Addison's disease and the adrenal glands

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and the
Adrenal Glands

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Presented to the College of Medicine,
University of Nebraska
April 6, 1942
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Introduction

It is the purpose of this paper to present an historical review of the pertinent literature concerning the work of the outstanding men in this field during the century since its recognition as a clinical entity.

The anatomy, gross and microscopic, physiology and pathology are presented as a background against which the treatment is developed.

There are two main points to be considered in any discussion of Addison's disease: 1. symptoms and diagnosis and 2. treatment. Treatment is, of course, the main objective, but it is necessary to make a correct and clear-cut diagnosis if the results of therapy are to be evaluated properly. Incorrect diagnosis in many patients with symptoms resembling those of Addison's disease has led to much confusion as to results obtained by various therapeutic measures.

Too many "cures" have been reported in cases in which the diagnosis was not confirmed. The literature is so overburdened with claims of "cures" that it is extremely difficult to locate the cases in which recovery did occur. Furthermore, it is extremely doubtful if any form of treatment used has ever cured or has been any more than a minor factor in those recoveries that have been proven.
A number of men report good results from treatment with extracts which later have proved to be relatively impotent. Therefore it is necessary to select a few men whose work is beyond question and use that work as a basis for most of the conclusions.
History

The adrenal glands were overlooked completely until 1563. At that time Bartholamaeus Eustachius published his "Opuscula Anatomica" and in the sixth chapter he presented the first clear description of the adrenal glands. Many theories were advanced as to their function during the next four centuries, but none were able to explain it completely. Spigelius thought that their function was to hold the stomach in place. Highmore believed that they absorbed humid exudates from the blood. Thomas Wharton thought that they withdrew toxic substances from the nerves. Sylvius suggested that they secreted a substance which prevented the coagulation of blood in the body. Others at that time thought that they were tied up in some way with reproduction.

Morgagni and Molinetti thought that the adrenal withdrew blood from the kidney and prevented the formation of urine in the fetus. Von Helmont believed that they secreted a substance which prevented the formation of renal calculi.

Bergman in 1839 first noted the relation of the adrenal medulla to the sympathetic nervous system.

It remained for Thomas Addison in 1849 to describe to the South London Medical Society the syndrome which we now know by his name. In 1855 he published his first paper with a report on the eleven cases he had seen.

Ecker in "Der feinere Bau der Nebennieren beim Menschen und den vaur Wirbeltierklassen" reported the
glandular structure of the adrenal cells in 1864. He suggested that these cells must pour a secretion into the blood or lymph.

Brown-Séquard in 1856 extirpated the adrenals from laboratory animals and proved that the secretions of those glands were essential for life.

Also in 1856, Vulpain added ferric chloride to the adrenal vein and obtained a green color. He also noted this reaction in the adrenal medulla.

In 1894 Oliver and Schäffer observed the remarkable pressor effects of extracts of the adrenal medulla. It wasn't until 1901 that Takamine and Aldrich obtained the active principle, epinephrine, in pure form.

In 1927, Stewart and Mogoff were able to prolong definitely the life of adrenalectomized animals with extracts of the adrenal cortex and salt solutions. In 1930, Swingle and Pfiffner prepared an extract which was much purer and much more powerful. The commercialized product of their preparation is on the market today. In 1936 Kendall isolated an adrenal cortical hormone in pure form. Reichstein later synthesized this hormone—desoxycorticosterone. Today pellets of this substance implanted beneath the skin constitute the main form of replacement therapy in this disease.

(4,6,6a)
Gross Anatomy

The adrenal glands are two small flattened yellowish bodies, lying behind the peritoneum in the superior, posterior portion of the abdomen. They are situated immediately above and in front of the upper pole of the kidney.

The right adrenal is somewhat triangular, the left is more semilunar in shape, larger and placed somewhat higher than the right. The glands are about three to five centimeters in length, and two to three centimeters in width. They are four to six millimeters in thickness and weight from 1.5 to 2.5 grams each.

The left adrenal gland is semilunar in shape, the concavity is closely applied to the medial border of the upper part of the left kidney. The superior portion of the anterior surface is covered with peritoneum and lies in relation to the cordia of the stomach. The lower surface is in contact with the lineal artery and the pancreas and is not vested with peritoneum. The posterior surface is divided into two portions by a vertical ridge. The medial area is in relation to the left crus of the diaphragm and the lateral area rests on the kidney.

The triangular right adrenal has its base directed downward which is in contact with the anterior and medial aspect of the upper end of the right kidney. It lies behind the inferior vena cava and right lobe of
the liver and in front of the diaphragm. The anterior surface of the gland is directed anteriorly and laterally. The inferior vena cava lies on the medial portion of this surface and it is, therefore, devoid of peritoneum. The right adrenal vein emerges from the hilum of the gland a short distance below the apex and joins the inferior vena cava. The portion of the gland below the hilum on the lateral side is covered with peritoneum reflected from the coronary ligament and is sometimes in relation to the duodenum. The part above the hilum and lateral to it lies next the base area of the liver and is devoid of peritoneum.

The posterior surface is divided by a ridge into a lower concave portion and an upper convex portion. The convexity rests upon the diaphragm while the concavity is applied to the kidney.

Accessory adrenals are often to be found in the connective tissue surrounding the glands.

"Accessory cortical nodules or interrenal organs are of embryonic origin. They are composed of small encapsulated rests of cortical cells radially arranged around a central vein. The layers are usually arranged in inverted order. Accessory interrenal bodies are often seen in the region of the suprarenal glands, in the celiac plexus, on the surface of the liver, about the genital organs, in the retroperitoneal space, along the intermediary line and rarely on the surface of the
The adrenal gland is well supplied with nerves from renal and celiac plexuses. Some men believe that part of the fibers originate from the phrenic and vagus nerves. The nerves enter the medial and inferior portion of the gland, traverse the cortex, form numerous small ganglia and then terminate around the medullary cells.

Arteries, of rather large size from the aorta, phrenic and renal arteries, subdivide into minute branches before entering the cortex of the gland. There they break up into capillaries which coalesce to form the venous plexus in the medullary portion. The adrenal vein drains the medullary plexus and the several branches from the cortex before emerging at the hilum of the gland. The left one drains into the renal vein. The right into the inferior vena cava. Lymphatics drain into the lumbar glands.
Microscopic Anatomy

The cut section of the gland presents a bright yellow cortex and a softer, reddish-brown medulla which appears as a thin line making up about one-tenth of the gland.

The cortex is made up of three ill-defined layers:

1. The Zona glomerulosa which lies just inside the capsule. It consists of small columnar cells lying in ovoid groups or in arcs which surmount the cells of the next zone. The free edge of each cell is adjacent to a capillary. The cytoplasm is scant and may contain small lipid droplets. It also has small lumps of granular material which take a nuclear stain in man. The nuclei are prominent and stain deeply.

2. The Zona fasciculata makes up the greater part of the cortex and is made up of polyhedral cells arranged in straight cords. These cells are very rich in fatty droplets of cholestrol esters, fatty acids (mainly oleic acids) and phospholipins. Only small amounts of cytoplasm are present forming thin walls for the fat droplets. These fat droplets are about the same size in any given cell. There may be more than one nucleus per cell. They are centrally placed and quite vesicular. Mitotic figures are common in the outer edge of this zone.

3. The Zona reticularis lies between the Zona fasciculatus and the medulla. In the outer portion of this zone the cells are almost identical with those in the
previous one except for a decreased lipoid content. Near the medulla, two new cell types, so called "light" and "dark", make their appearance. The former are large and rounded with a pale-staining granular cytoplasm and a pale, vesicular nucleus. The darker staining cells are small with deeply staining homogeneous cytoplasm and small hyperchromatic nuclei. These cells contain large amounts of lipoid substance and clumps of yellowish-brown pigment.

The boundary between the cortex and medulla is somewhat irregular and the cells are mixed. The cells of the medulla are arranged in small rounded groups or short cords surrounded by sinusoidal venules. The cytoplasm contains fine brown granules when stained with potassium dichromate and gives a green color when stained with ferric chloride.
Embryology

in all animals the medullary tissue and the sympathetic ganglion cells have a common origin. They develop from primitive cell masses which have separated from the neural crest. Migrating from their sites of origin, these masses of ectoderm cells undergo differentiation along two paths, some into sympathetic ganglion cells, others into chromaffin tissue. In the abdomen on either side of the mid-line, a relatively large mass of chromaffin cells becomes enveloped by cortical tissue to constitute the adrenal medulla. Other smaller masses persist as accessory chromaffin tissue in association with the ganglia and plexuses of the sympathetic nervous system. On the other hand, sympathetic ganglion cells may be found scattered among the cells of the adult adrenal medulla. The cortex is developed from mesoderm. It arises as a bud from the celomic epithelium covering the inner side of the fore part of the mesonephros. The celomic epithelium immediately behind this area gives rise to the germinal epithelium from which the sex glands develop. Interestingly enough, the hormones of the adrenal cortex and the sex hormones are very closely related, structurally.
Physiology of the Medulla

The medulla elaborates a hormone, first isolated by Takamine and Aldrich in 1901, known by several names, adrenalin, epinephrine, adrenin and suprarenin. It is closely related to the amino acid tyrosine and is a secondary alcohol, 3,4 dihydroxy-α-phenyl-β methyl-amino-ethanol. Stoltz first succeeded in preparing it synthetically in 1904 and his work was confirmed by Dakin in 1905. There are three isomers possible, a levorotatory, a dextro-rotatory and a racemic form. The levorotatory compound occurs naturally and is fifteen times as powerful as the dextro form.

Epinephrine, in its effects, imitates the action of the sympathetic nervous system perfectly and is therefore known as a Sympatho-mimetic substance. It produces dilatation of the coronaries, inhibits the intestinal muscles, increases the blood pressure and slows the heart. The last effect is a result of carotid sinus reflex due to increase in blood pressure and is not present if that reflex is abolished. 0.5 cc. of a 1-1000 solution injected subcutaneously in the human increases heart rate. It produces a dilatation of the vessels of the muscles and constricts the arterioles and capillaries of the skin, mucous membrane and splanchnic viscera. The vessels of the lung are little affected while the intestinal vessels may dilate. The action of epinephrine postpones muscular fatigue and increases capacity for work. The respiratory rate is deeper and more rapid. A
hyperglycemia is produced by epinephrine, antagonistic to insulin. Oxygen consumption is increased and the basal metabolic rate is raised. Epinephrine is inactive when administered by mouth.

The continuous secretion of epinephrine into the bloodstream is open to question. Stewart and Kogoff estimated that in anesthetized animals 0.0002 milligrams per kilogram of body weight was produced each minute. However, the effect of the anesthetic and operative procedures were not ruled out.

During rest and under physiological conditions, the concentration is believed to be not greater than 1-2,000,000,000 or 1-1,000,000,000. Cannon and Rapport measured the amount of epinephrine output during periods of excitement and found it to be between 0.003 and 0.004 milligram/kilogram/minute. The secretion of epinephrine is under control of the nervous system. None is liberated from the denervated gland. The fresh gland contains about 0.1% epinephrine by weight. The fatal amount in both adrenals in man is about 10 milligrams. The secretions of the adrenal medulla are not essential to life.
Physiology of the Cortex

The cortex of the adrenal, unlike the medulla, is essential to life. Removal of more than three-fourths to five-sixths of the cortex results in death. Stewart and Rogoff showed that completely adrenalectomized dogs could be kept alive by the injections of adrenal cortical extract and physiologic saline solution. Hartman's extract was called Cortin and possessed similar properties.

In 1930, Swingle and Piffner extracted, by means of lipid solvents, a very powerful substance which prolonged the life of adrenalectomized animals indefinitely. It has been used extensively in Addison's disease.

An extract five times as potent was isolated later by Grollman and Firor.

In 1936, Kendall isolated five closely related sterols from the cortex of which three were physiologically active.

About the same time, Reichstein isolated an active substance from the cortex in crystalline form, which he called "Corticosterone". Kendall stated that this substance was identical with one of his steroids.

Steiger and Reichstein developed a compound called "Desoxycorticosterone" from stigmasterol. It has one less oxygen atom and is about one-third of the natural product in potency.

It may be stated here also that several sterols with the actions of female and male sex hormones have been isolated from the adrenal cortex.
The action of extracts of the adrenal cortex on the normal animal are minimal. There are, however, a few changes in normal physiology which are noteworthy. The cortical hormones seem to postpone fatigue by depression of the metabolism of muscle during exercise. Britton states that its administration raises the blood sugar and increases the glycogen in the liver. A definite increase in potassium and decrease in sodium excretion was noted by Thorn. Animals may be partially protected from vitamin C deficiency by cortical hormone. Large doses, however, do not furnish complete protection.

Long and his associates have shown that cortin is capable of exerting a diabetogenic action in pancreatectomized animals. It also was found that pancreatectomized-adrenalectomized animals maintained on a high salt diet were not diabetic. This latter observation shows that cortin, Hartman’s name for his extract, exerts an influence which can be simulated but not replaced by sodium chloride. (4)

The full significance of these findings becomes clearer when we examine animals suffering from adrenal insufficiency. In these animals the blood sugar falls and the store of liver glycogen is depleted. The hormone of the adrenal cortex, then, must exert an action opposite to that of insulin. Nor does it have the same effect as epinephrine. The latter mobilizes glycogen stores from the liver, but produces a high blood sugar.
It follows, then, that in diabetes the adrenal cortex, as well as the pituitary, is concerned not only in the maintenance of blood sugar levels but in the vital process of sugar metabolism. (6)

In addition to the effects on sugar metabolism, adrenal insufficiency results in a fall of the total electrolytes of the extracellular fluid, sodium is lost from the blood and tissues and there is a redistribution of body fluids. Potassium is no longer excreted by the kidney and accumulates in the extracellular fluids. That this sodium loss was due to failure of the renal tubules to reabsorb that ion was demonstrated by Loeb and Harrop independently. (7) and (8) They found that in adrenal insufficiency, the loss of sodium ion was not paralleled by a loss of potassium in the urine. They point out that the sodium loss could not be due to acidosis, because in keto-genic as well as ammonium chloride acidosis the sodium level in the urine was paralleled by the potassium. Loeb (9) determined the titrable acidity and the ammonia content of the urine of a patient with Addison's disease maintained on a high salt diet. When the salt intake of this patient was restricted, there was no rise in either of the two products in the urine. Then salt was forced. The ammonia level increased only slightly, but not enough to indicate acidosis. The bicarbonate level in the blood remained constant throughout. This infers quite conclusively that the sodium loss in adrenal insufficiency not due to an acidosis but to a failure of the kidney to re-absorb it from the glomerular filtrate.
The loss of sodium from the extracellular fluids makes them hypotonic to the intracellular and there is a shift of water into the cells.

The loss of water into the tissues results in an anhydremia, with a consequent rise in plasma proteins, hemoglobin and oxygen capacity. The hemoconcentration produces a decreased plasma volume, a slowing in the rate of blood flow and lowering of the blood pressure. A rise in blood urea, sulfates and phosphates follows the impairment of renal function and shock may appear eventually.

The above seems to be an adequate and simple explanation of the fluid shift in adrenal insufficiency. Evidence to the contrary has been offered by Swingle. (10) He believes that the action of the hormone is not just upon the electrolyte substances but upon the capillary walls themselves. Animals showing shock due to adrenal insufficiency recover quite completely following the administration of cortical hormone alone without the additional sodium.

In certain species, adrenal insufficiency produces shock without any alteration in the electrolyte balance. Harrison and Darrow (11) and (12) investigated the sodium concentration and its relation to symptoms but failed to find any correlation between the two.

The role of potassium in Addison's disease is also of great importance. While sodium is eliminated in great quantities from the body, potassium is retained and accumulates in both the extracellular fluids and in the
If patients with Addison's disease are placed on a low potassium diet considerable improvement in their symptoms is noted. This would indicate that some of these symptoms were due to the accumulation of that ion. (13).

The foregoing indicates that Addison's disease, like the other hormonal dysfunctions, is not a simple deficiency of one substance. The cortex of the adrenal gland apparently secretes several factors which influence body economy.
Etiology

Numerous etiological factors have produced the syndrome known as Addison's disease. The typical cases described by him were due to tuberculosis of the adrenal glands. This group still constitute the largest number of cases. Since Addison's time, other causes have been found in sufficient numbers to warrant their consideration. Atrophy of the adrenals constitute the next largest percentage. Other causes are syphilis, pyogenic infection, trauma, hemorrhage, amyloidosis, fatty degeneration, neoplasms, both primary and secondary, vascular lesions such as arthritis and thrombosis and hypoplasia. Tuberculosis accounts for 69.72% of cases while atrophy was observed in only 19.48%. Amyloidosis was present in 1.73% of Guttman's 566 cases. (15)

Tuberculosis is usually secondary to a primary focus elsewhere in the body. In a study by Snell (20), 67 out of 164 cases of Addison's disease were complicated by tuberculosis elsewhere. The pulmonary lesion was the most common and those in the genito-urinary were next. Osseous tuberculosis alone accounted for about one-eighth of the complications.

Guttman (15) reports that tuberculosis of both lungs and urogenital system accounts for 65% of cases, joints and bones for 30%, while the lungs alone account for only 2 to 5%. Lewis found that tuberculosis was primary in the gland in 26.4% of cases, while Schwarz working in Gohn's laboratory found lung lesions of the same age or older in every case of tuberculosis of the adren-
als. But Guttman attributes this to the painstaking search made for these lesions by these men. However, Liborsch and Robinowitsch have shown that apparently healed lesions can act as foci, showering organisms in the blood stream.

Various men have advanced ideas as to the mode of infection of the adrenals. The most plausible are:
1. Intrauterine
2. Lymphogenous
3. Hematogenous (15)

The first is quite unlikely because evidence of such a mode of transmission is frugal. Usually in such cases the placenta is infected and the infant develops the disease clinically within three weeks of birth. Also the high mortality rate of tuberculosis in infants speaks for the pathogenicity and it is very highly improbable that the organisms would lie dormant in such a susceptible tissue for so long since the highest death rate from Addison's disease is encountered in the third and fourth decades of life.

The lymphogenous route has been considered but several things are against it. Tuberculosis tends to spread along the lymphatics in their direction of flow. The site of the lesion in the gland does not speak for the lymphatic route. Regional lymph nodes may be involved but they are due probably to direct extension from the lesion in the gland. The incidence of general lymphatic involvement in Addison's disease due to tuberculosis is negligible.
The third mode offers the best possibility. The lesion is seldom primary in the adrenals. (15) It is commonly associated with other visceral lesions. According to Guttman (15) and Snell (20) those sites which we feel quite certain are due to hematogenous spread, namely the urogenital system and bone, are most frequently seen associated with tuberculosis of the adrenals. As mentioned above, Lubarsch and Robinowitsch demonstrated the possibilities of even old healed lesions scattering organisms into the blood.

The incidence of tuberculosis of the adrenals is very low in comparison with other lesions which are known are of hematogenous origin.

The etiology of the next most common cause, atrophy, is quite controversial. Everything from trauma to acute infectious processes have been described as the cause but none quite fit.

Simmonds believed that atrophy was due to a completely healed tuberculous lesion. (18) But Guttman (15) states that an authentic lesion of that type has never been proven successfully.

Mats have rather large accessory adrenals consisting mainly of cortex. Jaffe (21) removed the adrenals, leaving the accessory cortical glands behind. He found that after several months of ill health and finally death that the accessory glands showed fibrotic changes similar to the atrophic lesions seen in many human adrenals in Addison's disease and attributed the changes to overuse. This theory is supported by the work of
Sussman (22) who found atrophy occurred more frequently in females between the ages of 35 to 45 than in males in a ratio of more than 2:1. He attributed this to some strain connected with sex function. More males were observed with atrophy between the ages of 10 and 30. Guttman also found the incidence of atrophy to be highest in the third decade. (15)

Thomas (15) and Aschoff (19) reported marked edema vacuolar, granular degeneration and loss of lipoids in cases of death from scarlet fever and diphtheria. Paunz made a study of 1,171 autopsies with death due to various causes and found changes in the adrenal cortex in 197 or 17% of cases which he describes as; production of plasma cells, lymphocytes and macrophages from the reticular network with some connective tissue replacement. This aroused the speculation that acute septic conditions might produce Addison's disease. Guttman (15) however, examined 125 cases in which the adrenals showed degenerative changes with Addison's disease. Twenty died of acute infection, 27 of simple chronic infection, 8 had chronic caseous tuberculosis, 16 had syphilis, 2 lymphogranuloma and 52 died with tumors. He found that the changes in the cortex were not peculiar to any specific disease or were they related to the acuteness or chronicity of the disease. He further states that the pathological changes in the adrenal cortex were not the same as those observed in atrophy of the cortex in Addison's disease.

Guttman (15) plotted the causes of death against those from Addison's disease. He offered, as support of
his view, the fact that the incidence of deaths due to Addison's disease during the influenza epidemic dropped instead of rising as would be expected during an epidemic or acute infection. It seems, though, that the acute infections would take most of these people before the symptoms appeared. Only after several months or years would the deaths due to atrophy show up. That seems to be the case. A rise of diagnosed cases of Addison's disease started in 1919 and reached its peak in 1924. Only a careful study of personal case histories would reveal any connection and this is not available.

If the work of Jaffe and Sussman is accurate and reliable, the theory of overwork of the adrenal cortex, perhaps in connection with sex functions, stands out as the most plausible possibility.

The question of hypertrophy during times of stress may well be raised. Guttman (15) describes regenerative changes in sections of the cortex of adrenals showing atrophy. These areas are adenomalike and show degenerative changes themselves, so their functional ability is questionable.

Amyloid degeneration of the adrenals is not infrequent in patients dying of tuberculosis of other systems, but it is frequently overlooked because of the general debility of the patient. (14)

Bronifin and Guttman (14) found 14 cases of amyloidosis in 100 cases of tuberculosis coming to autopsy. Eighteen bodies showed amyloidosis and 14 to 18 showed that change in the adrenal gland. The degree of amyloid degeneration
varied and had some relation to symptoms: 2 cases showed only a mild degree of involvement; 6 cases showed a moderate and 6 a marked degree; 5 cases had a clinical diagnosis which was called "doubtful", of these 3 were moderate and 2 were marked. The 2 cases of mild degree and 1 from each of the other groups had no clinical symptoms.

Syphilis of the adrenals producing Addison's disease has been reported (18) but constitutes only 0.25% of cases (15). Gummata and spirochetes are usually present. Aplasia has been reported (15). Franks (23) reported cancer, fatty degeneration and "sarcomatous" growth as causes. Guttman in his 655 cases listed such causes of Addison's disease as thrombosis of the adrenal vein, arteriolar sclerosis, trauma, hypoplasia and metaplasia of bone marrow.
Pathology

There are two lesions resulting from tuberculosis. The most common is the fibrocaseous type (17) and the other, an indirect lesion, is amyloidosis. (14) The lesion is usually bilateral, 68.72% of cases, and unilateral in only 1%. In the unilateral lesions, the destruction is seldom complete, while in the bilateral lesion it is often necessary to search for remnants of the glands by serial section. The caseating process in unilateral lesions is somewhat more active than in those involved in both adrenals. An acute caseous form involving both glands is rarely seen.

In the majority of cases the tuberculous lesion has almost completely replaced the body of the gland. Semi-caseous, confluent nodules of from a few millimeters to 2 and 3 centimeters in diameter, separated by septa of grayish-white connective tissue constitute the usual lesion. The medulla is apparently less resistent to tuberculosis than the cortex, for it is frequently destroyed leaving large portions of the latter uninvolved. (15)

McGuire (16) in 1884, described a quite typical lesion. In his case the capsule itself was enlarged and firm. It consisted of a whitish transparent stroma, containing yellowish patches. Microscopically, this stroma was fibronuclear. Some epithelial cells and many large giant cells were described. The yellowish patches were the result of
caseous degeneration. The blood vessels showed thickening of their adventitia and some endarteritis. Guttman (15) states that the lesion consists of one or more caseous nodules, single or confluent. The nodules in the cortex tend to be isolated and well delineated; those in the medulla tend toward confluence. The glands tend to be enlarged when not completely destroyed.

"No proved case of healed tuberculosis of the suprarenal glands has been reported in the literature". (15)

The less common of the two tuberculous lesions has not been studied extensively. The cause of amyloidosis is obscure. It is seen in chronic diseases, i.e. osteomyelitis, tuberculosis and syphilitic disease of the bone. (17). Bronfin and Guttman (14) report an incidence of 14% of amyloidosis of the adrenals in 100 autopsies on tuberculous patients. The lesion tends to be limited to the cortex, leaving the medulla intact. (18) The fibrous tissue in relation to the vessel walls is the primary site of amyloid formation. Further extension of the process leads to destruction by degeneration of the cortical cells. Bornstein and Gremels have shown that at least one-fourth of the cortex is necessary to support life.

The relation of symptoms to lesions has been described under "Etiology".

The atrophic gland is much reduced in size. Its weight varies from 0.75 Gram to 3.0 Grams. Grossly the cortex and medulla are ill-defined. The cortex occupies the greater part of the gland. The microscopic appearance is quite constant. The degeneration is usually limited to
the cortex. Involvement of the medulla appears to be secondary. The cortical cells disappear leaving a collapsed reticulum. The cortical cells themselves show a loss of cellular outline with swelling, vacuolation and fatty degeneration. There is nuclear degeneration and fusion of cells to form large multinucleated forms. Regeneration occurs. Scattered islands of cells are circumscribed adenoma-like nodules appear about the atrophic glands. These areas contain cells of low lipoid content. Central degeneration is often prominent. There may be lymphocytic infiltration or complete degeneration. (15) Guttman does not consider this condition to be simple atrophy in the restricted sense of the word. Since the organ does not shrink because of atrophy of its cellular elements, but because of necrosis and disappearance of cells, he prefers to call it "Primary contracted suprarenal gland".

In regard to the degeneration following acute infectious processes referred to in the preceding section, the microscopic appearance is not the same as in the idopathic atrophy just described. Thomas (15) found vacuolar degeneration under cells of the cortex following diphtheria, and marked edema with granular degeneration in scarlet fever. Aschoff (19) describes much the same thing in his cases with the addition of an apparent loss of lipoids.

Paunz made a study of 1,171 cases following various infectious diseases. He reports 20 cases of acute infection, 27 cases of simple chronic infection, 8 cases of chronic caseous tuberculosis, 16 cases of syphilis, 2 cases of
lymphogranuloma and 52 cases of tumors. He found in addition to simple degeneration marked infiltration of plasma cells, lymphocytes, macrophages and connective tissue. These findings, however, were not typical for any one disease and were not comparable to ideopathic atrophy. (15)

Simple fatty degeneration occurs rarely. There is replacement of the cortical tissue by fat. Vascular lesions of the adrenal vein are not uncommon in acute septic conditions, but death is usually rapid and often accompanied by symptoms of peritonitis. Massive hemorrhage occurs but is not a cause of Addison's disease. Infarction is rare. Thrombosis of the adrenal vein does occur and has been the cause of adrenal insufficiency. (15) Syphilis produces gummata and spirochetes are present.
The Symptoms and Diagnosis of Addison's Disease

In presenting the clinical picture of a patient suffering from this strange malady, one can do no better than to refer to the original work of the man for whom it was named: Thomas Addison. In 1855 he presented eleven cases to South London Medical Society. In his words then:

"For a long period I had from time to time met with a very remarkable form of general anaemia, occurring without any discoverable cause whatever—cases in which there had been no previous loss of blood, no exhausting diarrhea, no chlorosis, no purpura, no renal, splenic, miasmatic, glandular, strumous or malignant disease.

Accordingly, in speaking of this form in clinical lecture, I, perhaps with little propriety, applied to it the term "ideopathic" to distinguish it from cases in which there existed more or less evidence of some of the causes or concomitants of the anaemic state.

The disease presented in every instance the same general character, pursued a similar course, and, with scarcely a single exception, was followed, after a variable period, by the same fatal result.

It occurs in both sexes generally, but not exclusively, beyond the middle period of life, and, so far as I at present know, chiefly in persons of a somewhat large and bulky frame, and with a strongly-marked tendency to the formation of fat.

It makes its approach in so slow and insidious a manner that the patient can hardly fix a date to his earliest
feeling of that languor which is shortly to become so extreme. The countenance gets pale, the whites of the eyes become pearly, the general frame flabby rather than wasted; the pulse, perhaps, large, but remarkably soft and compressible, and occasionally with a slight jerk, especially under the slightest excitement; there is a increasing disposition to exertion, with an uncomfortable feeling of faintness or breathlessness on attempting it; the heart is readily made to palpitate; the whole surface of the body presents a blanched, smooth and waxy appearance; the lips, gums and tongue seem bloodless; the flableness of the solids increases; the appetite fails; extreme languor and faintness supervene, breathlessness and paltitations being produced by the most trilling exertion or emotion; some slight edema is probably perceived about the ankles; the debility becomes extreme. The patient can no longer rise from his bed, the mind occasionally wanders, he falls into a prostrate and half-torpid state, and at length expires. Nevertheless, to the very last, and after a sickness of perhaps several months duration, the bulkiness of the general frame and the obesity often present a most striking contrast to the failure and exhaustion observable in every other respect.

With perhaps a single exception, the disease, in my own experience, resisted all remedial efforts, and sooner or later terminated fatally."

A review of the literature reveals the consensus of opinion that for the most part a case cannot be called Addison's Disease unless actual lesions in the adrenals
with definite clinical symptoms are present. Many cases have been called Addison's Disease on the basis of clinical findings and at autopsy have been described as "Addison's disease without suprarenalopathy". (24) This was based on the prediction that the chromaffin system with the adrenal medulla was responsible for the symptoms of the disease, and that there was injury to the chromaffin system without changes in the medulla. This idea fails to hold today because of the knowledge concerning the function of the adrenal cortex.

A great many cases of Addison's disease have been reported with recovery. Today one tends to question this and to feel certainly it was a mistaken diagnosis. Brenner (18), however, reported a case in which a man with the diagnosis of Addison's disease made a complete recovery and remained perfectly well for many years. The diagnosis here also was questioned. Twenty-four years later the man died of carcinoma of the larynx and an autopsy was performed. A careful search failed to reveal the presence of any cortical material of the right adrenal. The left adrenal cortex was found to be hyperplastic. It weighed eleven Grams, twice normal size and apparently was functioning perfectly after twenty-four years. As was stated under pathology, unilateral lesions are rather uncommon, but the possibility of such a case must be kept in mind.

The symptoms of Addison's disease are best described as single entities. It should be kept in mind, however, that any one or of these symptoms and signs
may be absent.

The presence of abnormal pigment in the skin and mucous membrane is an indispensable sign. Pigmentation of the mucous membrane of the mouth and of the upper and lower surfaces of the tongue is particularly characteristic. When pigment does not occur, the diagnosis is uncertain. (25)

Snell (26) states that in addition to the pigment on the mucosal surfaces, the appearance of minute black freckles on the neck and shoulders is significant.

The blood pressure is usually low. A diagnosis of Addison's disease should not be made in the face of a systolic pressure of over 100 millimeters of mercury. The usual limit of systolic pressure is described by Harrop as being 90 mm. The pulse pressure is usually diminished and the diastolic may be lowered but usually not to the degree that the systolic is. A rapidly falling blood pressure upon assuming a sitting position has been described as characteristic. This fall in blood pressure may be associated with a drop in pulse pressure, rate and syncope, but it is seen in many patients suffering from chronic debilitating diseases and is not characteristic of any one clinical entity. (25)

Asthenia is one of the most prominent symptoms in most cases. It is, with the pigmentation, the most common presenting complaint. The duration of this muscular fatigability is variable.

Weller (27) described two cases in which symptoms of general languor and debility were present over periods
of three-eight years respectively before a clinical diagnosis could be made. Rowntree recognizes a "period of initial destruction" of the adrenals, but ascribes no definite clinical findings to it. He believes that the appearance of asthenia, pigmentation and loss of weight and strength mark the onset of the second stage of the disease. (28)

Rogoff says of this: "Diagnosis when made, has generally depended upon the existence of cutaneous pigmentation together with muscular asthenia, low blood pressure and sometimes gastro-intestinal symptoms, as reported by Addison. It should be recognized that this combination of symptoms when present in a patient as manifestations of adrenal insufficiency, must be regarded as evidence of well advanced of the glands". (29)

After reading many case histories, one finds that the asthenia usually starts as simple "tiredness". The patient finds that he can no longer work during the day and then carry on his normal social activities at night. This becomes progressively worse until he is no longer able to work. If he hasn't sought medical advice by this time he shortly finds that he is unable to leave his bed and even sitting up in bed may bring on "giddy" spells and nausea.

Gastro-intestinal symptoms are more marked in some cases than in others. They vary from a vague nausea and loss of appetite to almost cyclic vomiting. They may be warnings of impending crisis. (25)

In a study on amyloid disease of the adrenal,
associated with tuberculosis and showing clinical evidence of Addison's disease, Bronifin and Guttmann (14) state that the asthenia and gastro-intestinal symptoms are usually absent. As was pointed out under Pathology, amyloidosis tends to attack the cortex and leave the medulla intact. (18) This might lead one to believe that the lesions in the medulla are responsible for the gastro-intestinal symptoms. Harrop (25), however, reports that continued hypotension during remissions, hypoglycemia and pigmentation are associated primarily with lesions of the medulla. Those symptoms seen during relapse, namely; marked asthenia, gastro-intestinal symptoms, shock and hemocoagulation, are due to cortical deficiency. He further states: "It has long been observed that the duration of life is longer and severe crises are less frequent in patients in whom pigmentation is the outstanding characteristic, and in whom marked asthenia and gastro-intestinal symptoms are less evident".

Radiographic studies may be a valuable adjunct in the diagnosis of Addison's disease. Snell says: "In our experience, the presence of definite calcification is, for all practical purposes, pathognomonic of Addison's disease". (26)

R.G. Ball studied 23 cases with a positive diagnosis and found only 26% with demonstrable calcification. No definite calcification was noted in patients without symptoms

study of blood values may aid in making
a diagnosis. An analysis will show a decrease in the chlorides and a rise in urea nitrogen and N.P.N. The tolerance to ingested glucose may be increased. A low fasting blood sugar may be found, but it must be remembered that this occurs also in pancreatic tumors. There is a definite sensitivity to insulin. The injection of two units of insulin may produce an unusual degree of hypoglycemia. Patients with myxedema, however, or hypophysal dysfunction often show the same reaction. There is a definite sensitivity to thyroid extract also. (25) It tends to precipitate a crisis, probably by its action on the metabolic rate. The basal metabolic rate may be decreased as much as 50%, but usually is about -18%. (26)

A diagnostic test has been proposed by several men. (Snell, Harrop and associates) If the patient responds to cortical extract and high salt diet, the extract is adjusted to about maintenance levels with a high salt intake. Then salt is restricted. If the diagnosis was correct, clinical symptoms of relapse begin to appear. The asthenia, gastro-intestinal symptoms, low blood pressure and lowered pulse pressure recur and the patient begins to show signs of relapse. The high salt intake should be restored immediately before the patient passes into shock.

Rogoff (29) presents two criteria in diagnosis which he considers very important. They are: 1. Aversion to fatty foods. He has found this with great constancy both in patients and in experimental animals and attributes it to the congestion seen in the pancreas at autopsy. 2. an increase in N.P.N. and urea nitrogen along with
moderate hypoglycemia and hypercalcemia may be an indication of an impending acute exacerbation or shock.

Weller (27) considers differential diagnosis. He has found that a diagnosis of psychoneurosis or a neuroasthenia is usually the early diagnosis. This mistake is so common because of the fair degree of nourishment and development which they present in the early stages. Howntree and Snell (28) report pain in the upper quadrants in over one-half of their cases and found it most marked at the time of acute insufficiency. Weller states that this pain suggests acute appendicitis in many cases. The differential points are: appendicitis shows a localizing of tenderness to the right lower quadrant and finally to McBurney's point. It also produces a very rapid increase in the white blood count, with a predominance of segmented forms and a shift to the left.

Epidemic encephalitis is a diagnosis not infrequently made in early cases because of its various manifestations. Weller thinks these symptoms are due to the hypoglycemia. He found even such bizarre symptoms as hemiplegia in Addison's disease which cleared completely with the injection of glucose. Wechsler (31) confirms this statement.
Adrenal Preparations in the Treatment of Addison’s Disease

In 1897 Kinicutt summed up the theories on the function of the adrenal gland and found that they fell into two main categories: 1. They neutralized and destroyed toxins present in the blood; 2. They had a secretory function. (32) The latter view seemed to hold sway for Kinicutt was able to obtain case reports on forty-eight patients treated with some form of replacement therapy. He found reports of cures in six cases. Twenty-two showed improvement, 18 were unimproved while 2 had an aggravation of symptoms. The treatment recommended by him at that time was 45 grains of the fresh whole gland by mouth each day. He stated, in part: "....... the results secured justify that, perhaps with isolation and differentiation of the several active principles...... an efficient therapeusis may be obtained for the simple atrophies and fibroid degenerations of the adrenals,..."

Six years later Adams (33) found the results of grafting to be "untoward". He also summed up the results of treatment up to 1903. He stated that many cases appeared to derive benefit from some form of adrenal replacement therapy, although it was impossible to predict which cases would and which would not respond to that type of treatment. However, the probability is that more cases would be benefited by organotherapy than by any other means of treatment known at that time. The main principle of organotherapy, as pointed out by Adams, was to get a continuous and sufficient dose of
the pure substance into the blood stream unaltered. He noted that the intravenous route was impractical.

Some of the earliest work on the effect of adrenal extracts was reviewed by Oliver and Schaffer (34). The extracts used were very crude and probably contained many impurities for the animals almost invariably died in convulsions within 24 hours. These authors were unable to explain this reaction. They quoted Abelous and Langlois who likened the effects of adrenalectomy to those of curare and believed them to be due to accumulated toxins in the blood. They (Oliver and Schaffer) conducted some work on their own on normal cats, dogs, rats and guinea pigs. They used filtered, aqueous, alcoholic and glyceric extracts of the medulla and of the cortex. They got a pressor effect, like epinephrine, from the former, but concluded that the latter was inactive. They even made extracts of the diseased glands of humans who had died of Addison's disease, but could obtain no reaction and concluded that the active principle had been destroyed.

One of the first detailed accounts of a case of Addison's disease treated by whole adrenal gland with success was that of Daland. In 1912 he had a rather typical case which apparently was not in crisis. He gave that patient 15 grains of whole gland by mouth, daily. The blood pressure went from 90 to 102-110 millimeters of mercury. He gained ten pounds in weight, and was relieved of his malaise and dyspnea. The patient discontinued the extract for a time of his own volition.
and had a recurrence of symptoms. He was then placed on 35 grains of adrenal extract daily and recovered very well. During 1914 the patient was able to work and lead a rather normal life. He was kept alive until 1917 at which time he "died of asthenia following neglect" (35).

Osborne (70) in 1918 reported a case which was treated with "adrenal tablets and iron" with improvement of weight and circulation with some fading of pigmentation.

Dr. A.L. Muirhead of Omaha suffered from Addison's disease and it was for him that Howntree named the type of treatment used in his case. (36) This consisted of a combination of the injection of epinephrine subcutaneously twice each day and a solution of the same substance along with 10 grains of the whole dried gland by proctoclysis. Dr. Muirhead noted a disappearance of pigmentation; a slow steady gain in weight and a return of his basal metabolic rate to almost normal. He was able to carry on part of his daily routine without too great difficulty. He stated that disuse of epinephrine caused his gastro-intestinal symptoms to return. He died in 1922 after passing through a severe crisis.

The Muirhead regimen as organized by Howntree and Brown (37) consisted of epinephrine orally, rectally and hypodermically to the point of tolerance, with whole adrenal gland or adrenal cortex by mouth. They treated 57 patients at the Mayo Clinic over a period of eleven years. They observed no improvement in 25 patients, 32 cases were benefited only temporarily, and 20 cases
showed excellent immediate results which lasted for from a few weeks to seven years. (42) These results would indicate that this treatment did not alter the course of the disease to any great extent in most of their patients.

In 1926 they tried ephedrine as a substitute for epinephrine because the patients did not tolerate the latter very well and it had a greater effect by mouth. They found that it only raised the blood pressure a little and increased the pulse rate. It did not materially effect the course of the disease.

Numerous attempts have been made to graft adrenals into the subcutaneous tissues of patients suffering from Addison's disease. Some of them have been reported as successful, but on the whole they have been futile. Pybus reports a case believed to have benefited and Curie reports a case in which two grafts of sheep's adrenal were used with good results. (38 and 39) Bailey and Keele in England used fetal adrenals with good results. (72) In all cases which have benefited there are no reports on subsequent course or autopsy findings available. The fact that the procedure has found little favor in recent times is evidence enough to question its efficiency.

Various adrenal extracts were prepared by Hartman and his associates, (45), Swingle and Pfiffner (56), Grollman and Hiror (62) and finally Kendall (59).

In 1927, Hartman tested his extract on adrenalectomized cats and found that he was able to keep them
alive for 27 days, but that they all died eventually. Usually the cause of death was an acute infection. (45)
In 1928 he precipitated the hormone from an acetic acid extract, with sodium chloride (55). Cats tested with this extract survived for variable periods of time. They didn't gain weight and they invariably succumbed to infection.

Swingle and Pfiffner had experimented with an extract of the adrenal cortex since 1926. In 1931 (56) they obtained a protein-free, epinephrine-free extract. They tested various fractions of this extract and found the acetone soluble extract produced sterile abscess and local necrosis. The acetone insoluble and petroleum ether extracts had little potency, while the alcohol extract apparently contained all the various hormone necessary for life. Grollman and Rior also obtained an extract of some potency in 1933 (62). Kendall carried this work much farther and obtained a hormone in crystalline form in 1935 (59).

In 1930 Szent-Gyorgi (44) isolated an isomer of glycuronic acid, hexuronic acid, which seemed to be related to pigmentation, but it was of no therapeutic value.

Before considering the use of these hormones in Addison's disease, the aims of treatment should be outlined. This was done by Howntree and Greene at the Mayo Clinic in 1931 (42) They said: "Several factors must be be taken into consideration in Addison's disease; 1. The nature of the underlying disease and its treatment;
2. The natural course of the disease; 3. The general care of patients; 4. The treatment of symptoms and complications; and 5. The results of specific organotherapy.

Many individuals reported on the efficacy of the extract of Swingle and Pfiffner (42, 47 and 53). Britton and Silvette found that Swingle and Pfiffner's extract was superior to Hartman's and that it could be used intravenously, intramuscularly, intraperitoneally, subcutaneously or even intracordially in laboratory animals.

Hartman in 1932 reported 9 cases of Addison's disease treated with his preparation. (46) Five of them survived, the other four died of various causes not directly attributable to the extract.

It will be recalled that under Physiology, the diabetogenic effect of cortical extracts was mentioned. Simpson (47) in 1932 reported a case of Addison's disease in a 16 year old boy, which he treated with the hormone of Swingle and Pfiffner. The results were not satisfactory. There seemed to be a great deal of difficulty in establishing a definite dosage. While under treatment, the boy suddenly developed polyuria and glycosuria. In spite of frantic efforts to control the two diseases, he died of diabetes, and perhaps of Addison's disease.

Loeb (50) studied the effects of sodium chloride in Addison's disease. He reviewed the literature and especially the work of Marine and Bauman (48). The latter found they were able to keep adrenalectomized cats alive for indefinite periods of time by the use of saline injections. Soddu (51) confirmed this in dogs.
In 1932 Rogoff stated that "The intravenous injection of physiologic solutions of sodium chloride becomes an indispensable adjuvant in the treatment of Addison's disease with extracts representing the adrenal hormone". He believed that the salt relieved the "toxic accumulations". Loeb reports the case of a woman with typical symptoms of Addison's disease. Her blood pressure was 90/60 millimeters of mercury. During a week in the hospital, the patient's condition became much worse. Her blood pressure dropped to 65/48. Nausea, vomiting, exhaustion and dyspnoea developed. He began to treat this patient with 9.5 Grams of sodium chloride per day by proctoclysis and 5 Grams per day orally in addition to her normal diet. In four days very striking improvement was noticed. Rectal administration was stopped. Five to 7 Grams of sodium chloride was continued by mouth plus a liberal amount in the diet. The patient continued to improve and was discharged on a normal diet plus one and one-half teaspoonfuls of salt daily. Her blood pressure had risen to 102/70. After 6 weeks at home, her blood pressure was 106/70 and the patient was able to do light housework with no great discomfort. She had gained 7 pounds. Three months after discharge, the patient returned complaining of puffiness about the eyes and ankles. She had gained four pounds more. She returned home on seven grams of sodium chloride daily. Five months later her blood pressure was 122/80, her urine was normal and the blood chloride level had increased. Because of the presence of edema, she was placed on a low salt diet. Two
days after this regime, she was so weak she was forced to go to bed. During the next five days she became progressively weaker, vomited frequently and had lost 7 pounds. She was readmitted to the hospital with a blood pressure of 86/60. She was placed again on a high salt diet and rectal taps of normal saline. In 8 days she had gained 4 pounds and her blood pressure had reached 122/80. She suffered no ill-effects from her experience.

Silvette and Britton (53) had four patients which they were treating with the hormone of Swingle and Pfiffner. These patients failed to gain weight, and two had nausea and vomiting. One to six grams of sodium chloride per day was added to their diet. The symptoms were relieved definitely, nausea and vomiting stopped and the weight gain was excellent compared with the inability to gain on cortical extract alone. By using the changes in plasma electrolyte values as one guide to the amount of salt required in treatment, they avoided the usual nausea, vomiting, diarrhea and edema from an excess of salt. When salt alone does not restore the proper plasma electrolyte levels, cortical extract should be employed. In addition, they advised the use of one to three ounces of cottonseed oil daily. The latter treatment is based on the fact that the dosage of cortical hormone required to maintain adrenalectomized dogs in a normal state is materially lowered when cottonseed oil is given simultaneously.

Blankenhorn and Hayman (58) studied the effects of various sodium salts in Addison's disease. They report-
ed a case of Addison's disease in which cortical extract alone failed to prevent a crisis. They demonstrated that sodium salts other than sodium chloride could be used. Potassium chloride with sodium chloride produced abdominal distress, but did not precipitate a crisis. They used a combination of sodium phosphate, sodium carbonate and sodium sulphate instead of sodium chloride. The level of serum chlorides fell, but there was no change in the condition of the patient.

Grollman and Miror (62) studied the potency of commercially available adrenal preparations. They found that the dried preparations and glycerine extracts of the cortex were of no value whatsoever in maintaining the lives of adrenalectomized 30-day-old rats. They also found at that time that the commercially available extracts of Swingle and Pfiffner were not up to claims. This was corroborated by Rogoff (63). In regards to this latter finding, they said "The presence of toxic impurities may easily mask the beneficial effects of any hormone in a given extract. Thus, in an experiment in which completely purified extract was administered intraperitoneally to adrenalectomized rats, doses of 1 cc. per rat per day failed to provide complete replacement therapy. The same extract administered orally mixed with the animal's food served as complete replacement therapy in doses as small as 0.05 cc."

In 1937, one of the greatest potential steps in the treatment of Addison's disease was made by Reichstein. He isolated and synthesized desoxycorticosterone.
Since that time numerous men have extolled its virtues and cursed its shortcomings. Some have found it to be adequate replacement for cortical extracts, others have not. One of the latter was Rowntree. He compared the efficiency of various methods of treatment of Addison's disease.\(^{(74)}\) His "backbone of treatment was Eschatin (Parke-Davis), an extract of the adrenal cortex. He supplemented this hormone with 5-15 Grams of sodium chloride daily. In one case, this treatment has kept the patient ambulant, in relatively good health and crisis free for 18 months. He found that vitamin C could not replace the cortical hormone. This had been reported previously by Szent-Gyorgi\(^{(44)}\). He did not find PerCorten, a commercial brand of desoxycorticosterone acetate, to be as effective in controlling symptoms as Eschatin. He found he got the best results with the hormone of Swingle and Pfiffner but did not use it extensively because of unavailability and prohibitive cost to the patient. A glycerol extract by mouth was found to be very good. But here again prohibitive cost prevented its continued use. This latter finding is contray to that of Grollman and Firor who state that glycerol extracts by mouth are ineffective.\(^{(62)}\) This can be explained perhaps, by variations present in the methods of preparation of the two extracts, as they were both commercially prepared.
Thorn(75) has presented a very complete resume of the various forms of treatment used up to 1941. He points out that use of the new, synthetic hormone, desoxycorticosterone acetate, does not constitute complete replacement therapy. It apparently controls the electrolyte balance of the blood, especially sodium and potassium, very well but has no effect on carbohydrate metabolism.

He discusses the possibility of regeneration of adrenal cortical tissue by the use of the adrenotropic factor of the anterior pituitary and states that the supply of that hormone is too limited at this time to allow adequate evaluation of its effects.

The article brings out the fact that transplants of the adrenal gland have not been particularly successful on the whole in animals higher than the rat. He believes, however that his field warrants further investigation.

He agrees with Rowntree(74) that the cortical hormone can be absorbed by the oral route, but states: "There are two disadvantages to giving hormone by this route. 1. The requirement of hormone administered orally appears to be at least three or four times that required by injection. 2. There is no assurance that uniform absorption takes place when hormone is administered orally."

Aqueous extracts of the cortical hormone provide
an excellent form of therapy but are impractical for
two reasons: 1. They must be injected frequently (six
to eight hours) and 2. they are too expensive.

Thorn advocates the use of the synthetic product
because it obviates most of these difficulties. It can
be injected as a sesame oil solution once a day, or im-
planted subcutaneously once every several months.

The implantation of pellets of desoxycorticosterone
was first used in animals by Deansley and Parker
(68) in 1938. Thorn (69) confirmed this work and tried
implantation methods in patients with Addison's dis-
ease. (67) He found that it was necessary to supply ex-
tra hormone at times of stress when crisis might occur.
He also presents an excellent regimen for the treat-
ment of the patient with Addison's disease who is in
 crisis.

McCullagh and Ryan report six cases in which des-
oxycorticosterone acetate was used. In two cases treat-
ed with the hormone and sodium chloride, they were able
to obtain complete symptomatic control. In another two
cases they obtained only a moderate response, while in
two cases they were unable to control the symptoms.
They found that with this hormone the blood pressure
reached hypertensive levels in five cases. Arterial
hypertension and edema are apparently evidence of over-
dosage of desoxycorticosterone. (77) Kepler in a com-
ment on the above report (77), said that at the Mayo
Clinic they had five deaths which they attributed to
the synthetic hormone. In three cases the patients apparently died from toxic reactions to the drug. While in two patients the drug failed to prevent crisis and death.

Kendall (78) thinks that the synthetic hormone is still in the experimental stage and should not be used clinically until it has had further trial on laboratory animals. He makes a statement in his article which just about sums up the present status of the use of adrenal cortical hormones in Addison's disease. "......
The adrenal cortex does not elaborate any single substance which can be described as the vital hormone of this gland. An extract of the adrenal cortex contains a surprisingly large number of closely related steroid derivatives which have specific effects, qualitatively different, one from the other. Substitution therapy in adrenalectomized animals is inadequate unless the compounds which influence glyconeogenesis and the efficiency of muscle are given together with the compounds that influence renal function and the distribution of water and electrolytes."
Summary

It has been noted that the treatment of Addison's disease has progressed considerably in the 90 years since its first description in 1855 by Sir Thomas Addison. The treatment today still leaves much to be desired. The use of the synthetic hormone is attended by too many dangers to be practical and is not complete replacement therapy. The hormone of Swingle and Pfiffner and its commercial counterpart, Eschatin, (Parke-Davis) offer fairly complete replacement therapy, but require frequent administration by the hypodermic route. Also, the concentration of the secondary hormones in these extracts are not high enough to be completely effective in controlling muscle efficiency, carbohydrate metabolism and, to a certain extent, blood pressure. These preparations are too expensive, at the present time, to be within the reach of the average patient. Eschatin costs about twenty-five cents per cc. and it is necessary to use at least 5 cc. daily to obtain any effect whatsoever. (Kendall, 7 & 8)

Oral administration of extracts of the adrenal cortex, in some cases, have been the most satisfactory method of treatment. We have no way, however, to determine the amount of these hormones that will be absorbed from day to day. Also, it has been found necessary to supply extra hormone in times of stress when crisis might occur. During acute exacerbations of the disease, nausea and vomiting appear, making oral use questionable at such
times.

The charcoal adsorbate of Grollman and Firor, however, should be investigated further to ascertain all of its possibilities.

Sodium chloride and other sodium salts are valuable adjuncts to treatment with the cortical hormones. In some cases, it may be possible to control symptoms by merely increasing the amount of salt in the diet. In event of crisis, however, it is necessary to fall back on the cortical extracts. If our hormonal therapy were complete, it should be possible to discontinue the control of sodium and potassium intake.

The ultimate treatment of Addison's disease is in sight. It will come when we have isolated successfully and synthesized all the adrenal cortical hormones and combined them into a substance resembling the natural extracts of the adrenal cortex.
Bibliography

4. Best and Taylor, The Physiological Basis of the Practice of Medicine. 2nd ed. 1940
5. Gray, Developmental anatomy. 3rd ed. 1936


19. Aschoff, Lectures on Pathology, 1924.


30. Ball, K.G., Roentgenologic Evidence of Calcification


35. Diland, J., The Use of Adrenal Products in Addison's Disease, Endocrinology, 2:301, 1918.


70. Osborne, O.T., Two Cases of Suprarenal Disease, Am. J. M. Sc., 156:202, 1918.


