5-1-1941

Addison's disease : with special reference to progress in treatment""

Willard W. Peck
University of Nebraska Medical Center

ADDISON'S DISEASE

With Special Reference to "Progress in Treatment".

by

Willard R. Peck

Senior Thesis

University of Nebraska College of Medicine

Omaha, 1941

TABLE OF CONTENTS

I, INTRODUCTION

Thomas Addison, connected with Guy's hospital, first brought to light the association of constitutional symptoms with disease of the suprarenal glands. His early thoughts on this subject were communicated to the South London Medical Society in 1849. Six years later (1855) he published his matured views with a report of eleven cases. As Addison admits in his paper, "On the Constitutional and Local Effects of Disease of the Suprarenal Capsules," he accidently "stumbled" on the suprarenal syndrome while trying to solve the etiology of "Idiopathic Anemia" now referred to as "Pernicious Anemia" or"Addisonian Anemia". (1) It was the French physician, Armand Trousseau (1801-1867) who first proposed to call the suprarenal syndrome "Addison's disease".(2) It is interesting to note that while the greater number of the cases of the disease are believed due to tuberculosis of the suprarenal glands and only rarely due to some other disease such as malignant tumor, syphilis, etc., Addison's first report of eleven cases included some of the raretie.

It is not possible to discover from the literature that this disease was known to the older physicians. No descriptions are found which attest its definite recognition and no early museum specimens illustrating disease of the adrenals are known.(3) However, Maranon (4) reproduces the description by a priest, in the sixteenth century, of a young priest who died three years after the onset of the first symptoms of his malady. The lay

description protrays "Addison's disease" perfectly , according to Maranon.

The adrenals were overlooked in early autopsies and were not regarded with any special interest until the stimulating effect of Addison's researches. In 1837 Rayer wrote that the study of the morbid changes of the suprarenal capsules offered so little that was interesting, that it might without detriment be neglected by pathologists. (3)

In 1856, Brown-Sequard, stimulated by the work of Addison, undertook extirpation experiments to ascertain the function of the suprarenals, and announced that these glands were indispensable to life. (5) Little more than this is known of the actual function of these glands at the present time and most clinicians admit it is difficult to improve on the description of the disease as given originally by the keen clinical observer, Thomas Addison.

Little progress had been made in the treatment of this disease from the time of its recognition by Addison, until the isolation of the cortical hormone by Swingle and Pfiffner in 1930.(6) Since that time advances in treatment have taken place more rapidly and the future looks hopeful.

In such a paper as this it seems logical that some space should be devoted to the consideration of the anatomy and physiology of the suprarenal glands which appear to play a major role in the production of the clinical

syndrome known as "Addison's disease". Following this, the disease will be discussed under specific headings with special reference being placed upon "progress in treatment".

II, SUPRARENAL GLANDS.

I.

Developmental and Gross Anatomy.

The suprarenal gland arises from two separate and distinct sources. The medulla arises from the ectoderm while the cortex has its origin from the mesoderm. These two portions of the gland secondarily unite to form a single anatomical structure, but, in function, it continues to behave as two separate and distinct glands. Early in the development of the organism, the primordia of the glands project from the dorsal wall of the coelom between the mesentery and mesonephros. These glands are comparatively huge at the time of birth but soon after birth they decrease in comparative size. The inner and middle zones of the cortex undergo involution while the thin outer layer now begins to grow rapidly and differentiates into the three permanent zones of the cortex.

The chromaffin cells of the medulla have their origin from the celiac plexus of the sympathetic nervous system. The suprarenal tissue contains a profuse meshwork of sinusoidal capillaries as is found to be true in most of the ductless glands.(7)

Grossly, these glands are found to lie in the posterior portion of the abdomen and are located retroperitoneally. They lie closely attached, with thick connective tissue, to the superior pole of the kidney. In shape they appear somewhat triangular and the left gland is slightly larger than the right.

They measure, on the average, from 3 to 5 cm. in length and somewhat less in width. They weigh, as a rule, from I.5 to 2.5 grams. During the early months of fetal life they are huge in comparison to the kidneys, but this proportion gradually changes until in the adult the kidneys greatly preponderate in size.(3)

The suprarenals are endowed with a very rich blood supply. Some of the supplying arteries are of surprisingly large size and are derived from the aorta, inferior phrenic and renal arteries. These arteries break up into smaller branches just before entering the capsule of the gland and become capillaries as they pass through the cortex ending in the venous plexus of the medulla. The blood is returned from the medullary plexus by the suprarenal vein which emerges from the hilum of the gland. The right vein drains into the inferior vena cava while the left drains into the left renal vein.

The nerve supply of the gland is derived from the celiac and renal plexuses. The nerves are very numerous and enter the lower and medial portion of the capsule, move across the cortex and terminate around the cells of the medulla.(8) The medulla is found to be very richly supplied with nerves while the supply to the cortex is quite sparse. According to Jaffe(5), the activity of the chromaffin cells of the medulla are entirely controlled by the nervous system while the cortex may continue to function if deprived of its nerve supply.

There does not appear to be any embryological connection between the kidney and the adrenal bodies. This is evidenced by the fact that it is usual to find an adrenal body in its normal position in cases of congenital abscence of the kidney. This fact also indicates that there is no physiological dependency between the two organs despite their close anatomical association. (3)

The finding of accessory suprarenal bodies in man is not uncommon. This is more commonly true in the newborn than in the adult as the accessory glands undergo atrophy and disappear with advancing age because they are physiologically unnecessary in the presence of properly functioning main glands.

Physiology.

We, today, know very little more concerning the actual function of the suprarenal glands than did the workers of Addison's time. The existence of these glands was first noted by Eustachius in the sixteenth century, but modern studies on their significance date from Addison's description, in 1855, of the clinical disorder which results from destruction of these glands by disease.

In 1856, Brown-Sequard (5), after experimentation upon laboratory animals, announced that these glands were indispensable to life because all his animals died within a few days after bilateral suprarenalectomy. We cannot deny that his conclusions were correct but we now know that he drew these conclusions on a false premise, as the death of his animals so soon after removal of both adrenal glands must have been due to some cause other than adrenal insufficiency. Modern workers, using a more refined surgical technic, find that their most susceptible animals live longer than those of Brown-Sequard.

A great amount of experimental work has been done since the time of Brown-Sequard to determine the physiological function of the adrenal glands. It is rather surprising after reviewing the literature, to find that our present day knowledge is little more enlightening on this subject than that of Brown-Sequard. Duckworth (3) summed up the situation in 1895 by stating in substance, that

the adrenals were ductless glands and probably form a part of the lymph system of the body but with actual functions which still remain unknown. In 1931, Rowntree and Snell, as cited by Kipler (9) found that the knowledge on this subject was no greater than in 1895. They state, "Our exact knowledge of the physiology of the suprarenal glands can be expressed in two statements: the cortex of the gland is essential to life and the medulla of the gland, although apparently not a vital organ, secrets a substance which has powerful pharmacodynamic properties". Grollman (10) in 1939 plainly infers that the actual function of these glands is still unknown while Green (11) in 1940 speaks of the function of the adrenal cortex as "a mystery".

Medulla.

It is known that the medulla produces a specific hormone, epinephrin, which is believed to be its most important function. It has been found that this hormone is excreted whenever the splanchnic nerves are stimulated and exerts its chief effect upon the sympathetic nervous system and organs which it innervates. (12) However the true function of this hormone in the intact animal has not yet been determined with certainty as, according to Grollman (10), the medulla may be removed without any apparent functional disability to the organism. Stewart (13) also is of the opinion that a complete suppression of the output of epinephrin has no noticable ill effects

on the organism and that its suppression has nothing to do with the fatal symptoms of adrenal insufficiency.

Cortex.

Undoubtedly the cortex and medulla of the gland work in close association but just what this association is we still do not know. We are, however, quite certain that it is the cortical portion of the gland which is essential to life and it appears for this reason, that more of the recent work has been confined to this protion of the gland.

Auld, cited by Duckworth (3), previous to 1895 was of the opinion that one of the functions of the cortex was to destroy a certain class of red corpuscles which he believed was accomplished by means of a ferment. This theory, as yet, has not proven worthy of acceptance.

Stewart (13) in 1924 proposed several theories as to the function of the cortex. He postulated that the cortex might secret some substance essential to health or that it might produce some substance which aids in elimination of toxic substances normally produced in the body tissues. He cited the picture of profound intoxication in animals dying of cortical deficiency as support for the latter contention. He warns against the acceptance of this belief, however, without more proof, by calling to attention the fact that the thyroid and pancreas were also thought to be detoxifiers before their real functions were discovered.

Britton and Silvette (I4) in I932 attempted to explain the function of the cortex as being that of a regulator of carbohydrate metabolism. They were of the opinion that it was chiefly concerned with the utilization and storage of the carbohydrate. However, in a more recent article Silvette (I5) stressed the importance of the shift in the water and chloride balance that occurs in adrenalectomized animals.

Swingle and Pfiffner et al (I6) from their experiments on adrenalectomized dogs, reported in I933, were not impressed by any effects of cortical function upon carbohydrate metabolism. They, in turn, express the opinion that perhaps the only function of the cortex was in the regulation and maintenance of the normal circulating volume of blood. They attempt to show from their experiments that all other factors in adrenal insufficiency are secondary to inability of maintenance of the blood volume. They felt that the cortical hormone acted as a mobilizer of water and salt of the tissues thus making it available for transfer to the blood stream and in that manner aid in maintaining the blood volume.

Hartman and his associates (I7) as a result of their experimental work were of the opinion that the cortical hormone was closely related to the functions of the muscle and nervous tissue as well as the kidneys and gonads. They prophesied that other tissues would be found to be just as directly concerned when investigated. From this

they concluded that the cortex will produce a general tissue hormone.

In 1933 it was found by Harrop and associates (18) that the electrolyte structure of the blood plasma, in adrenalectomized dogs, was indefinitely altered when injections of cortical extracts were stopped. They found this alteration to progress parallel with a hemoconcentration and weight loss during the course of suprarenal insufficiency. The resumption of injection of cortical extract brought the electrolyte pattern of the blood back to its original form paralleled with a dilution of the blood and gain in weight. Along with these factors they also observed that withdrawal of cortical extract brought about an immediate loss of sodium and chloride, accompained by their proper complement of body water, through the kidney. They concluded that the cortical hormone had some function in the regulation of sodium and chloride metabolism as well as water balance.

The results of the work of Silvette et al (14) in 1934, on adrenalectomized cats failed to support the circulatory theory proposed by Swingle and also failed to offer further support to the carbohydrate theory of Britton and Silvette proposed in 1932.

Kendall, cited by Greene (11) found that adrenalectomized rats fed on cortin, excret as much as ten times the amount of potassium in the urine, as those not fed.

Long and associates (19) from their experiments

on adrenalectomized rats offered further evidence against the carbohydrate theory of Britton and Silvette in 1940. They found no drop in carbohydrate levels in adrenalectomized rats which were well fed and whose blood electrolyte pattern was maintained.

Howell (20) calls attention to the fact of the interrelationship between the cortex and the other ductless glands, especially the anterior lobe of the pituitary and the gonads. Atrophy of the adrenal cortex has been found secondary to the removal of the anterior lobe of the pituitary.

It appears that today we must admit, as did Brown-Sequard in 1866 and Duckworth in 1895, that the true function of the suprarenal glands is not as yet completely understood.

III, ADDISON'S DISEASE

I.

Definition.

It would be difficult to improve upon the definition of this disease as given by Addison in 1855. "The leading and characteristic features of the morbid state to which I would direct attention are, anemia, general languor and debility, remarkable feebleness of the heart's action, irritability of the stomach and a peculiar change of color of the skin occurring in connection with the diseased condition of the suprarenal capsule." And to this we might add today, without intention to distract from the above excellent definition, characterized by a marked lowering of the systolic, diastolic and pulse pressures.

Incidence and Etiology.

Incidence.

There are about three hundred to four hundred cases of Addison's disease reported annually in the registration area of the United States. The death rate is remarkably constant, being about 0.4 per 100,000 of the population. Snell (52) states that about one hundred and fifty-five cases have been encountered at the Mayo clinic in the last twenty-two years. Osler (21) classes the disease as rare.

It is a disease of middle life occurring most commonly between the twentieth and fortieth year. However, cases have been reported in children. Biltorf in 1921 (22) reported a case of a child, age four, who was found at autopsy to be suffering from Addison's disease. The youngest patient observed at Mayo's clinic was thirteen years of age.

The disease occurs much more frequently in males than females, according to GreenHows inquiries (23), the relative proportion is as 119 to 64. According to Snell (24) about 2 to 1.

It occurs in negroes but apparently not as commonly as in the white race. However, this may be only apparent rather than real as the pigmentation is much harder to identify in the colored race. Guttman (25) states that seven cases in negroes were reported from 1900 to 1929.

Reports of the disease in Jews are rare, but cases have been reported among the Japanese.

It is doubtful whether or not heredity plays a significant role. Proved cases in more than one member of a family are exceedingly rare, but there are scattered reports in the literature with more than one member of the same family afflicted.

GreenHow (23) found that nine-tenth of the cases occurred in the laboring classes. The majority of cases in females occur in hard working servants and poor married women.

Etiology.

The immediate cause of the disease is rather definitely agreed upon today. It is due to a deficient production of the cortical hormone by the suprarenal gland. This deficiency may occur after approximately four-fifths of the adrenal cortex has undergone destruction. (26) Some of the older workers questioned disfunction of the adrenal cortex as an etiological factor in the production of this syndrome. It was GreenHow's (23) opinion that the disease was due to envolvement of the sympathetic nerves and ganglia by spread of inflammation from psoas and lumbar abscesses rather than a malfunction of the adrenal gland. He did consider tuberculosis as the most important pathological factor envolving the nerves.

A more debated question today is the underlying pathology giving rise to the cortical damage thus causing an

insufficient production of the hormone. It was reported in 1927 by Jaffe (5) that bilateral tubercular lesions of the adrenals were found in seventy-five percent of the cases. Among other etiological agents were considered syphilis, hemorrhage, neoplasms and atrophy.

Some workers feel that an enlargement of the thymus gland is often associated with Addison's disease and thus consider a definite relationship between Status Thymico-lymphaticus and Addison's disease.

Guttman (25) reviewed 566 cases from the literature in 1930, concerning the etiological factors envolved. The following is a reproduction of his findings, in table form.

1. Tuberculosis-Bilateral suprarenal envolvement. 69.72 %
2. Syphilis---1 case.....0.25 %
3. Atrophy----65 cases.....16.13 %
4. Amyloidosis--7 cases.....1.73 %
5. Fatty degeneration--2 cases.....0.50 %
6. Neoplasms----5 cases.....1.24 %
7. Vascular lesions--5 cases.....1.24 %
8. Miscellaneous lesions such as trauma, pressure atrophy, hypoplasia, undetermined nature--18 cases.....4.48 %

In an analysis of thirty recent cases which were examined at autopsy Snell (27) found atrophy of the adrenals to be present bilaterally in seventeen of the cases or 57 %. This disagrees with Guttman's findings, but of course the latter series is much smaller. Most workers,

however, are in agreement that a greater portion of the cases of Addison's disease are associated with bilateral tuberculosis of the suprarenal glands. Harrop et al (28) fix the percentage of this etiology at between seventy and eighty percent but were of the opinion that only a small percentage of these cases show any evidence of tuberculosis elsewhere. They also concluded that evidence of tuberculosis elsewhere in the body did not prove that tuberculosis of the adrenals was the etiological agent of the Addison's disease from which the patient may be suffering.

An entirely different theory was set forth by Buhlo. (29) He conceived the idea that Addison's disease was the result of a particular form of chronic miliary tuberculosis, arising from a "peculiar condition of the blood," the cause of which is unknown. This theory has little to support it.

Packard and associates (30) felt that some types of adrenal insufficiency might be on a nutritional basis. They based this opinion upon the study of several cases of suprarenal insufficiency which simulated Addison's disease but lacked some of the cardinal symptoms.

That atrophy of the cortical tissue is an important etiological factor in some cases of Addison's disease, is a recognized fact. The cause of the atrophy is still an unknown fact. Brenner (31) suggested in 1928 that it was a necrosis of the cortical cells caused by the action of

some unknown toxin upon them which is just another method of stating that the cause of the atrophy is still unknown.

Cases due to some of the more rare etiological factors have been reported in the literature. Bicknell (32) reports a case of Addison's disease presumably due to malignant envolvement of the solar plexus. Rogoff (33) reports a case which developed following a denervation of the adrenal glands in an attempt to benefit a diabetic patient.

It is the opinion of some of the English workers that pellagra may be closely associated with the etiology of Addison's disease. They have shown that experimentally produced pellagra, in dogs, produces degenerative changes in the adrenal cortex similar to changes often found in Addison's disease. Simpson (34) reported a case in 1934 in which he felt pellagra and Addison's disease were present simultaneously. He is of the opinion that vitamen deficiency might cause both pellagra and adrenal insufficiency in the same patient or that adrenal insufficiency might occur in the course of pellagra as a result of malnutrition or pellagra might occur in the course of Addison's disease as a result of the anorexia.

As is seen from the above we have learned of various factors which are often associated with the syndrome of Addison's disease but as yet have no definite proof that they are the cause of the syndrome. In the words of Boyd (35) "we know as much of the cause of the disease as

Addison did and no more."

Symptoms and Signs.

Addison's original description, in 1855, of the symptoms and signs of the disease is a masterpiece and upon which it would be very difficult to improve. In his paper "On the Constitutional and Local Effects of Disease of the Suprarenal capsules", he states, "The patient, in most of the cases I have seen, has been observed gradually to fall off in general health; he becomes lanquid and weak, indisposed to either bodily or mental exertion; the appetite is impaired or entirely lost; the whites of the eyes become pearly; the pulse small and feeble, or perhaps somewhat large but excessively soft and compressible; the body wastes, without however, presenting the dry and shrivelled skin and extreme emaciation usually attendant on protracted malignant disease; slight pain or uneasiness is from time to time referred to the region of the stomach and there is occasionally actual vomiting and it is by no means uncommon for the patient to manifest indications of disturbed cerebral circulation."

Along with the above symptoms and signs Addison also describes the pigmentation of the skin which he considered so important and characteristic, "This discoloration prevades the whole surface of the body but is commonly most strongly manifest on the face, neck, superior extremities, penis and scrotum and in the flexures of the axillae and around the navel." He describes the color as

varying from a smoky, dingy shade to the deep brown of a mulatto.

Addison makes no definite distinction between the symptoms and signs found in the chronic stage of the disease and those found in the stage of crisis. However, it is important to bear in mind that the symptoms observed in the stage of crisis differ distinctly from those observed in the chronic stage.

The symptoms of chronic adrenal insufficiency are often very vague and deceptive in their onset and progress. Often the first symptom is nothing more than an unusual fatiguability. This plus weakness, anorexia, pigmentation of the skin and loss of weight are the most common early symptoms. Hypotension of some degree is the usual rule. An increased fondness of salt is not uncommon. (37) Severe neuralgic pains throughout the body are complained of quite frequently. (38)

In the stage of crisis the usual findings are: nausea and vomiting, marked weakness and prostration, fever, often pain in the epigastric, lumbar, dorsal or precordial regions and occasionally diarrhea. Nervous symptoms such as irritability, mental wandering and poor memory are common. The abnormal findings in the blood are accentuated, the reduction in the concentration of serum sodium being the most marked but along with this is usually found an increase in potassium. There is a marked hypotension and the intensity of the pigmentation

usually increases. In Thompsons (39) opinion any patient with Addison's disease who developes nausea should be considered to be in a state of emergency.

Anemia, in contrast to the emphasis placed on this factor, by Addison, has not been found to be of common occurrence by more recent workers. (28) According to Mohler (38) the blood is found to remain unchanged, in so far as the erythrocytes are concerned, during the chronic stage and may be only slightly altered in the stage of crisis. The leucocyte count is usually normal but Curschman (12) believes a marked lymphocytosis is not uncommon.

Absence of free hydrochloric acid in the stomach and a marked reduction in total acidity are quite frequent findings in these patients. (12) Kipler (9) believes hiccup is a very important manifestation and should not be overlooked. It is often one of the first signs of an impending crisis.

The development of the pigmentation of the skin and mucosa is usually found to parallel the other symptoms and signs. However, as observed by Curschman (12) some patients never develope this sign. This may be true in very rare cases but from the opinions of others it appears that pigmentation in some degree and extent will be found if carefully searched for. It may occur only on the mucosa of the mouth, the patient escaping generalized pigmentation. Development of areas of vitiligo,

which stands out in marked contrast to the dark pigmented skin, has been reported in some cases. (38)

Sergent's "white line" is considered by some an important sign. (38) It is a line produced upon the skin by drawing a blunt instrument across it firmly. It is a broad white line which appears slowly, remains several minutes and then slowly disappears.

Sex changes may occur but are not frequently found. Dysmenorrhea not uncommonly occurs in women or exacerbations of the symptoms of the syndrome may occur with the menstrual period. Conception is usually terminated in abortion. In the male, loss of libido and potentia are not uncommon findings. (26)

Clinical Course.

The onset of the disease is gradual. An impairment of general health is to be noted and the patient complains of languor and debility. The order of symptomatic development is not uniform and differs from patient to patient.

GreenHow (23) points out that though the asthenia, the constitutional symptoms generally and the change of color in the skin are all progressive, yet the great peculiarity of this disease is the paroxysmal mode of progress, the alternate exacerbations and remission. He points out that the disease may run a rapidly fatal course in the younger subjects.

Pigmentation may or may not occur early in the disease. In dark people it seldom attracts attention early, in fair people it is more apt to appear earlier. It may precede any marked change in general health by a period of from eight to sixteen months. On the other hand, progressive asthenia, together with indications of cardiac failure and gastric irritability may be the chief symptoms long before pigmentation appears. (3)

The duration of the disease varies. It is difficult to determine the exact date of onset because the early symptoms may be mild and unnoticed. Many cases end fatally in about eighteen months, others last for years.

The condition of the patient in crisis rapidly goes from bad to worse and unless treatment is started at

once death is very likely to ensue. (39)

Snell (40) states that many persons whom he and his associates have observed, the terminal symptoms have appeared suddenly while in others they are preceded by a long slow decline. "The terminal condition has been likened to the flickering of a dying flame, but the time of death may be very stormy with convulsions and pronounced cerebral symptoms." Sudden death is not infrequent.

Diagnosis.

The diagnosis of Addison's disease is not difficult if all of the cardinal symptoms are present. In a patient who presents pigmentation of the skin or mucous membranes or both; gives a history of general weakness and malaise accompanied by gastro-intestinal disturbances the diagnosis of Addison's disease must be seriously considered.

In regards to the diagnosis of this syndrome Addison (2) in 1855 remarked concerning one of his patients, "The slow and insidious approach and progress of the constitutional loss of strength, the extreme feebleness of the pulse, the absence of all evidence of any lesion sufficient to account for the patients declining condition, the loss of appetite, the uneasiness and irritability of the stomach and the indications of disturbed cerebral circulation were all so strongly marked and so exactly corresponded in kind with what have been observed to accompany the most extensive disease of the capsules, that coupled with the excess of dark pigment in the integument, we did not hesitate to anticipate with much confidence an extensive diseased condition of these organs." (Suprarenal glands.)

Although in Addison's opinion pigmentation of the skin and mucous membranes was the most reliable sign for diagnosis some workers, both recent and early, are inclined to disagree with him on this point. After an

analysis of three hundred and fifty cases Greenmow (23) came to the conclusion that it was not the most conclusive sign. He gives as his reason for this conclusion that pigmentation frequently does not develope until late in the disease and that similar pigmentation may occur in other diseases such as vagabonds disease, pityriasis versicolor, syphilis, malarial poisoning etc. Franks (41) agrees with this conclusion for the same reasons. Harrop (28) however believes pigmentation is an indispensable sign and if not present a diagnosis of Addison's disease is questionable. Mohler (38) does not consider pigmentation of the skin, without other symptoms and signs, enough evidence for a diagnosis of the syndrome as this sign is too frequently found in other conditions. It is certain, however, that pigmentation in the presence of other cardinal symptoms is of great aid in making a diagnosis of this disease with assurance.

There are some characteristics about the pigmentation in this disease which, if kept in mind, will help to distinquish it from the pigmentation of other disorders. Most frequently the pigmentation is the most pronounced on the exposed parts of the body. It usually is diffuse but pressure points such as bony prominences are definitely darker than surrounding areas of skin. In the absence of a generalized pigmentation minute freckles may be noted on the neck and shoulders. If observed the anus, genitalia, axillae, nipples and lips

may show this dark dirty grayish hue even in the absence of generalized pigmentation. The oral mucous membranes may be the only site of the pigmentation in some cases.

Wilder (42) suggests seven factors, which will be used as a basis for discussion, that may be of aid or were thought to be of aid at one time, in the diagnosis.

I. "Addison's syndrome as expressed in his original description". This has been discussed above.

2. "Calcification of the adrenals-negative result means nothing." The ground work for the use of roentgenology as a diagnostic aid in Addison's disease was laid by Camp and associates (43). They found that misinterpretations of the rib shadows for calcification in the adrenals could be largely overcome by use of the oblique position for roentgenographic studies. In a series of twenty-three consecutive cases of Addison's disease, they demonstrated calcification of the adrenals. Snell (24) considers calcification of the adrenals as almost positive evidence of tuberculous envolvement and hence as very important evidence in favor of a diagnosis of the disease. However, the absence of this sign can not be considered as evidence to rule out the diagnosis as it is absent in many otherwise typical cases.

3. "In crisis, assistance in diagnosis may be obtained from chemical examination of the blood. Findings of high values for non-protein nitrogen and potassium, and low values for chlorides, sodium and sugar is very suggestive."

It has been only in comparatively recent years that workers have started using the laboratory to any great extent as an aid to diagnosis, but as yet, no completely satisfactory test has been developed. However, some of our present methods are found to be of aid in atypical cases. According to Dryerre (44), Baumann and Kurland first appreciated, 1927, the corresponding fall in serum sodium and the rise in serum potassium in adrenalectomized cats. Loeb made similar observations in cases of Addison's disease in 1932. This work gave rise to the idea that cases of adrenal insufficiency might be diagnosed from the finding of lowered concentrations of sodium chloride and abnormalities in the urea concentration of the blood, but since that time it has been found that frequently the blood composition and electrolyte pattern are normal in cases of Addison's disease. Allot (45) points out, however, that a "crisis" is often indicated by changes in the blood chemistry especially by a rise in potassium and urea.

It was found by Zwemer and associates (46) that the serum potassium rose more rapidly in adrenalectomized cats than in normal cats when potassium was administered. From this finding they suggested that cases of adrenal insufficiency might be detected by their intolerance to potassium as evidenced by a rapid and gross rise of the serum potassium. Dryerre (44) gave large amounts of potassium to several patients with Addison's disease and

found no consistent changes in the serum potassium although there appeared to be a tendency for it to rise. Greene et al (47) ran potassium tolerance curves on patients suffering from a variety of diseases, including some cases of Addison's disease. This work did not indicate a characterictic curve for serum potassium in patients with Addison's disease. They concluded that the test was not specific for adrenal cortical insufficiency. Nilson (48) confirmed the work of Zwemer. . He found that a high level of blood urea, changes in the concentration of blood sugar, sodium, chloride and hematocrit values may or may not accompany the symptoms of adrenal insufficiency but the increase of potassium was characteristic. Talbot (49) reports a case in which metabolic studies showed a negative sodium and chloride balance, an increased concentration of serum protein, and decreased concentration of total bases. The symptoms regressed for a period when the patient was placed on a high sodium intake. However at autopsy the adrenal glands were found to be normal.

A marked rise in blood serum amylase activity in adrenalectomized dogs was reported by Cope et al (50). They were of the opinion that this was the most sensitive measurement in the blood of cortical insufficient dogs, yet developed. It was found that a significantly high level of amylase activity is reached before any changes in the nitrogenous or electrolyte pattern of the blood

could be detected.

4. "Salt deprivation test."

The use of a low salt diet as a diagnostic procedure in doubtful cases of Addison's disease was first suggested by Harrop and associates (28) in 1933. This test consists of placing the patient on a salt free diet and observing him carefully for the development of pronounced symptoms of Addison's disease. They report from their observations that patients with Addison's disease showed marked signs of relapse and marked fall in plasma sodium and chloride within three or four days after being placed on a salt free diet, while control cases showed no abnormalities, either clinically or biochemically. Kline (51) confirms their work and adds that a characteristic elevation of potassium and nitrogen in the plasma accompanies the lowering of the sodium and chloride. Winkler and Crankshow (52) found low serum chloride and sodium in cases other than Addison's disease and hence were of the opinion that a lowering of the sodium and chloride in patients on a salt free diet was not characteristic of Addison's disease alone. Wilder et al (53) agree that the salt test is of value as a diagnostic aid but they are of the opinion that the response is dependent on the potassium intake at the time of the sodium chloride restriction rather than on the absence of the salt.

There seems to be little doubt but that this test is

of value in the diagnosis of this syndrome but it must also be remembered that its use is not entirely void of serious danger. It should not be undertaken unless the physician is fully prepared to treat a patient in crisis as it is quite common for a crisis to be precipitated by this procedure. Several cases of sudden death have been reported following the use of this test as a diagnostic procedure, one by Garvin et al (54) and another by Lilienfeld. (55)

5. "Injection of insulin has been proposed as a diagnostic procedure but has not proven to be helpful."

It has been found that patients suffering from cortical insufficiency are very sensitive to insulin but there are too many other diseases in which the same is found to be true for this test to be of any diagnostic value.

6. Theraputic tests with cortin have been proposed."

Here again the difficulty lies in the fact that other conditions are benefited by its use as well as patients suffering from Addison's disease. Asthenia entirely on a neurotic basis often respond remarkably to its use.

7. "The level of excretion of chlorides and other electrolytes in the urine are believed by some to be of diagnostic aid."

The inability of a case of Addison's disease to conserve chlorides was noted by Anderson and Lyall (56)

in 1937. As a result of this observation they suggested that in the absence of diabetes or renal disease the finding or a chlorine concentration in the urine of over 120 mgm. percent when the plasma concentration is below the minimal normal level of 320 mgm. percent would be strongly suggestive of Addison's disease. However for this test to be of meaning the chloride level of the plasma must be below normal, a finding not always present in Addison's disease. Further evidence against this suggestion is given by the reporting by Winkler and Crankshow (52) of cases with no adrenal insufficiency showing biochemical figures which would satisfy the above criteria.

A new technic for the diagnosis of adrenal insufficiency has been suggested by Cutler and co-workers. (57) They feel it has none of the above disadvantages and the results can be clearly and rapidly interpreted. The test consists of giving the patient a low sodium chloride and high potassium diet for two and one half days. At the end of this time cases of Addison's disease continue to excret comparatively high amounts of sodium and chlorine in the urine whereas in normal individuals their is a marked decrease in excretion of these substances. The authors suggest that a concentration of chlorine in excess of two hundred and twenty-five milligrams percent in the urine on the morning of the third day of the test is strongly suggestive of some abnormality of the cortical function. This test was carried out by Dryerre (44) on

fourteen patients, four with Addison's disease and others either healthy or suffering from some other disease. His results tend to confirm the work of Cutler.

The above considerations indicate that progress is being made toward laboratory tests of aid in diagnosis of Addison's disease but as yet no completely satisfactory or reliable test has been developed.

Morbid Anatomy and Pathological Physiology.

It is now quite generally agreed that the basis of Addison's disease is a suppression of the function of the cortex of the adrenal gland and that the medulla has nothing to do with it.

In 1837 Rayer, quoting from Duckworth (3), wrote that "the study of the morbid changes of the suprarenal capsules offered so little that was interesting that it might, without detriment, be neglected by pathologists and that it had not thrown any light upon the function of these organs."

In most of the cases reported by Addison(36) there was extensive tuberculous destruction of both adrenals. In one case the lesion was secondary carcinoma and in another simple atrophy. He reports only one case in which the lesion was unilateral and this case presented mild symptoms.

Virchow, who examined the suprarenals in a case of Addison's disease for Franks (58) in 1882 gives this description, "The development of the tubercular masses begins in this case, as is the rule in others, in the medullary tissue. On making a section through the suprarenal capsule, we observe occasionally in the middle of the medullary portion the first stages of the development in the form of small gray nodules. These gradually increase in size, become caseous, amalgamate with one

another and thereby produce the caseous masses. It not infrequently occurs that this process is but partial and that both internally and externally some normal tissue remains."

Duckworth (3) states "of the earlier changes in the organs in Addison's disease we are quite ignorant and must be content to remain so." He goes on to describe the appearance of the suprarenals at post-mortem and agrees with Virchow in the fact that the morbid process starts in the medulla and spreads to envolve the cortex, destroying it in part or in whole. He states that the caseous degeneration may become so complete as to soften and liquefy into creamy, puriform matter. A still later stage shows a process of absorption and shrinking which results in small puckered masses in which calcareous material is deposited. A chronic inflammatory process simultaneously envolves the investing fibrous tissue of each organ leading to a thickening of the capsule and adhesions to adjacent organs. GreenHow (23) agrees with this latter statement.

Dreschfeld (59) in 1884 reports a discussion by Dr. Mcquire in which he showed sections of the suprarenal capsule from a case of Addison's disease. The capsule was enlarged and firm, consisting of a whitish transparent stroma, containing yellowish patches which he believes were the result of caseous degeneration.

In 1927, Jaffe (5) reports a still divided opinion

in regard to the relative importance of the cortex and medulla in the production of Addison's disease. Karak - ascheff, according to Jaffe, affirms that cortical destruction is the important lesion, while Wiesel considers the degeneration or disappearance of the chromaffin cells as the essential lesion. Still others believed the causative lesion might lie outside the glands entirely and be envolvement of the semilunar ganglion and solar plexus, but Jaffe felt that the lesion must be sought in the suprarenals where the disturbance might be either a gross pathologival destruction of the gland or merely a physiological insufficiency.

Snell (24) in 1935 states that about eight percent of cases of Addison's disease are associated with fibrocaseous tuberculosis of the suprarenal glands and agrees with Virchow that the lesion appears to start in the medulla and extend peripherally envolving the cortex. In the other twenty percent he believes atrophy of the glands is the most common pathology. This condition, the etiology of which is not known, begins in the cortex, which appears to collapse on the medulla, occasionally leaving a portion of the medullary tissue intact. Ordinarily the entire structure is destroyed, and a careful search may be required to reveal any suprarenal tissue at autopsy.

Boyd (35) in his text book states in reference to atrophy. "It is possible that the condition may be the

result of toxic necrosis of the adrenals. On the other hand, it may be that there has been some degree of atrophy from birth."

Gravin et al (54) report the microscopic examination of the suprarenal glands from a case of Addison's disease. The examination demonstrated the following; no medulla was present; extending thrcugh out the central portion of the gland there was a band of acellular connective tissue; the cortical cells did not show the usual regularity of architecture, but were present in scattered foci or nodules. Some of these nodules showed degenerated cortical cells in which only shadows of the cellular structure could be seen. In other places the cells were still present but ther were swollen and showed small dense nuclei. There were other nodules which originally had been cortical in situation. These now consisted of cho - lesterol and calcium. There was no evidence of tuberculosis.

The characteristic blood changes in experimental suprarenal insufficiency, according to Allot (45), consist of a fall in the sodium and chlorine content of the serum, a rise in the potassium and magnesium , a retention of nitrogen (high blood urea and non-protein nitrogen) and increased concentration of the blcod. These findings have been noted in rabbits, cats and dogs after suprarenalectomy.

Loeb (60) noted blood changes similar to the above

in untreated cases of Addison's disease. . Harrop and his associates (28) also confirm these findings in untreated cases.

Kipler (9) states. "It is reasonably well established that the abnormal behavior of the serum electrolytes is of fundamental significance in the pathological physiology of Addison's disease and that this abnormality in patients during periods of relapse or crisis is manifested by a decreased concentration of the sodium and chloride ions in the serum, a decreased concentration of the titrable total base and an increase in the concentration of the potassium ions. The values for calcium and magnesium are increased or unchanged."

Thorn et al (6I) observed that a high proportion of untreated patients with Addison's disease have a disturbed carbohydrate metabolism. This abnormality appeared to them to be specific since it persisted despite the correction of the disturbance in electrolyte balance, plasma volume and blood pressure by means of desoxycorticosterone acetate therapy.

Lewis et al (62) after experiments concluded that the ability of adrenalectomized animals to convert three carbon atom intermediate substances of carbohydrate and protein metabolism to glucose or glycogen is markedly impaired.

Silvette (I5) reports that the water content of the muscle in cats progressively increases after adrenal

removal while the chloride concentration in the tissue falls. Hepatic water and chlorides follow the same course and serum water and chlorides slowly though steadily fall.

Thompson (39) reports that about two-thirds of his patients show a depression of the basal metabolic rate varying from -16% to -35%. This rose to within normal limits in most cases during intensive treatment with cortical extracts but if treatment was not adequate the depression of the basal metabolic rate tended to persist.

The pigmentation, due to an accumulation of melanin in the skin and mucous membranes, has never been satisfactorily explained. Boyd (35) states, "It seems that melanin is formed in certain cells, melanoblasts, as the result of an interaction between a specific ferment in these cells and a colorless chromogenic mother substance, melanogen, which the cells take up from the blood. Increased pigmentation may be due to an increase in the ferment, owing to cellular activity as in the melanomata, or to an increase in melanogen."

7.

Prognosis.

The prognosis of this malady, with our newer forms of therapy is somewhat improved today in comparison to the prognosis at the time the disease was first described by Addison. However we still must consider the prognosis as extremely grave and make predictions regarding the life of the unfortunate individual with extreme caution.

Addison (2) felt that the disease was irremediable. Years later, Duckworth (3) felt that "cures" for the disease were out of the question and only temporary improvement could be hoped for. As late as 1929 the prognosis in a typical case was still considered as very unfavorable (12) and reported cures were, by many workers, considered as incorrect diagnosis. Although today, we still must consider the prognosis in the typical case as unfavorable, we can justifiably give a better prognosis for morbidity and can generally give hopes of prolonged life but as yet we can offer no "cures".

In the opinion of some workers the prognosis appears to be better in cases in which pigmentation is the first predominate symptom than in those cases in which weakness alone or weakness and pigmentation occur simultaneously as the initial predominate symptom. (25)

The treatment of crisis is much more successful today than it was even ten years ago and the patient has a much better chance of surviving a relapse and in this

manner the life of the patient can be prolonged even though it is impossible to restore him to full efficiency Snell (27) and Wilder (63) agree that present day treatment is not satisfactory but feel that the reduction in morbidity alone makes it well worth while and also makes possible a much better prognosis in case of surgical emergencies or complications in these patients.

In attempting to arrive at a prognosis of the individual case we must evaluate the patient, as a whole, very carefully. The history of the case, the general condition of the patient, the laboratory findings, the immediate response to treatment and the economic situation of the patient must all be taken into consideration carefully. As an indication for a grave prognosis, we must consider the development of collapse, extreme asthenia, lowered temperature, protracted vomiting, loss of weight, marked drop of sodium level in the plasma, marked hypotension, poor response to adequate treatment and the presence of active tuberculosis. (26)

Even though the prognosis is not yet as bright for this malady as we should like to see, we have grounds for an optimistic outlook today. Only a few years ago patients rarely lived longer than four years but with adequate therapy today life has been prolonged beyond such a length of time. (39)

8.

Treatment.

The treatment of Addison's disease has undergone some rather radical changes in the last twelve years with the introduction of an active cortical hormone, and more recently a synthetic hormone, and the recognition of the importance or salt. In the early days there was no specific plan of treatment and the results were almost uniformly bad. Addison used symptomatic treatment entirely on his patients, of course with only meager success but we today must not forget careful and complete symptomatic treatment along with our more or less specific form of treatment if we desire to obtain the best possible results. It has also been found that a patient in crisis requires a different and more concentrated type of treatment than the patient in the chronic stage of the disease.

Addison (I) reported a case which was treated for two months with Lyn. Ferri Iodide, drahms i ter die; and a middle diet. He left the hospital somewhat improved but the dingy smoky discoloration of his skin remained unchanged. However soon after his dismissal from the hospital he became weaker, developed an acute pericarditis and pulmonic inflammation and died.

The only treatment which Averbeck (64) mentions in his monograph written in 1869, for Addison's disease, is that which is best suited to support the enervated powers

times.

i. Over fatigue is especially to be guarded against.

j. For nausea, retching, hiccup and qualms, the use of nitroglycerine is recommended.

Duckworth also reports that Messrs. Willows, Francis and Butler prepared an extract of the adrenal bodies in the form of a tincture which caused a marked rise in the blood pressure and caused a powerful contraction of the arteries when injected into the veins of dogs. Dr. Oliver believed this extract would be found of service in Addison's disease.

Sir T. Grainger Stewart, according to Duckworth, employed feeding adrenal bodies to a patient with Addison's disease but without benefits.

According to the literature the first attempts to make use of organotherapy in the treatment began along about 1895. Kinnicutt (65) in 1897 reports on forty-eight cases of Addison's disease he collected from the literature, treated with suprarenal preparations by mouth. He reports the following results.

6 cases reported as cured or practically well.
22 " " " improved.
18 " " " unimproved.
2 " " " symptoms aggravated.

After this report, he recommends the therapatic use of a daily dosage equivalent to forty-five grains of the fresh gland.

Johnston (66) in 1900 reports a case of Addison's disease which he treated with suprarenal extract plus rest, full diet and strychnine sulfate upon which regime the patient steadily improved and stated he felt perfectly well after five months of such therapy.

Adams (67) in 1903 reports on 97 cases of Addison's disease treated by organotherapy by one means or another including glandular transplants, glandular extracts, race capsules, fresh whole suprarenal glands etc. The results were of a varied nature. Some seemed to receive benefits, others none at all. The author questioned the diagnosis of those cases which seemed to derive permanent relief and on the whole did not feel that organotherapy as yet had much to offer in true cases of the disease.

In 1920 the use of epinephrin in the treatment of Addison's disease was in vogue. Dr. Miurhedd was treated at the Mayo Clinic in 1920 with epinephrin and from this arose the famous, so called, Miurhead treatment (11). This treatment consisted of giving epinephrin solution to the point of toxicity, in as many ways as possible combined with rest and a few variations in diet. Snell of the Mayo Clinic in 1929 was still of the opinion that this treatment was the best advocated up to that time.

In 1927, Jaffe (5) discussed the use of transplantation of adrenal tissue as a theraputic measure against

Addison's disease. He felt that the reason for failure by this method of treatment thus far was due to the poor operative technic and inability to obtain "a take" of the transplant. He believed that if successful transplants could be accomplished some few patients would at least obtain palliative relief.

The same year, 1927, Rogoff and Stewart (68) injected into the veins of suprarenalectomized dogs, extracts, made from fresh dog adrenals with nin-tenths percent salt solution and glycerine. They felt that this extract in some way prolonged the life of these dogs but they were not convinced that it was due to a hormone contained in the extract.

Curschman (12) in 1929 states in his book, "Treatment so far has accomplished little or nothing. There is at present no effective substitution therapy and fresh sheep glands whether given by the mouth or subcutaneously or intravenously have been of no avail." He continues, "There is therefore hardly ever anything to be done except to treat the pains in the abdomen, limbs and back, and the achlorhydria, vomiting and diarrhea."

Probably the greatest single advance in the treatment of this disease thus far, was made in 1930 when Swingle and Pfiffner (6) announced the preparation of an aqueous extract of the suprarenal cortex which would maintain the life of bilaterally suprarenalectomized cats indefinitely.

Rowntree and Greene (69) in 1930 were attending a patient with Addison's disease who was in a state of complete collapse and whose outlook with ordinary treatment looked quite hopeless. As a last resort they asked Swingle and Pfiffner for a supply of their cortical extract which they received and started giving daily doses of two hundred cubic centimeters subcutaneously with marked results. Within thirty-six hours the patient's appetite and strength were markedly improved. Their supply of extract was limited and they were forced to put the patient back on the Miurhead regime. He did well for several weeks but gradually failed and again went into collapse. A new supply of the extract was received and again favorable results were obtained.

A short time later, Rowntree and Greene had the opportunity to try this extract on three other cases. Results in two of the cases were comparable to those above but the third case showed no striking improvement, however this patient was not considered in serious condition when treatment was started. These results convinced Rowntree and Greene of the efficacy of this cortical extract. They noticed no remarkable change in the blood pressure but the disappearance of anorexia, increase of appetite to a point of hunger, the gain in weight and the definite feeling of increased strength and well being were striking.

In 1931, Rowntree et al (70) outline factors which

must be taken into consideration in the treatment of Addison's disease.

a. The nature of the underlying disease and its treatment.

b. The natural course of the disease.

c. The general care of the patient.

d. The treatment of symptoms and complications.

e. The results of specific organotherapy.

In another article in the same year (71) these authors report the results of treatment of twenty cases by the use of the cortical hormone. They make this statement, "The results showed that this extract is strikingly effective in these cases of Addison's disease and is life saving in some." They continue, "The response of the majority of these patients to treatment has been striking. The nausea and vomiting stop and the appetite reappears. There is gain in weight and strength. The pigmentation decreases and the patients regain a sense of both physical and mental vigor and well being."

In 1932, Hartman et al (72) report seven cases treated with cortin, three cases represented severe stages of Addison's disease and the other four presented less severe aspects of the syndrome. They felt that conclusive evidence had been advanced to indicate the value and effectiveness of this suprarenal extract in alleviating the symptoms of Addison's disease.

However, in 1933, Harrop and associates (28) make

this statement, "We believe that the clinical value of injections of the cortical hormone as a routine treatment during the remissions of Addison's disease has not been satisfactorily demonstrated." They were of the opinion however, that its use during remission would not have any untoward or toxic effect on the patient. They were also definitely of the opinion that the extract had no effect on the hypotension or pigmentation. They concluded that the chief value of the extract was in the treatment of crisis.

Greene et al (73) in this same year reports a case of Addison's disease who was maintained in fair condition by the use of cortical hormone and then was necessarily subjected to a major surgical procedure which was successful and the patient survived. As far as these authors could determine, from the literature, this was the first successful major operation performed on a patient with Addison's disease.

Loeb (74) and Harrop and associates (28) in this same year both suggested the use of salt by mouth or physiological saline solution and dextrose solution intravenously in the treatment of acute relapse.

Snell (37) in 1934 states, "On the basis of observations it is now believed that one of the principal functions of the suprarenal cortical hormone is to maintain a normal distribution of electrolytes within the organism and, specifically to retain sodium chloride

within the blood and tissues." He maintains that if this contention be correct then sodium chloride is as necessary a therapeutic agent in crisis as is the cortical hormone. He emphasizes the fact that often during the chronic stage of the diseasethe composition of the blood and electrolyte pattern are within normal limits and in such cases cortical hormone appears to exert no striking clinical effect. He is not of the opinion that because of the above facts, the cortical extract should be considered of no value in states of remission nor should it be withheld until the patient goes into a state of crisis and until there is definite evidence of hemoconcentration and loss of sodium chloride. He is in agreement with Harrop et al (28) that the hormone exerts its most marked effect in crisis.

Wilder (63) in 1934 advanced the idea that secondary deficiency of the anterior lobe of the pituitary body may be a factor in the production of the Addison's syndrome. He reports two cases in which use of an extract of anterior lobe of the pituitary seemed to make the patients less sensitive to deprivation of sodium chloride. As a result of these two cases he suggested that anterior lobe pituitary extract may be employed with advantage in treatment of this disease as a supplement to cortin.

Snell (24) in 1935 sums up the important features in the treatment of Addison's disease as follows:

a. The first is to maintain an adequate supply of sodium

salts and fluids.

b. The second is to supply the missing cortical hormone.

Allers and associates (75) in 1935 confirmed the results of Harrop et al that adrenalectomized dogs cannot be maintained with sodium chloride alone but can be maintained with the simultaneous administration of sodium chloride and sodium bicarbonate or better sodium citrate for an indefinite period but Harrop states, "It is only by the administration of both extract and salt in normal amounts that entirely normal plasma electrolyte levels may be sustained in the totally adrenalectomized dog." Allers, however, went a step farther and showed that by using a diet low in potassium and giving sodium chloride and sodium citrate simultaneously he could not only maintain suprarenalectomized dogs indefinitely but in addition maintained entirely normal plasma electrolyte levels. He also showed that dogs maintained in such a manner could quickly be thrown into a grave state by increasing the potassium intake.

Wilder and Kendall et al (53) made observations on patients with Addison's disease regarding their sensitivity to addition of potassium to their diet. They reported this work in 1937. From this investigation the authors drew the following conclusions:

I. The potassium content of the diet of patients with Addison's disease affects the course of the disease and the development of the symptoms of crisis.

2. An intake of potassium not greater than four grams a day, an amount comparable to that contained in a normal diet, may promote the excretion of sodium and chloride whereby significant losses of sodium and chloride occur and symptoms of crisis are precipitated.

3. If the intake of potassium is restricted to about I.6 grams a day the requirement of sodium and chloride is materially diminished and it becomes possible, although not necessarily desirable, to maintain patients with smaller doses of sodium salts than are otherwise needed and without injections of extract of the adrenal cortex.

They summarize by stating, "Optimum theraputic results demand not only restriction of potassium but optimal rather than minimal doses of sodium salts and when possible and certainly in emergencies, injections of an active extract of adrenal cortex."

In this same year, Goldzieler (76) again brought up the question as to the value of transplantation of cortical tissue. He reports a case in which transplantation was successfully accomplished. The patient died nine months later and autopsy showed his own adrenals very small but the transplants were found in good condition and so far as can be determined by histology were capable of functioning. The patient apparently was benefited by the precedure as evidenced by a rise in the blood pressure, increased physical strength, improved appetite and feeling of well being, gain of weight and loss of

pigmentation. The author states, "Thus transplantation seems to be a promising procedure in the treatment of Addison's disease and might, under improved conditions, approach a real cure.

Because of the disadvantages occasioned by the frequent subcutaneous injections of adrenal cortical extract in patients with advanced Addison's disease, Thorne and associates (77) made some studies with a concentrated adrenal cortical extract preserved in glycerol administered orally to bilaterally adrenalectomized dogs and five patients with Addison's disease. They published the results of the work in 1938. They found that substitution of oral extract resulted in a maintenance of sodium and chloride balance body weight, blood pressure and serum electrolyte concentration. Withdrawal of the oral extract was attended by an opposite set of findings. They found the oral extract requirement to maintain adrenalectomized dogs and patients with Addison's disease to be two or three times that of the injected extract.

In 1937, Stiger and Reichstein, according to Firor (78) announced the synthesis of a steroid compound capable of preventing death from adrenal insufficiency. This crystalline compound was desoxycorticosterone. One year later Reichstein and Von Euw isolated this same substance from beef adrenal glands thus proving its natural occurrence.

Simpson (79) in 1938 reported the use of

desoxycorticosterone acetate in the treatment of two patients with Addison's disease and found it to produce an effect qualitatively similar to that of adrenal cortex extract.

Thorn (80) in an editorial appearing in the annals of internal medicine in 1939 remarks that the synthesis of desocycorticosterone acetate marks a new step in the study of the hormone of the adrenal cortex and in the treatment of patients with Addison's disease. He states further, "It is to be noted that whereas aqueous extracts of adrenal cortex can be given in almost unlimited quantities with no apparent untoward reaction the marked sodium chloride retaining property of desocycorticosterone acetate permits the development of edema and hypertension when administered in excess particularly when added sodium chloride therapy is given simultaneously.

In 1937 Deanesly and Parkes (81) reported that subcutaneous implantation of pellets of estrogens and androgens produced a prolongation of hormonal effect and provided an efficient and convenient method of administering sex hormones. Thorn and his co-workers (82) utilizing the technic of Deanesly and Parkes, studied the effect of subcutaneously implanted pellets of desoxycorticosterone acetate in bilaterally adrenalectomized animals and six patients with Addison's disease and reported their results in 1939. They observed that adrenalectomized dogs could be maintained in excellent condition by this form of

treatment. The hard consistency of the pellets and the slight water solubility of the compound resulted in a slow rate of absorption and hence prolonged the action of the hormone. They state that the number of pellets required for maintenance could be predicted rather accurately from the daily requirement of hormone in oil.

The advantages which resulted from experiments with implantation of pellets of synthetic hormone in dogs prompted these workers to investigate the use of this methods in patients with Addison's disease. In this report, Thorn et al (83) selected six patients with Addison's disease for treatment with pellet implantation. None of these patients could be maintained in good condition by means of sodium chloride therapy alone. These six patients were provided with a diet of constant mineral intake. The daily requirement of hormone was determined by daily injections of desoxycorticosterone in oil. The maintenance of optimum body weight, normal blood pressure, normal plasma volume, positive sodium and chloride balance and normal concentration of plasma electrolytes were considered as evidence of adequate treatment. They found that one pellet of one hundred to one hundred and fifty milligrams gave a daily effect equivalent to five-tenth milligrams of hormone in oil injected subcutaneously. They also observed that the hormone requirement of the patient did not seem to modify the rate of absorption of the pellets.

From this investigation they found that these six patients treated by implantation of pellets produced results similar to those obtained by daily intramuscular injections of desoxycorticosterone acetate in oil i.e., a positive sodium and chloride balance, an increase in the plasma volume, a gain in body weight, an increase in blood pressure and a return to normal activity. They conclude that pellet implants of crystalline hormone appear to be the most efficacious and economical method available for administering adrenal cortical hormone.

Firor (78) reports seventeen cases of Addison's disease treated by implantation of pellets of synthetic hormone subcutaneously. The results of his series are as follows: all but two have returned to full activity and are working as strenously as they did before the onset of their illness. Every patient has gained weight and improvement in both diastolic and systolic blood pressure has been uniform. Some of the patients have shown decrease in pigmentation but none of them has lost all the pigmentation. However, Firor sounds a word of warning concerning the use of desoxycorticosterone pellets. He states, "Since the rate of absorption depends upon the consistency and surface area of the pellets, one can easily imagine that improperly prepared pellets might crumble. This accident would result in a rapid absorption of large

amounts of the potent hormone with disastrous results." He had one such case called to his attention. The patient's blood pressure rose to above two hundred and there were signs of impending cardiac failure. This required removal of most of the pellets. In several other cases, Firor has removed some of the pellets because the rate of absorption has appeared to be too rapid.

Moehlig (84) reports a case treated by implantation of pellets of desoxycorticosterone acetate with marked general improvement, gain in weight and substantial increase in blood pressure which has been maintained over a period of five months.

Ferrebee et al (85) sound a note of pessimism in regards to this type of treatment. He states, "The treatment of Addison's disease has been significantly furthered by the introduction of synthetic desoxycorticosterone esters. Nevertheless many patients with this treatment have not recovered full strength, others have developed severe hypoglycemia and some have died suddenly, perhaps without adequate explanation for their demise."

He cites the work of Ingle (86) who has shown that the work capacity of adrenalectomized rats treated with desoxycorticosterone acetate is far less than that of animals receiving another steroid of the adrenal cortex namely corticosterone. Long and his co-workers (19) have also presented strong evidence favoring the view that corticosterone and dehydrocorticosterone as well as

cortical extract have a much greater effect upon the carbohydrate metabolism of adrenalectomized rats than does desoxycorticosterone.

For these reasons, Perrebee and associates thought it desirable to compare the effects of desoxycorticosterone acetate, corticosterone and cortical extract upon the electrolyte and water metabolism, carbohydrate metabolism, protein metabolism, and also upon the circulation of a patient with Addison's disease. From their study they obtained the following results:

I. All three preparations had some effect upon the excretion of sodium and potassium salts, most marked in the case of desoxycorticosterone.

2. None of these preparations had demonstrable effects upon protein metabolism as measured by nitrogen excretion.

3. The effects of corticosterone and cortical extract upon the carbohydrate metabolism, over the time administered in this study were not of a magnitude sufficient to be of practical value in the Addisonian patient regulated with desoxycorticosterone acetate.

The subject of the study, who was generally reserved in his appraisal of theraputic efforts, voluntered at the conclusion of the administration of large doses of cortical extract that "that stuff" made him feel stronger than he had felt at any time since the onset of the illness. If this investigation is to be used in the evaluation of the effectiveness of desoxycorticosterone it must be

remembered that this report was for only one patient.

Soffer et al (87) report their results in treating five patients suffering from Addison's disease with desoxycorticosterone acetate intramuscularly and four of which received pellet implantation later. Their results were favorable and quite comparable to those of Firor, above. He also sounds a word of warning about the dangers of the implantation of pellets, namely the development of hypertension, edema and cardiac failure. In three of their four patients they were required to remove some of the pellets because of the development of hypertension. They conclude that pellets are more economical to use than injections but that their use requires a much closer clinical observation of the patient for development of complications.

Anderson and associates (88) state that administration of desoxycorticosterone in pellets under the skin is a precarious practice since there is no way of controlling the dosage. On the other hand, she feels that administration by the subcutaneous or intramuscular route is too inconvenient and expensive. These workers found that desoxycorticosterone acetate dissolved in propylene glycol adminstered by drops under the tongue was as effective in the six cases they studied as it was when injected subcutaneously or intramuscularly. The dose was adjusted to the needs of the patient and given in daily divided doses. They report all six patients thus treated to be in

excellent condition and carrying on their usual occupations for a period of six weeks to eight weeks of such therapy.

This type of therapy if future work confirms the above findings, would certainly appear to be desirable, at least so far as the convenience and comfort of the patient requiring treatment are concerned. The cost of therapy which requires use of the cortical hormone, regardless of in what form it is administered, is still extremely expensive and almost prohibitive in many cases.

The present status of treatment may be summed up briefly as follows:

In the chronic stage of the disease.

I. Treat the underlying disease as far as possible.

2. Supply a high caloric diet, low in potassium, high is sodium chloride plus additional sodium chloride if deemed necessary.

3. Daily supply of the cortical hormone, present evidence seems to favor desoxycorticosterone acetate administered by one or another method.

In crisis.

I. Intravenous administration of sodium chloride and sodium bicarbonate or sodium citrate.

2. Large doses of cortical hormone.

3. Symptomatic treatment of symptoms as they arise.

4. Complete rest for the patient.

IV, SUMMARY AND CONCLUSIONS

Thomas Addison was the first physician to recognize and describe the syndrome to which Armand Trousseau applied the term "Addison's Disease". Physicians today still stand in awe of the remarkable power of observation and description which Addison possessed.

The suprarenal gland has a double origin but combines into a single anatomical unit which in reality functions as a double gland. Despite the great amount of study the true function of the gland remains unknown. The cortex is essential to life but the medulla is not.

Addison's disease is a rare disease occurring more commonly in males than females of middle age. It is seen more commonly in the laboring class of prople than in those of wealth.

The cause of the syndrome is a deficiency in the function of the adrenal cortex but the cause of this disfunction is not, as yet, completely understood. Tuberculosis of the adrenals is the lesion most frequently found associated with the disease while atrophy of the cortex is the second most common.

The symptoms and signs of the disease are those described by Addison in his original report, i.e., asthenia, feebleness of heart action, gastric irritablility and a smoky discoloration of the skin to which we may well add, hypertension. The symptoms of crisis differ somewhat in both type and severity from those observed in the chronic stage. A marked decrease in serum sodium and increase in

a low serum chloride and sodium accompanied by an increase of serum potassium is quite suggestive. The level of excretion of the various electrolytes in the urine has more recently been suggested as a diagnostic aid but as yet has not been proven to be of specific value. That definite progress has been made in the development of diagnostic tools cannot be denied but as yet we have no completely satisfactory or accurate tests.

The pathology of the adrenals in a greater percentage of the cases is found to be tuberculosis of both glands. The lesion appears to begin in the medulla and spread peripherally envolving the cortex. Atrophy of the cortex, the cause of which is entirely unknown, is the second most commonly found pathological lesion.

There is a disturbance of the blood electrolyte pattern in this disease but the exact nature of the disturbance is not yet agreed upon. It is quite well established that there is a disturbance in the level of blood serum sodium, chlorides and potassium. A disturbance in the carbohydrate metabolism is much more debated.

The prognosis of the disease must still be considered as grave. However, our more modern methods of treatment have improved the prognosis somewhat especially for morbidity but as yet we cannot offer a "cure".

Definite progress has been made in the treatment of Addison's disease, more rapidly in the past decade than in the previous seventy-five years. But as yet we cannot

boast such a satisfactory method of handling this disease as we can some of the other endocrine disturbances such as diabetes and thyroid disease.

Our present day treatment is far advanced to that used by Addison but we cannot discard the fundamentals of symptomatic treatment laid down by him and other early workers. We must incorporate his treatment, modernized of course, with our more or less specific form of therapy.

The early treatment consisted of the use of tonic medicines, well balanced diets and treatment of the underlying disease as much as possible. Iate in the nineteenth century andin the early part of the twentieth century attempts were made in the use of organotherapy but with meager results. Transplantation of adrenal gland was also attempted but only with failure. Theoretically this latter form of treatment would seem most desirable but as yet we have not been able to overcome the technical difficulties thus allowing it to be successful.

In 1920 the famous Muirhead regime came into vogue and won much enthusiastic support for about a decade. Its benefits are now considered doubtful.

The greatest progress in treatment began in 1930 with the isolation of the cortical hormone by Swingle and Pfiffner. It was found to be of great value in prolonging the life of adrenalectomized animals. It met with varying degrees of success and failure when used in the treatment of Addison's disease by various workers.

The suggestion, by Loeb, that sodium chloride be used as a theraputic agent marked another theraputic advance. Sodium chloride in combination with some other sodium salt was found to be of great aid in carrying the patient in the chronic stage. Later the use of a low potassium diet, as suggested by Wilder, in combination with the sodium chloride treatment seemed to improve the results.

One of the greatest obstacles met with in the use of the cortical hormone is its great expense. Hence the discovery of a synthetic product was heralded with enthusiasm but as yet its cost of production is about as great as that of the cortical extract. Nevertheless, the preparation of the synthetic hormone has marked another important milestone in the progress of therapy. It must not be forgotten, however, that this product has some disadvantages in that it has an action of causing marked sodium retentim thus initiating the development of edema and also excessive doses may produce hypertension. These disadvantages are not possessed by the cortical extract even if used to excess,

The use of the synthetic hormone, i.e., desoxycorticosterone acetate, in the form of pellets implanted subcutaneously is a recent develcpment introduced by Thorn and his co-workers. At present this method of administering the missing hormone appears to be the most practical and economical. The results have been gratifying in most cases but the dangers of this method must not be considered

V, BIBLIOGRAPHY

I. Long, Esmond, R. : Selected Readings in Pathology. 610.9, 1858, 280-289, 1929.

2. Addison, Thomas, : On the Constitutional and Local Effects of Disease of the Suprarenal Glands. Reprint M. Classics. 2:244-277, Nov., 1937.

3. Duckworth, Sir Dyce. : Addison's Disease and Other Diseases of the Adrenal Body. Twentieth Century Practice of Medicine. Edited by Stedman, T.L. 2:3-31, 1895.

4. Maranon, G. : The Oldest Known Case of Addison's Disease Siglo Med. 70:605, Dec., 1922

5. Jaffe, H.L. : The Suprarenal Gland. Arch. Path. 3:414, Mar., 1927.

6. Swingle, W.W. and Pfiffner, J.J. : An Aquecus Extract of the Supra-renal Cortex which Maintains the Life of Bilaterally Adrenalectomized Cats. Science 71:321, 1930.

7. Arey, L.B. : Developmental Anatomy. A Textbook of Embryology. 3rd Edition, 443-444.

8. Grays. : Textbook of Anatomy. 23rd Edition, 1269-1270.

9. Kipler, E.J. : Diseases of the Adrenal Glands, A Review with Special Reference to the Clinical Aspects. Arch. Int. Med. 56:104-135, 1935.

10. Grollman, Arthur. : The Role of the Adrenal Glands in the Animal Economy. Endocrinology. 25:413-416, 1939.

11. Greene, M.M. : Addison's Disease, with Report of Case Successfully Treated Through Three Critical Periods. Southwestern Med. 23:110-113, Apr., 1939.

12. Curschmann, Hans. : Endocrine Disorders. Oxford Medical Publications. 110-120, 1939.

13. Stewart, G.N. : Adrenalectomy and the Relation of the Adrenal Bodies to Metabolism. Physiol. Rev., 4:163, 1924.

14. Britton, S.W. and Silvette , H. : On the Function of the Adrenal Cortex, General, Carbohydrate and Circulatory Theories. Am. J. Physiology, 107:190, Jan., 1934.

15. Silvette, Herbert. : Chloride, Carbohydrate and Water Metabolism in Adrenal Insufficiency and Other Conditions. Am. J. Physiology. 108-135, June, 1934.

16. Swingle, W.W., Pfiffner, J.J., Vars, H.M., Bott, P.A. and Parkins, W.M. : The Function of the Adrenal Cortical Hormone and the Cause of Death from Adrenal Insufficiency. Science. 77:58, Jan., 1933.

17. Hartman, F.A., Brownell, K.A. and Lockwood, J.E. : Studies Indicating the Function of Cortin. Endocrinology. 16:521, 1932.

18. Harrop, G.A., Soffer, L.J., Ellsworth, Read and Treacher, J.H. : Studies on the Suprarenal Cortex. III Plasma Electrolytes and Electrolyte Excretion During Suprarenal Insufficiency in the Dog. J. Exper. Med. 58: 17, July, 1933.

19. Long, C.N., Katzin, B. and Fry, E.G. : The Adrenal Cortex and Carbohydrate Metabolism. Endocrinology. 26:309, 1940.

20. Howell : Textbook of Physiology. 13th Edition, Saunders

21. Osler and McCrae. : The Principles and Practice of Medicine. 10th Edition. 882-885.

22. Bittorf, A. : Addison's Disease in Child. Deutsches Arch.F. Klein. Med. 136:341. Ab. J.A.M.A. 76: 1376, May, 1921.

23. GreenHow, E.H. : On Addison's Disease. The Croonian Lectures for 1875. Ab. Brit. Med. Jour. I: 132, 1872.

24. Snell, A.M. : The Present Status of the Diagnosis and Treatment of Addison's Disease. Med. Clin. North America. 19:383, 1935.

25. Guttman, P.H. : Addison's Disease, a Statistical Analysis of 566 Cases and a Study of the Pathology. Arch. Path. 10:742-785, Nov., 1930. Arch. Path. 10:895-935, Dec., 1930.

26. Cecil : Textbook of Medicine. 4th Edition. 1231-, 1938.

27. Snell, A.M. : The Treatment of Addison's Disease. Proc. Staff meeting, Mayo Clinic. 9:57, Jan., 1934.

28. Harrop, G.A., Weinstein, A., Soffer, L.J. and Treascher, J.H. : The Diagnosis and Treatment of Addison's Disease. J.A.M.A. 100-1850, June, 1933.

29. Buhlo, Prof. : Addison's Disease. Ab. Boston Med. and Surg.Jour. 65:375.

30. Packard, F. and Wechsler, H.F. : Chronic Suprarenal Insufficiency. Arch. Int. Med. 54: I8-26 I934.

3I. Brenner, C. : Addison's Disease with Atrophy of the Cortex of the Suprarenals. Quart. Jour. Med. 22: I2I-I37 I928.

32. Bicknell, F. : Addison's Disease Due to Malignant Involvement of the Solar Plexus. Brit. M.J. 2:206 Aug, I934

33. Rogoff, J.M. : Addison's Disease Following Adrenal Denervation. J.A.M.A. I06:279-28I I936.

34. Simpson, S.L. : Secondary Pellagra. Quart. Jour. Med. 4: I9I-20I I935.

35. Boyd : A Textbook. Pathology of Internal Diseases. 3rd Edition 468-472.

36. Thomas Addison's Disease. M. Classics. 2:242-243 Nov. I937.

37. Yater, W.M. : A Textbook. The Fundamentals of Internal Medicine. 493-497.

38. Mohler H.K. : Addison's Disease--Discussion of Symptoms. Report of a Case with Autopsy Findings. M. Clin. N. America. 4: I255-I264 Jan., I92I.

39. Thompson, W.O. : Addison's Disease, Recent Contributions to Treatment. Jour. Mich. Med. Socie. 39:648-652, I939.

40. Snell, A.M. and Rowntree, L.G. : Clinical Experience with Addison's Disease. Ann. Int. Med. 3:6-28 I929.

4I. Franks, K. : Addison's Disease. Dublin Jour. Med. Science 73:279 I882.

42. Wilder, R.M. : Recent Clinical and Experimental Observations in Adrenal Insufficiency. The New International Clinics. 3: I Sept. I938.

43. Camp, J.D., Ball, R.G. and Green, C.H. : Calcification of the Suprarenal Glands in Addison's Disease : Roentgenologic Study. Am. J. Roentgenol. 28:594 Nov., I932.

44. Dryerre, H.W. : The Diagnostic Significance of Sodium and Chloride Content of Blood and Urine. Endinburgh M. J. 46:267-277 Apr., I939.

45. Allot, E.N. : Chemical Changes in the Blood in Addison's Disease and their Alterations in Response to Treatment. Lancet I: I406-, I936.

46. Zwemer, R.L. and Truszkowski. : Factors Affecting Human Potassium Tolerance. Proc. Soc. Exp. Biol. and Med. 35:424-426, I936.

47. Greene, J.A., Levine, H. and Johnston, B.W. : Is the Potassium Tolerance Curve of Value in the Diagnosis of Adrenal Cortical Insufficiency in Man? Endocrinology. 27:375-377, Sept., I940.

48. Nilson, E.W. : Corticoadrenal Insufficiency : Metabolism Studies On Potassium, Sodium and Chloride. Am. Jour. Physiol. II8:620-63I, I937.

49. Talbot, J.H., Gall, E.A., Consolazio, W.V. and Combs, F.S. : Dermatomyscitis with Scleroderma, Calinosis and Renal Endarteritis Associated with Focal Cortical Necrosis. Arch. Int. Med. 63:476-496, I939.

50. Cope, C., Kapnick, I., Lambert, A., Pratt, T.D. and Verlot, M.G. : Endocrine Function and Amylase Activity II. Changes in Activity of Blood Amylase in Respone to Changes in Adrenal Cortical Function in Dog and Rabbit. Endocrinology. 25:236-247, I939.

5I. Kline, E.M. : The Diagnosis of Addison's Disease. J.A.M.A. I08:I592-I593, May, I937.

52. Winkler, A.W. and Crankshaw, C.F. : Chloride Depletion in Conditions other than Addison's Disease. Jour. Clinical Investigation. I7:I.

53. Wilder, R.M., Kendall, E.C., Snell, A.M., Kepler, E.J., Rynearson, E.H. and Adams, M. : Intake of Potassium, Important Consideration in Addison's Disease. Metabolic Study. Arch. Int. Med. 59:367-393, I937.

54. Garvin, C.F. and Reichle, H.S. : Death Presumably Due to the Use of the Salt Restriction Test in the Diagnosis of Addison's Disease. Ann. Int. Med. I4:323-, Aug., I940.

55. Lilienfeld, A. : The Use of the Low Salt Diet in the Diagnosis of Addison's Disease. J.A.M.A. IIC:804-, I938.

56. Anderson, I.A. and Lyall, A. : Addison's Disease Due to Suprarenal Atrophy with Previous Thyrotoxicosis and Death from Hypoglycemia. Lancet I:I039-I043, I937.

57. Cutler, E.H., Power, M.H. and Wilder, R.M. : Concentration of Chloride, Sodium, and Potassium in Urine and Blood. Their Diagnostic Significance in Adrenal Insufficiency. J.A.M.A. III: II7-I22, July, I938.

58. Franks, V. : Addison's Disease. Dublin Jour. Med. Science. 73:279-, I882.

59. Dreschfeld, J. : Addison's Disease. The Brit. Med. Jour. I:462-, I884.

60. Loeb, R.F. : Chemical Changes in the Blood in Addison's Disease. Science 76:420-, I932.

6I. Thorn, G.W., Koepf, G.F., Lewis, R.A. and Olsen, E.F. : Carbohydrate Metabolism in Addison's Disease. The Jour. Clin. Investigation. I9:8I3-832, I940.

62. Lewis, R.A., Kuhlman, D., Delbue, C., Koepf, G.F. and Thorn, G.W. : The Affect of the Adrenal Cortex on Carbohydrate Metabolism. Endocrinology 27:97I-982, Dec., I940.

63. Wilder, R.M. : The Use of Anterior Lobe Pituitary Extract in the Treatment of Addison's Disease. Proc. Staff Meeting, Mayo Clinic. 9:689-, Nov., I934.

64. Averbeck, Von D. : Eine Monographic Praktiochend Artze in Bremen. Erlagen, P. II4, I869. Ab. Brit. and For. Medico Chirurgical Review. 46:I64-, I870.

65. Minnicutt, F.P. : The Theraputics of the Internal Secretions. Am. J.M. Sc. II4:I-23, July, I897.

66. Johnston, W.W. : A Case of Addison's Disease with Marked Exacerbations and Remissions in the Early Period. Treatment by Suprarenal Extract for Five Months with Gain in Weight and Strength but with Increasing Pigmentation. Tr. A. Assn. Physicians I5:65-70, May, I900.

67. Adams, W.W. : The Results of Organotherapy in Addison's Disease. Practitionar 7I:472-502, Oct., I903.

68. Rogoff, J.M. and Stewart, G.N. : The Influence of Adrenal Extracts on the Survival Period of Adrenalectomized Animals. Science 66:327-328, I927.

69. Rowntree, L.G. and Greene, C.H. : The Treatment of Patients with Addison's Disease with the "Cortical Hormone" of Swingle and Pfiffner. Science 72:482-, I930.

70. Rowntree, L.G., Greene, C.H., Swingle, W.W. and Pfiffner J.J. : Addison's Disease Experiences in Treatment with Various Suprarenal Preparations. J.A.M.A. 96:23I-235, I93I.

71. Rowntree, L.G., Greene, C.W., Bell, E.G., Swingle, W.W. and Pfiffner, J.J. : Treatment of Addison's Disease with Cortical Hormone of the Suprarenal Gland: Summary of Immediate Results in Twenty Cases Treated with the Preparation made by Swingle and Pfiffner. J.A.M.A. 97: I446-, Nov. I93I.

72. Hartman, F.A., Thorn, G.W., Lockie, M.L., Greene, C.W. and Bowen, B.D. : Treatment of Addison's Disease with an Extract of Suprarenal Cortex. J.A.M.A. 98:788-, I932.

73. Greene, C.W., Walters, W. and Rowntree, L.G. : Surgical Operations in Addison's Disease. Successful Epididymectomy and Orchidectomy for Tuberculosis. Ann. Surg. 98; I0I3-I0I7, I933.

74. Loeb, R.F. : Effect of Sodium Chloride in Treatment of a Patient with Addison's Disease. Proc. Soc. Exper. Biol. and Med. 30:808-, I933.

75. Allers, W.D., Wilson, H.W. and Kendall, E.C. Studies on Adrenalectomized Dogs: The Toxic Action of Potassium. Proc. Staff Meet., Mayo Clinic. II:283-288, I936.

76. Goldzieher, M.A. and Barishaw, S.B. : Transplantation of Adrenal Tissue in Addison's Disease. Endocrinology 2I:394-, I937.

77. Thorn, G.W., Emerson, Kendall, Jr., and Eisenberg, H.: Oral Therapy in Adrenal Insufficiency. The Efficacy of a Concentrated Adrenal Extract Preserved in Glycerol. Jour. Clin. Investigation. I7:525-, I938.

78. Firor, W.M. : The Treatment of Addison's Disease by the Implantation of Synthetic Hormone. Ann. Surg. III:942 - June, I940.

79. Simpson, L.S. : The Use of Synthetic Desoxycorticosterone Acetate in Addison's Disease. Lancet 2:557-, Sept, I93

80. Thorn, G.W. : Editorial : Progress in Adrenal Cortical Hormone Therapy. Ann. Int. Med. I3:552-555, I939.

8I. Deanesly, R. and Parkes, A.S. : Factors Influencing the Effectiveness of Administered Hormones. Proc. Roy. Soc. B. I24:279-, I937.

82. Thorn, G.W., Engel, L.L. and Eisenberg, H. : Treatment of Adrenal Insufficiency by Means of Subcutaneous Implants of Pellets of Desoxycorticosterone Acetate. (A Synthetic Adrenal Cortical Hormone). Bull. Johns Hopkins Hospital 64: I55-I66, Mar., I939.

83. Thorn, G.W., Howard, R.P., Emerson, K. Jr. and Firor, W.M. : Treatment of Addison's Disease with Pellets of Crystalline Adrenal Cortical Hormone (Synthetic Desoxycorticosterone Acetate) Implanted Subcutaneously. Bull. Johns Hopkins Hospital. 64:339-365, 1939.

84. Koehlig, R.C. : Addison's Disease Treated by Implantation of Desoxycorticosterone Acetate Pellets. Endocrinology 27:633-637, Oct., 1940.

85. Ferrebee, J.W., Ragan, C. Atchley, D.W. and Loeb, R.F.: A Comparison of Certain Effects of Desoxycorticosterone Acetate, Corticosterone and Cortical Extract on a Patient with Addison's Disease. Endocrinology 27:971-982, Dec., 1940.

86. Engel, D.J.: The Work Performance of Adrenalectomized Rats Treated with Corticosterone and Chemically Related Compounds. Endocrinology 26:472-, 1940.

87. Soffer, L.J., Engel, F.L. and Oppenheimer, B.S. : Treatment of Addison's Disease with Desoxycorticosterone Acetate by Intramuscular Injections and Subcutaneous Implantation of Pellets. J.A.M.A. 115:1860-1866, Nov., 1940.

88. Anderson, E., Haymaker, W. and Henderson, E. : Successful Sublingual Therapy in Addison's Disease. J.A.M.A. 115:2167-2168, Dec., 1940.