926 disclosed but six cases and of these two were doubtful.

Guttman (32) in an analysis of 566 cases of Addison's disease contained in the literature from 1900 to 1930, found only seven cases, or 1.73% in which amyloid infiltration of the adrenals occurred.

Colton (20) reported a series of 14 cases of Addison's disease may be as McCutchion (53) quoted from Hunter and Rush (41) pointed out that more often than not the cells of the cortex are not completely destroyed, many cell groups escaping and enough cells still remain to prevent the appearance of Addison's disease.

Two other possibilities for the rarity of Addison's disease resulting from amyloidosis are given by Bronfin and Guttman (13) first, that the medulla, which is spared in amyloid infiltration, prevents the development of Addison's disease, and second that symptoms of Addison's disease may be masked in many cases by the underlying pathological process, usually a widespread chronic pulmonary tuberculosis. They

state that it is true that even in extensive amyloid involvement of the adrenals, small islands of cortical tissue and the outer portion of the zona glomerulosa are entirely free of amyloid deposit and appear normal histologically.

Hunter and Rust (41) believe that in cases of Addison's disease which at autopsy reveal apparently healthy suprarenals amyloid should be considered as a possibility, even though rare, and searched for before placing the case in the class of Addison's disease without histological changed in the adrenals.

In the following table are listed six cases of Addison's disease compiled by Hunter and Rust (41) resulting from amyloidosis of adrenals.

Author	Sex	Age	Adrenals, gross and microscopic
Riesman (62)	Male	60	Firm, enlarged, greyish translucent, waxy appearance suggestive of amyloid changes. Amyloidosis adrenal cortex, especially zona fasciculata and reticulosa; also about veina in medulla.
Rittorf (18)	Male	32	Normal in size but strikingly firm. Amyloidosis of cortex; slight in medulla
Schultz (84)	Male	25	Practically complete amyloid infiltration of both suprarenals.

Author	Sex	Age	Adrenals, gross and microscopic
Schlesinger (85)	Male	47	Usual size, somewhat dense and hard, cut surface almost evenly gray shiny and hard. Pronounced degeneration of cortex, all cells in left severely injured, less pronounced in right. Medulla affected but to less degree than cortex.
Bauer (9)	Male	66	Moderately increased in size whitish yellow. Marked amyloidosis of cortex with great atrophy of cells. Only few isolated patches of amyloid medulla.
McCutcheon (53)	Female	53	Normal size and shape but of increased consistency. Cortex pale yellow to gray. Amyloidosis of fasciculata and in medulla about blood vessels with some extravascular collection.

MISCELLANEOUS

It is generally agreed that Addison's disease is due to a lack of secretion of the hormones of the suprarenal glands. Therefore, any pathologic lesion which gradually destroys the suprarenal glands may produce the characteristic syndrome of Addison's disease, at least in part. (66)

There is evidence that Addison's disease may be of syphilitic origin, but such cases must represent a small minority (68). That the condition is of rare occurrence is shown by the scant reference to the subject in textbooks on syphilis.

Schaffner and Howard (82) have reported two cases of Addison's disease terminating fatally, which on autopsy showed gummatous infiltration and connective tissue overgrowth of the adrenals.

Fordyce (28) quoting from Schaffner and Howard (82) in describing the pathology in syphilitic involvement of the adrenals producing Addison's disease, state that interstitial changes as well as focal gummatous inflammation may occur.

If the etiological factor is syphilis the patients respond immediately to antiluetic therapy.

Cases recently have been described in which the Addisonian syndrome has been present with intact suprarenal glands. Bittorf (18) explains this phenomena on the basis of injury to the secretory nerves of the gland.

Snell (69) states that irritation or interruption of the sympathetic nervous system is responsible for some cases of Addison's disease; the cases of malignant involvement of the solar plexus reported in the literature being on this basis.

Malformation of the adrenal glands has been given as the cause of Addison's disease in rare cases. Wahl (91) reported a case of Addison's disease which on autopsy showed a pair of unusually small but otherwise apparently normal suprarenal glands. The left adrenal weighed 2½ grams as compared with normal of 5 - 6 grams. The left adrenal is also called congenital hypoplasia of the suprarenals. There has been very little written in the literature on this condition due to its rare occurrence.

A few cases of Addison's disease have been reported in which the etiological factor was claimed to be malaria. Lellis (50) reported a case of Addison's disease developing a few weeks after an acute malarial

infection. The condition cleared up on the administration of epinephrin. He believes that the suprarenals had been injured by malaria and were given a chance to recuperate on the administration of epinephrin.

Hemorrhagic infraction of the adrenals has been listed as a rare cause of Addison's disease. Ellis (26) states that this condition occurs as the result of thrombosis of the adrenal veins. The etiology of the thrombosis of the adrenal veins is uncertain.

Pituitary disfunction has been considered by investigators as to its possibly being an etiological factor in the production of Addison's disease. Crooke and Russel (23) state that there is a close relationship between the anterior lobe of the pituitary and the suprarenal cortex. Smith (83) and Richter (67) quoting from Crook and Russel (23) state that destruction of the anterior lobe of the pituitary either by disease or experimental methods is followed by atrophy of the suprarenal cortex. The exact part that the pituitary plays in relation to Addison's disease if any, is as yet unknown.

Snell and Rountree (69) state that stress, nervous strain, and exposure are important etiological factors. They point out that the relatively high incidence of the disease in combatant troops during the war supports their theory.

Other etiological factors mentioned in the literature are, carcinomatous deposits in the suprarenals; vitamin deficiencies, vitamin C and vitamin B being mentioned; trauma; pressure atrophy, arterial emboli, and cycosis fungoides. The incidence of the occurrence of these factors however is extremely rare.

TREATMENT

Since 1855, when Addison's disease was first described, investigators have been trying to devise an adequate treatment for this condition.

Grollman (35) states that Addison's disease is noteworthy for the great number of methods which have been reported as curative of the condition. Thompson and Whitehead (86) quoting from Grollman (35) state that Addison mentions the case of a patient who was believed cured by drinking large quantities of brandy. Since this early date writers have reported cures with dissicated adrenals, epinephrine, etc. These supposed sures, to which many may be added of recent years, illustrate the possibility of error in estimating the value of a given treatment by purely clinical observations.

Previous to 1930 physicians relied chiefly on the Muirhead regime for the treatment of Addison's disease. This consisted in the administration of epinephrine by mouth, by rectum, and subcutaneously at frequent intervals and up to the patients tolerance, together with "desiccated cortex" by mouth, 10-15 grains daily. Results from this regime were observed in 10-20% of the cases. (54)

The successful treatment of Addison's disease should be directed along four main lines: (a) treatment of the underlying disease; (b) protection of the patient; (c) symptomatic therapy; (d) specific organotherapy. (34)

Treatment of the Underlying Disease

The underlying cause must not be overlooked in Addison's disease and should be treated. It is generally agreed that tuberculosis is in the majority of cases the etiological factor in the production of Addison's disease. The problem is therefore, one of treatment of tuberculosis. Rest, general hygienic care, diet, and stimulation, moderate exercise, outdoor life and sunshine are all important. (81)

If the pathological process involved is one of cortical atrophy, treatment is more difficult as the cause of this condition is unknown. In this case however, those factors listed when the condition is caused by tuberculosis should be resorted to here.

If the condition is due to syphilis, specific therapy is possible. This is a very infrequent factor in the production of the disease, however, and so offers little when all the cases of Addison's disease are considered. (34)

The remainder of the cases of Addison's disease may be considered in much the same manner; whether due to amyloidosis, malignancy, malaria, etc., an attempt should be made to treat the underlying disease.

Protection of the Patient

Greene (43) states that the sensitivity of the patient with a mild or moderate degree of adrenal insufficiency to the stress and strain of daily life and the ease with which a crisis can be precipitated is sufficient warning to indicate that the patient should be protected in every possible way.

Symptomatic Therapy

This consists chiefly in the provision of an adequate intake of fluids and salts and the limitation of potassium intake.

Allott (1) in 1936 in reviewing the development of treatment of Addison's disease from 1926 states that Bowmann and Kurland (10) and Marine and Bowmann (52) in studies on the electrolyte pattern of the blood following adrenalectomy in cats and rabbits shows that the life of the adrenalectomized animals could be prolonged by the administration of sodium chloride.

Sister Mary Victor (88) working at the Mayo

foundation states that clinical investigation by members of the faculty of the Mayo foundation have indicated that in order to get optimum therapeutic results on the treatment of Addison's disease, it is necessary that large doses of sodium salts be administered along with the other therapeutic measures as well as the intake of potassium be restricted.

Rogoff, and Stewart (61) oberved extension of survivals after adrenalectomy on animals as a result of injecting sodium chloride.

Nelson and Kendall (58) showed in 1936 that the restriction of potassium facilitated the maintenance of adrenalectomized dogs with sodium chloride and sodium bicarbonate or citrate, no hormone being used, and by this means the constituents of the plasma remained at perfectly normal levels. Investigating previously had revealed that potassium was retained in adreno cortical insufficiency, and Hastings and Compere (45) had previously commented on the possible bearing of this retention on the development of symptoms of adreno cortical insufficiency. (56)

Newbold (56) states that this information received no practical application until Nelson (57) showed that even small amounts of potassium by mouth

would precepitate a crisis in dogs that were being maintained with sodium salts on a diet low in potassium, and that a dietary intake low in potassium was highly beneficial for the continuous maintenance of such animals.

Newbold (56) concluded from this that the tolerance for potassium of man and animals depends on the competency of the cortical tissue of the adrenal glands.

Atchley and Loeb (3) quoting from Root (63) sought to explain the mechanism of salt in the treatment of Addison's disease. These investigators wondered whether the level of serum electrolytes in Addison's disease resembled that of a high intestinal obstruction, diabetic coma, or cholera. They found that there was even less sodium in the blood of patients with Addison's disease than in the above conditions.

They concluded from their clinical observations that "the adrenal exerts a regulatory effect upon the sodium metabolism, through the medium of the kidneys, and that when the adrenals are removed, the rate of sodium excretion is abnormally increased to the detriment of the whole organism." They further conclude that although salt feeding will not maintain life for more than three weeks in adrenalectomized animals,

"numerous physiologic and clinical disturbances of acute suprarenal insufficiency may be controlled by the injection of large amounts of sodium chloride without any other therapeutic measures."

In conclusion it may be said that there is a close correlation with the degree of retention of potassium and the loss of sodium in Addison's disease, and the beneficial effects of an increased intake of sodium are not obtained in patients unless the intake of potassium salts is limited.

Specific Organotherapy

In 1930 Swingle and Pfiffner (80) announced the preparation of a potent extract of the adrenal cortex and with Hartman and others developed the cortical hormone (64). Hartman (42) suggested the term "cortin" for the extract and this name has been generally used by to the present time.

This early experience with extracts of the adrenal cortex aroused the hope that a method of substitution therapy had been found. A period of discouragement followed however which was the result of the bulkiness of the injections required, their painfulness, occasional occurrence of abscesses at site of injection, and the costliness of the material. (56)

Greene (34) has attempted, along with many others to compare diabetis mellitus and Addison's disease. He states that "as the discovery of insulin was the final step in establishing the role of insufficiency of the islands of Langerhans in the pathogenesis of diabetes, the discovery of the cortical hormone has furnished final proof of the rold of adrenal insufficiency in the pathogenesis of Addison's disease."

The loss of the cortical hormone in Addison's disease apparently removes the normal regulatory mechanism of the blood sodium level, which falls, resulting in the train of symptoms known as adrenal insufficiency. (64) As mentioned in the discussion of physiology, there is a lesser fall in the blood chlorides and a decrease in the blood volume associated with a proportionate increase in the concentration of the plasm protein, exygen capacity, sulphate and phosphate, where as both the non protein nitrogen of the plasm and the potassium increase disproportionately. Investigation has shown that these various alterations may be reversed by administration of adrenal cortical hormones. (56), (92)

There has been a great deal of debate by various

investigators as to the exact position as regards the proper employment of the cortical extract. Wilkinson (92), Reifinstein (64), Victor (88), Newbold (56), Greene (34), and many others agree that extracts of the adrenal cortex have their greatest value in the treatment of patients in crisis. They agree also that the requirements for treatment in the various stages of Addison's disease are difficult to anticipate and must be highly individualized. Cleghorn (22) for example states that in certain cases, when the cortical extract has been given over prolonged periods of time, the patients have been restored to a measure of health not attained by treatment with salt alone. Allott (1) believes that when treating the chronic stage of Addison's disease with salt and the potassium and urea begin to rise, it is advisable to give cortin. Newbold (56) advises the periodic administration of cortin as a precautionary measure.

Cortical extract has been administered both orally and parenterally with advantages and disadvantages cited for both methods. Grollman (35) believes that the oral administration of the extract is the better method as the parenteral administration of any therapeutic agent has the disadvantage that it must be a

highly purified product. He also states that when given by mouth the drug can be given in divided doses which is more effective than when administered in a single dose as would be necessary if given parenterally.

Greene (34) states that oral therapy is out of the question in that it takes three to five times as much to produce comparable results as when the extract is given parenterally. This, considered with the cost of the extract which amounts from $5 to $15 a day even when given parenterally precludes its oral use.

Root (63) states that subcutaneous and intramuscular adminstration is possible with most preparations but in an emergency, the intravenous administration is necessary.

Dosages required have been determined largely on the basis of clinical experience; a process of trial and error. The requirement in crisis is 10-20 cc or more daily (63). The dosage is subject to much variation as for example, the slightest sign of infection is an indication for immediate intensive treatment with adrenal cortex extract. The same factors apply in cases in which operations are to be performed. (34)

The maintenance dosage can be determined only by gradual reduction in the dosage with careful

observation of the general condition of the patient. Root (63) states that small doses, 1-5 cc are useless, and that the patients need either 5 cc or none at all.

There has been little mentioned in the literature as to the possible harmful effects of overdosage with cortical extract. Wilkinson (92) Grollman (35) and others, however, state that large doses may be given safely intramuscularly or intravenously, and are free from unpleasant reactions.

In order to determine the therapeutic value of the cortical hormone in the treatment of Addison's disease it is necessary to review results obtained from its use. It is difficult however to interpret the statistical data on the results of treatment of Addison's disease because occasionally long survivals occur without any treatment. (56)

Newbold (56) gives an account of the last survey of the literature made July 1, 1937 by Runearson, Snell and Hausner (65). They reported a series of 43 patients and state that 24 of the 43 were still alive at the end of the period and that the condition of the survivors was better. It must also be considered that not all of the 43 patients received the advantage of all the newer knowledge available.

Greene (34) reports a series of 34 cases of

Addison's disease in which treatment with salt and an extract of the adrenal cortex was used during a period from 1930-37. He states that the treatment added little to the apparent life expectancy in many cases but definitely prolonged life in a limited group of cases.

It is probable that a synthetic preparation with adreno cortical activity will be available before long. This should greatly reduce the cost of substitution therapy in Addison's disease and increase its efficiency. (56)

In conclusion to the discussion of cortical and salt therapy in Addison's disease, it may be said that the successful management of a case of Addison's disease depends not on the choice of hormonal or of salt therapy but the combination of the two to secure the best results.

Homeografts of Adrenal Cortex

Before concluding the discussion of therapy in Addison's disease it is necessary to mention some recent work on this problem which consists of homeografts of adrenal cortex.

Newbold (56) states that the most that can come from the efforts to prepare a synthetic substance with

cortin like activity will be something to replace what is permanently lacking in Addison's disease. The patient still will require treatment as long as he lives and in order to accomplish a permanent cure some way must be found to transplant adreno cortical tissue successfully.

Homeografts, which consist of transplants from one animal to another of the same species have failed to grow in most instances. This has been attributed to some biologic incompatibility displayed by the host toward the graft. (56)

Goldzieher and Barishaw (36) reported a case of Addison's disease in which transplantation of cortical tissue was successfully accomplished. The adrenal tissue was obtained from a case of hypercortical syndrome and was transplanted into the rectus muscle. The patient survived for a period of nine months and appeared to be restored to comparative good health. Death was due to pneumonia. Autopsy revealed survival of the transplanted cortical tissue in a morphologically adequate state of preservation.

In conclusion it may be said that transplantation seems to be a promising procedure in the treatment of Addison's disease and might under improved conditions, approach a real cure.

SUMMARY AND CONCLUSIONS

The adrenal glands are made up of two phylogenetically distinct structures, the cortex, which is derived from the Wolffian bodies, and the medulla which arises from the embryonic sympathetic nervous system. The medulla which is concerned with the secretion of epinephrine is not the indespensable function of the adrenals. The cortex of the adrenal glands is essential for the maintenance of life. The cortex is concerned with the elaboration of a hormone which regulates the salt and water balance of the body. Addison's disease occurs primarily as a result of a deficiency of the cortical hormone. The clinical manifestations of the disease occur when approximately four fifths of the gland substance is destroyed.

The cardinal symptoms of Addison's disease are asthenia, pigmentation of the skin and mucous membranes, anorexia, loss of weight, hypotension, and collapse with circulatory failure.

The diagnosis of Addison's disease is based on the presence of the cardinal symptoms, but chiefly on the characteristic pigmentation in the disease. In case of doubt resort may be had to (1) effect of cortin

on sodium and chloride balance; (2) restricted salt intake; (3) adminstration of potassium; (4) x-ray evidence of calcium of adrenal glands.

The disease is rare; mortality figures quoting 0.4 per 100,000 population in the United States. It is twice as common in the male as in the female and is most frequently a disease of middle life, occurring most commonly in the fourth and fifth decades.

The clinical course of Addison's disease is divided for practical purposes into three periods, depending on the degree of destruction of the cortical tissue. The disease usually pursues a gradually downward course, starting with a period of latent adrenal insufficiency, followed by a period of partial adrenal insufficiency and terminating by crisis.

Tuberculosis of the adrenal glands accounts for 80-90 per cent of the cases of Addison's disease. The primary tuberculous infection is in the lungs in the majority of cases, and reaches the adrenals by the hematogenous route.

Atrophy of unexplained origin accounts for approximately 10 percent of the cases of Addison's disease. Many theories have been suggested as to the nature of the process but none of them are based

on sufficient evidence to be adopted.

Amyloidosis of the adrenals although rare accounts for the majority of the remaining cases of Addison's disease. The process is the result of the deposition of chondroitin in the adrenal glands with atrophy of the parenchymatous cells due both to pressure and diminution in the blood supply.

Syphilis when involving the adrenal glands may produce the characteristic clinical symptoms and signs of Addison's disease. The condition is extremely rare. An immediate response is seen to antiluetic therapy.

Other etiological factors in Addison's disease are so rare that they warrant little discussion.

Treatment of Addison's disease consists of treatment of the underlying disease; protection of the patient; symptomatic therapy, and specific organotherapy. The administration of sodium chloride is of unquestionable value. The administration of sodium chloride along with the limitation of the potassium intake and the occasional administration of cortical extract will suffice in the treatment of most cases. Cortical extract has its chief value in the treatment of crisis. The parenteral adminstration of the extract is advisable in view of the cost of the material. The

successful management of a case of Addison's disease depends not on the choice of hormonal or of salt therapy but the combination of the two to secure the best results.

Homeografts offer promise in the treatment of Addison's disease and may in the near future, give rise to a real cure for Addison's disease.

The future offers much for the study and treatment of Addison's disease. Once the cortical extract is made available to the patient at a reasonable cost there is reason to hope for a better understanding of the role of adrenal insufficiency in medicine and of the clinical indications for the therapeutic uses of the extract of the adrenal cortex.

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