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Hypersecretion of the suprarenal cortex

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HYPERSECRETION
OF THE
SUPRARENAL CORTEX

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TABLE OF CONTENTS

INTRODUCTION

In the consideration of the subject of hypersecretion of the suprarenal cortex, it has been herein attempted to cover the evidence which is present in the literature pertaining to such a syndrome, its cause, effect, and outcome.

Such consideration demands a discussion of the subject as a whole, including the various headings and subheadings into which the subject may naturally be divided. There is considerable controversy over various points which have been brought up, but as the author has had no experience with such clinical cases, it will be more or less difficult to present anything which is new or startling. It is only possible to note the work of the various workers in the field and then to take the view which seems to be the most logical and present such as the final outcome.

At present the subject is in a considerable state of flux, and to find two authorities who agree upon the same matters is practically impossible. Therefore, it is necessary to note the work of all, report the like, and endeavor to organize it into a logical sequence and view the final outcome with an open mind.

In view of the fact that the subject is in such a state of flux, the last five years of literature have been the subject of the majority of the discussion in order to

get away from some of the conflictions. With these facts in view, the material to follow has been compiled in the hope that such may help in the clarification of the subject at hand.

HISTORY OF THE SUPRARENAL

In olden times the adrenals were probably overlooked due to their small size and yellow color as a part of the renal fat. It has been claimed that the adrenals were mentioned in the Bible, but this was an error of Vulgate translation. Here the kidney and the fat surrounding the kidney are mentioned, but no special reference is made to an adrenal (Leviticus 3:4) Bartholomaceus Eustacius gave the first description of the adrenal in his "Opuscula Anatomica" published in 1563 in Venice, where he describes and illustrates the adrenals by drawings. Many of his followers denied their presence, and Piccolomini spoke of the gland as "displaced fragments of the kidney." Others completely ignored its existence. Eustacius called the adrenal the "glandulae renibus incumbentes" out of which has come our modern word "suprarenal." Casserius called them the "renes succenturiate" and the term "reins succenturieux" is still used in the French literature, but is mainly replaced by the word "glandes surrenales." Winslow was first to use the English term "suprarenal" which is descriptive of the gland in man, but a misnomer when applied more generally, and is being gradually replaced by the word "adrenal".

In the seventeenth century, there was little work done along the lines of the adrenal. Most of the literature

consisted of anatomical descriptions which were distorted in order to lend support to the various hypothetical and fantastic theories. Spigelius considered the adrenals as an abdominal filler to help in the support of the stomach. Highmore, also considered this as correct, and added the fact that the adrenals absorbed humid exudates from the nearby vessels. Riolan gave the adrenals the task of supporting the nerve (abdominal) plexus thus preventing their weighing on the renal vessels. Molinetti rather ironically pointed out that the adrenals lay above the nervous plexus which already had the firm support of the vertebral column, thereby needing no support. Thomas Wharton suggested that the adrenals withdrew something from the nerves due to their close proximity to the nerves. He therefore, called them the "Glandulae ad nerveum plexum". Glisson supported this theory, but Collins suggested that the adrenals transmitted a fermentive liquor from the nerves to the kidney. Molinetti advanced the theory that the adrenal diverted the blood supply from the kidney in the fetus, thereby, preventing fetal excretion of urine. This theory was supported by Coxe of the University of Pennsylvania, the earliest American writer on the subject. Sylvius advanced the theory that the adrenals prevented the blood clotting in the vessels, and was supported by Boerhave, Deider, Tauvry and others. Bartholin described

a brownish fluid present in the adrenals sometimes seen after death. This fluid is due to an autolytic process in the medulla, but he considered it to be an "atabiliary" juice derived from the spleen and liver. Kerckring claimed that the adrenals secreted a juice which is the coloring substance of the blood and produces the fermentation of the heart.

Severinus mistook a band of connective tissue for a duct leading from the adrenals to the testicles, and Valsalva described similar ducts to the ovary and testicle, and thereby assumed that the adrenals were necessary for proper sexual function. He supported his theory by adrenalectomizing a dog on side, and removing the testicle on the other. The dog failed to copulate after this operation, and Valsalva took this to be positive proof that the adrenals were part of the reproductory system. Meckle also believed and supported this theory.

In 1716 the "Academie des Sciences" of Bordeaux offered a prize for the best thesis on the subject of the function of the adrenal. Montesquieu was appointed to judge the works, but after many severe and ironical criticisms of the theories that were expounded to explain the presence of the glands, stated that there were no contributors worthy of a prize.

The eighteenth century brought forth a better

anatomical knowledge of the subject, but the same bizzare theories were advanced for the function of the adrenals. Senal suggested that the adrenals secreted meconium in the fetus, while Von Helmont believed that they prevented the formation of renal claculi. Goodsir considered the adrenals, the thymus, and the thyroid functional only during fetal life. Riegal considered the adrenals the factors that deposited fat in the abdominal cavity. Morgagni noted that the adrenals were larger in fetal life than in the adult, and deduced that they functioned only in fetal life, and found that Hartmann had made the same observations in dogs. He also believed that they filtered a fluid into the "receptaculum chyli" during fetal life to insure the patency of the thoracic duct, as ther was no chyle in the fetal period. Winslow gave a very accurate account of the anatomy of the adrenal, but subsequent writers failed to take into consideration the anatomy when correlating physiologic function with the gland.. Consequently, Boerhave thought that the gland was responsible for diluting the blood after it left the kidney.

In the 19th centure, the study of the adrenal was approached along the comparative anatomy lines. Meckle described the variations in the birds and mammals, but

missed the glands in the reptiles. He also noted the absence of the adrenals in ancephalic monsters, and linked the adrenals with the reproductive system. Retzius in 1819 described the adrenal homologues in the Selacion fishes, and Stannius, in the teliost fishes. Rathke in 1825 described the true nature of the glands in the amphibia, and Nagel first recognized the adrenal glands in the birds. In 1839 Bergmann noted the relation of the medulla to the central nervous system, and Meckel, Hohannes Muller, and Rokitansky finally disposed of the idea that the adrenals were related to the kidneys. During the middle of the nineteenth century, studies were made in the microscopic structure of the adrenals. Ecker first noted that the adrenal was of a glandular type, and concluded that the organ must pour some secretion into the blood directly or by the lymphatics. Iollicker in 1854 gave a good description of the adrenals in his "Microscopischen Anatomie oder Gewebelehre des Menshens". Arnold first introduced the conventional division of the gland into zones, while Leydig demonstrated the relation of the adrenals to the central nervous system.

The modern study of the physiology of the adrenals was begun by Thomas Addison when he published his findings of a syndrome which later was to bear his name. His description which was published in 1855, is still one of the

most accurate descriptions of the disease up to the present date. He not only recognized the condition as a disease entity, but correlated it with the pathological condition of the adrenals. Addison's publication stimulated Brown-Sequard in 1856 to extirpate the adrenals from laboratory animals. Death followed this procedure rapidly so they concluded that the organs were essential for life. (13)

The adrenal cortex was neglected for the most part in previous times. Later it was realized that the essential part of the gland was the cortex, and not the medulla. This turned an ever increasing interest on the subject, and in the light of the present studies of endocrinology, new fields are being opened for the uses and function of the secretion of the adrenals.

ANATOMY OF THE SUPRARENAL

The suprarenal glands differ in their relations on the two sides of the body. The right suprarenal gland is situated on the upper end of the right kidney, in front of the diaphragm, behind the inferior vena cava and the right lobe of the liver. Its shape is somewhat triangular and its base is directed downward and is in contact with the medial and anterior aspects of the upper end of the kidney. The anterior surface is slightly rotated so that it faces anterior and laterally. It is made up of two areas: a medial, narrow and non peritoneal which lies behind the inferior vena cava; and a lateral, somewhat triangular, in contact with the liver. The upper part of the lateral has no peritoneum and is in contact with the bare area of the liver near its lower and medial angle, while the inferior portion is covered by peritoneum reflected onto it from the inferior layers of the coronary ligament. The hilum is a short furrow below the apex and near the anterior border of the gland, from which the suprarenal vein emerges to join the vena cava. The posterior surface is divided into upper and lower parts by a curved ridge; the upper, slightly convex, resting upon the diaphragm; the lower, concave, is in contact with the upper end and the adjacent part of the anterior surface

of the kidney.

The left suprarenal is somewhat larger than the right, being somewhat concave and adapting itself to the concavity along the medial border of the upper part of the left kidney. The anterior surface has two areas: an upper one covered by peritoneum of the omental bursa, which separates it from the cardiac end of the stomach and sometimes from the superior extremity of the spleen; and a lower one, which is in contact with the pancreas and lienal artery, and is therefore, not covered by the peritoneum. Near the lower end of the anterior surface is a furrow or hilum which is directed downward and from which the suprarenal vein emerges. The posterior surface has a vertical ridge which divides it into two areas; the lateral area rests on the kidney, and the medial and smaller on the left crus of the diaphragm.

On miscroscopic examination, the suprarenal consists of two parts. The external portion is termed the "Cortex" and the internal the "Medulla". The cortical portion is made up of fine connective tissue with glandular epithlium imbedded therein. The epithelial cells are polyhedral in shape and possess rounded nuclei. Many of the cells contain coarse granules, other lipoid globules. Three distinct zones can be made out. The Zona Glomerulosa, situated beneath the capsule, consists of cells arranged in

rounded groups, and here and there indications of an alveolar structure. The cells of this zone are very granular and stain very deeply. The Zona Fasciculata, continuous with the Zona Glomerulosa, is composed of columns of cells arranged in a radial manner. These cells contain finer granules and in many instances globules of lipoid material. The Zona Reticularis, in contact with the medulla, consists of large cylindrical masses of cells irregularly arranged. These cells often contain pigment granules which give this zone a darker appearance than the rest of the cortex.

The medulla of the gland is very vascular and consists of large chromaphil cells arranged in a network. The irregular polyhedral cells have a finely granular cytoplasm that are probably concerned with the secretion of adrenalin. In the meshes of the cellular network are large anastomosing venous sinuses which are in close relationship with the chromaphil or medullary cells. In many places the endothelial lining of the blood sinuses is in direct contact with the medullary cells. With such an arrangement, the secretion of these cells may be poured directly into the blood stream for distribution.

The blood supply of the suprarenal are of comparatively large size. The arteries are derived from the aorta, the inferior phrenic, and the renal. These then break up into innumerable branches to be distributed

through the substance of the gland. The suprarenal vein emerges from the hilium of the gland after collecting the blood from the venous sinuses within the gland, and on the right side empties into the inferior vena cava and on the left into the renal vein.

The nerves of the gland are numerous and are derived from the celiac and renal plexuses, and, according to Bergman, from the phrenic and vagus nerves. They enter the lower and medial part of the capsule, traverse the cortex, and end around the cells of the medulla. They have numerous small ganglia developed upon them in the medullary portion of the gland. (12)

In the consideration of the embryology of the suprarenal gland it is well to, more or less, correlate its origin with the pathological syndrome which at times can be seen after birth. By this manner it may be possible to throw some light upon the etiology of the masculinizing syndrome. Various authors have attributed the androgenital syndrome to a hyperfunction of the suprarenal cortex, with elaboration of an excess amount of the hormone. This idea is not in accord with Grollman. He points out that the adrenal has the same embryological origin as do the gonads. The adrenal cortex is developed from the mesothelium of the abdominal hollow contiguous to the point of origin of the testicles and ovary. Thus there is an intimacy in the development of the adrenals and the sex glands.

The origin of the ovary is hermaphroditic. The ovary passes through a stage in which its cortical portion may be considered female and its deeper portion male. During further development the male part remains rudimentary. This is the portion that is so intimately related to the adrenal cortex in the beginning stages. If these fetal testicular cells by developmental anomaly are included in the adrenal, they might develop into tumors which physiologically would manifest their testicular origin. This theory was proposed by Krabbe.

It isn't necessary to resort to Krabbe's hypothesis in order to explain the adrenogenital syndrome associated with adrenal tumors. The adrenal cortex of man contains a tissue which is anatomically and functionally distinct from the rest of the cortex. This tissue is designated as the androgenic zone and is only temporary normally, disappearing after the first few years of life, but it sometimes remains as a few scattered cells in the adult. (the Juxta-Medullary zone). The exact embryological origin of the androgenic tissue has not been determined. It may be that it has a common origin with the testicular cells of the ovary as is assumed by Krabbe to be the cause of the andro-genital syndrome.

The differentiation of the androgenic tissue as a unit distinct functionally from the remainder of the adrenal

cortex would explain the fact that adenoma or carcinoma of the cortex proper do not give rise to abnormalities of the reproductive system. It would also account for the failure of large doses of the cortical hormone to affect the reproductive system. Grollman admitted that the clinical significance of the androgenic tissue in clinical medicine need further experimentation to put it upon a firm basis, but this view allows one to look at the facts and the outcome of the adrenogenital syndrome without the usual confusion about the adrenals and the reproductory system. (13)

PHYSIOLOGY OF THE SUPRARENAL CORTEX

In the consideration of the physiology of the suprarenal cortex many conflicting opinions are encountered and there seems to be no absolute criteria upon which to base all of the various findings and thereby draw absolutely valid conclusions. However, a composite of the views may be presented and thereby allow the reader to draw his own conclusions from the works which seem to be the most in accord with his views.

Grollman and his colleagues feel that the cortex gives only one hormone which maintains all the normal body functions. They found that this hormone had little effect upon the genitals as far as stimulation, for extracts ten times as potent as necessary to maintain life had no effect upon the genitals. They feel that the androgenic syndromes are due to tissue functionally distinct from the remainder of the cortex and that it does not cause precocious development of the reproductive system, but only a masculinization. This same feature has also been reported by Loos and Rittman.

The weight of the present evidence indicated the life sustaining principle does not affect the gonads and that certain cortical extracts have a marked effect upon the sexual development of experimental animals and therefore,

are present in the adrenal gland substances distinct from cortin and which have gonadic activity. (25) Scholl feels that the adrenal cortex elaborates two hormones. One essential to life and the other possibly ascorbic acid. He also states that he feels with further investigation that more will be found. (11) Thorn and Eisenberg isolated only one hormone from the cortex and were able to synthetically reproduce it. The formula was pregnene-21-ol$_3$,20 dione acetate, and has been otherwise named desoxycortico sterone. (36)

The development of the secondary reproductive organs of male rats and mice were compared in normal, in castrated, and in castrate-adrenalectomized rats and mice maintained on adequate doses of cortical hormone. The results indicate that the adrenal gland does not exert an androgenic function in the normal animal. Neither the "juvenile" cells of the rat nor the x-zone of the mouse normally exert an androgenic function.

The adrenal cortical hormone was found to exert no androgenic effects on the development of the ventral and dorsal prostate glands or Cowper's gland, or of the seminal vesicles of normal or castrated mice and rats. Extracts of human or pig fetal adrenal glands and of x-zone bearing glands of mice were also found to be devoid of androgenic activity. (15) A moderate excess of the

hormone of the adrenal cortex has no appreciable influence on the size of the gonads, the oestrous cycle, or the course of gestation in the rat. Contradictory previous results of others are attributed either to the presence of toxic impurities in the extracts used, or to natural variability among experimental animals. The growth of normal young rats is not appreciably influenced by a moderate excess of the hormone of the adrenal cortex.

No causal relation of the adrenal cortex to intersexuality has been detected with the methods employed. The frequent but not invariable coincidence of intersexuality or precocious sexual maturity with adrenal cortical tumor is probably a result of a common inducing factor. (19)

In considering the role that the cortical hormone plays in the control of carbohydrate metabolism in the body, there are various factors which may be considered. It now appears that in the absence of the adrenal glands that the organism is unable to fix or synthesize glycogen in the liver and skeletal and cardiac muscles to any degree. Cats were treated for varying periods of time after adrenalectomy with large amounts of glucose and saline solution by (2), and were thus kept in apparently normal condition. At autopsy of the animals, not one tenth as much glycogen was found in the liver as similarly treated

but unoperated animals. Exhaustion levels of liver glycogen were observed. Skeletal muscle and heart glycogen were also lower than normal by fifty per cent or more. Corticoadrenal extract treated animals, however, under the same conditions,formed large amounts of liver, muscle, and heart glycogen after adrenalectomy. (2)

Zwemer, Britton, and Riddle feel that the effects of cortical extracts on the blood sugars causes a hyperglycemia in normal animals. Others say that the blood sugars are notoriously labile, and no evidence is present that indicates that the cortical hormone was the cause for such. Grollman feels that in adrenalectomized animals, cortical extracts furnished a hormone which probably maintained life, but has little effect upon the blood sugar levels. He also feels that deficiencies in carbohydrate levels in adrenal insufficiency are due to secondary pathological changes in other organs (liver, muscles and hypophysis) and that the adrenal cortex is probably not involved in the maintenance of normal carbohydrate metabolism. (14)

Long, Fry and Thomson mention that crystalline compounds isolated from the adrenal cortex by Kendall, provoke glycosuria in partially depancreatized rats. Now synthetic adrenal cortical material has been made available by Steiger and Reichstein. Although highly potent so far

as activity in salt water metabolism is concerned, the synthetic material seems to lack the power to provoke diabetes in partially depancreatized rats. Wilder has also found that this hormone injected in 30 mg. daily doses failed to raise the blood sugar or increase the twenty-four hour excretion of dextrose in a case of diabetes. The absence of adrenocortical activity frequently is associated with an abnormally low level of blood sugar has been long known from observation of patients with Addison's disease. Ferrebee, Ragan, Atchley and Loeb, feel that the synthetic compound desoxycorticosterone acetate has no influence on this abnormality. (39)

On the contrary, Kulhlman, Belbue, Koept, and Thorn, find that the administration of 17-hydroxy-11-dehyrocorticosterone restores the ability of the adrenalectomized rats and dogs to resynthesize glucose and glycogen from intermediate products of carbohydrate and protein metabolism, and to correct the defects in carbohydrate metabolism. (23) Britton and Silvette have maintained that the adrenocortical hormone plays a primary role in the regulation of carbohydrate metabolism. They have shown that following adrenalectomy, before changes in sodium and chloride in the serum can be observed, the blood sugar falls about forty per cent below normal. In

addition, the liver glycogen is reduced eighty-five per cent, and the muscle glycogen to forty-five percent of the normal. Furthermore, administration of adrenocortical hormone to normal and adrenalectomized animals is followed by hyperglycemia and considerable increase in muscle and liver glycogen. Katzin and Long have contributed some confirmatory evidence to support the view expressed by Britton and Silvette. They have shown that the crystalline compounds A and B isolated from adrenal cortex by Kendall, produce a marked increase in liver glycogen, a questionable increase in muscle glycogen, and a slight hyperglycemia. Furthermore, Long showed that the adrenocortical hormone causes a glycosuria in pancreatectomized-adrenalectomized animals, a finding not obtained by the administration of NaCl alone. (18)

Loeb and Harrop seem to feel that the cortex is the regulator of the sodium and water balance of the body. Following the removal of the adrenals, the kidney allows sodium and chloride to escape, and the administration of adrenal cortex causes the retention of sodium and chloride. Zwemer and Truskowski believe that the primary defect in adrenal cortex insufficiency is a disturbance of potassium metabolism, and that such changes as sodium loss, dehydration, low blood sugar, and kidney damage are secondary changes. If this were true, then in hyper-

corticoadrenalism there would be a low serum potassium and an elevated sodium.

Swingle feels that the cortical hormone is concerned with the maintenance of water and electrolyte distribution between the intracellular and extracellular spaces. Since sodium is the chief cation of the extracellular fluids, and potassium the principle cation of the intracellular fluids, the distribution of these ions will to a large extent govern the distribution of body water. In the absence of the adrenal cortex, the sodium and chloride ions are depleated by increased renal elimination and a shift of these ions across the cell membrane. Simultaneously, with the fall in extracellular electrolytes, the intracellular electrolyte increases by renal retention of potassium and uptake of the potassium by the cells, and also by the passage of some sodium and chloride into the cell. As a consequence, of this increasing inbalance of ions, there is an upset in osmotic equilibrium, and shift of fluid from extracellular to intracellular compartments. The result is a decrease in blood pressure, increase in hemo-concentration, and eventually death from dehydration, shock, and circulatory collapse.

If the converse of this reasoning holds, then one would have reason to expect arterial hypertension, and in contrast to circulatory collapse, circulatory

suffusion, in hypercorticoadrenalism. That the adrenal cortex bears some relationship to hypertension, has been suggested by Goldblatt. He found that bilateral adrenalectomy interfered with the development of the hypertension brought about by renal ischemia. The exact way in which the adrenal cortical hormone acts in conjunction with the hypothetical renal pressor substance in the development and maintenance of hypertension due to renal ischemia has not been elucidated. Although the cortical hormone acts in conjunction with the hypothetical renal pressor substance, yet it may prepare the arteriolar musculature for the action of the hypothetical effective renal substance, or the reverse may be the case. (18) Thorn and Eisenberg fed adrenalectomized dogs a diet low in sodium and chloride and showed that daily subcutaneous injections of 1 to 1.5 mg. of desoxycorticosterone acetate (synthetic)dissolved in oil will maintain an animal weighing ten kilograms. Withdrawal is accompanied by prompt changes of renal electrolyte excretion and signs of adrenal insufficiency. Resumption of therapy results in restoration of electrolyte balance, and the animals return to good health. (36)

Zwemer and Pike showed electrical stimulation of the splanchnic nerve of a laboratory animal resulted in death from hypopotassemia. It has been shown that the regulation

of potassium metabolism is a function of the cortex, and therefore, a patient depleted of cortex is left vulnerable to fluctuating potassium levels which may reach toxic proportions. (24)

The role of the cortex in fat metabolism and particularly in relation to cholesterol metabolism seems well established. Enlarged adrenals are accompanied by basophilism (pituitary). However, it seems that the adrenals are the primary factor while the pituitary is secondary. (10)

It has also been demonstrated that glycerinated adrenal cortex given orally to patients suffering from psychoneurosis marked by asthenia were definitely benefitted by the oral administration of adrenal cortex, and there was also an increase in weight in about fifty per cent of the patients. The experiment was begun with a placebo and after one to two weeks, the extract itself was given, thereby, ruling out any psychic improvement which may have been present. (21) Looney and Darnell have observed that a glycerol extract of the cortex given orally causes prolonged increases in blood pressure.(17) This may be a cause of the feeling of alleviation of fatigue which has been observed.

Cortical extract has been noted to change the permeability of the capillaries and it is, therefore, con-

ceivable that the effect of the hormone in relieving secondary secondary shock in adrenalectomized animals after hemorrhage may be in part referable to its inhibitory effect on the seepage of blood plasma through the capillary walls. The effect of an exudate or of leukotaxine of increasing capillary permeability is wholly or in part inhibited by the presence of the extract of the adrenal cortex. This inhibitory effect may be brought about by adding the hormonal preparation to the exudative material and then injecting the mixture into the cutaneous tissue of a normal rabbit. Similar results can be attained by separate injections several minutes to hours apart and at the same site of the hormone followed by either the exudative material or leukotaxine. The apparent property of the horome of the adrenal cortex to influence capillary filtration and, therefore, its possible significance in various conditions such as traumatic or secondary shock is pointed out. (29)

Suprarenal cortical hormone and salt have been used in the treatment of pneumonia and other infections with fairly good results. Desoxycorticosterone acetate in amounts of five to ten miligrams a day was administered with salt and isotonic saline (1000-1500cc) daily prior to operation, and thereafter. In a series of patients with chronic diseases in whom such operative procedures were performed

as resection of colon or stomach, thoracoplasty, spinal fusion, and the like. Preparation of patients in this manner had a striking beneficial effect. In all cases, there was no objective shock, the blood pressure was maintained or elevated from 10 to 30 mm. of Hg, and there was no hemoconcentration, and the temperature returned to normal within forty-eight hours. Post-operative exhaustion and toxemia were definitely lessened. Complications did not occur, wound infection was avoided, and operative recovery including wound healing was more rapid than is the case in similar conditions in patients not so prepared. The values of parenterally administered suprarenal cortical hormone (together with salt and excess fluid by mouth) was demonstrated in a number of severe infections, including seventeen cases of pneumonia, a case of induced malaria with periods of collapse, and severe grippal infections. The criterion of its value was noted in maintenance of normal blood pressure, decrease in signs of toxicity, avoidance of circulatory collapse, maintenance of appetite, and sense of well being, decrease in the tendency to complications, absence of distention and shortening of the convalescence. (31)

To consider the intestinal absorption of the adrenalectomized dog, the dogs were maintained on high sodium, high bicarbonate, low potassium diets following withdrawal

of adrenal cortical hormone, and a decrease in the rate of absorption of sodium, potassium, and chloride from chronic loops of ileum was noted. After cortical hormone withdrawal on high sodium intake, high bicarbonate, and low potassium diet, the rate of sodium absorption in general declined more than that of potassium. The most striking observation was that in this state, there was often an actual reversal in the direction of net movement of sodium, which sometimes excreted into the gut in relatively large quantity, although potassium still was being absorbed. The decrease in osmotic pressure of the gut fluid seen in normal animals during absorption is less rapid after withdrawal of adrenal cortical hormone and dietary maintenance. This finding is interpreted to mean that the passive as opposed to the active processes in absorption are relatively more important. In spite of essentially normal blood chemical determinations and objectively excellent health, the behavior of the intestine in the adrenalectomized dog could not be maintained normal in the absence of adrenal cortical hermone. The adrenalectomized dog, therefore, remains distinctly abnormal if adrenal cortical hormone is withheld. (28)

Troth showed that the elimation of adrenal secretion from the circulatory system by tying off the adrenal glands does not prevent the oliguria in normal kidneys

that usually results from the inhalation of low oxygen gas mixtures by anethetized dogs. Under the same experimental conditions, the urine rate from the denervated kidney does not decrease, but accords with that expected from the changes that occur in the general systemic blood pressure. (37)

Lastly, the influence of the adrenal cortex extract upon compensatory hypertrophy of the adrenal cortex should be considered. When one adrenal is removed, the cortex of the remaining gland undergoes hypertrophy. This does not occur if the hypophysis is removed simultaneously, and in time if hypophysectomy is done, the remaining cortical tissue atrophies. Cortical repair follows anterior pituitary transplants. An anterior pituitary extract is now available which prevents adrenal cortex atrophy in the hypophysectomized organism, and stimulates the cortical tissue in normal animals. It is fairly obvious that the integrity of the adrenal cortex is, therefore, dependent upon the hypophysis. The maintenance of a normal amount of adrenal cortex tissue is dependent upon the concentration of adrenal cortex hormone circulating in the organism. When one adrenal is removed, the adrenal cortex secretion is reduced and the stimulation received by the other gland from the anterior pituitary becomes increased.

A compensatory hypertrophy is the result. Experiments have shown that an active adrenal cortex would reduce or entirely prevent compensatory hypertrophy of the adrenal cortex following unilateral adrenalectomy. This compensatory hypertrophy is supressed or prevented by the administration of adrenal cortex extracts. It is probable that the hypertrophy is dependent upon stimulation by an anterior pituitary hormone, the production of which depends on the concentration of adrenal cortex hormone circulating in the organism. When the lack of this hormone follows unilateral adrenalectomy, compensatory hypertrophy does not ensue when the stimulation by the anterior pituitary is prevented by supplying the deficiency in cortical hormone from outside sources. (27)

ETICLOGY OF THE ADRENOCORTICAL SYNDROME

A few historical notes may be of interest to introduce the hypersecretion or abnormal function portion of this discussion. In 1835 Bouillaud and Manec reported a case of a married man discovered at autopsy to be female. The patient had a large clitoris and the urinary opening was in the perineum. It had been thought that the individual was one of a hypospadius character. A uterus, tubes, ovaries and a vagina which opened into the urinary tract were found. Around the urethra above the vaginal opening was a "veritable prostate". In 1865 another pseudohermaphrodite with adrenal hyperplasia, a prostate, and penis was recorded. He had enjoyed a normal sex life as a male until at the time of marriage he found that his birth record stated him to be female. He then turned to dissipation and died at forty-three. The urethra was surrounded by a prostate, which was below the orifice of the vagina. On each side was an opening which simulated an ejaculatory duct. The adrenals were almost as large as the kidneys and the ovaries were small and showed no evidence or trace of corpus lutea. (41)

There are numerous theories about the etiology the adrenogenital syndrome which has been more or less ascribed to the abnormal or excessive function of the suprarenal

cortex by some pathological process. Hamblen considers the cause to be a diffuse cortical hyperplasia or neoplasm, either adnomatous or malignant. These are often called hypernephromata, and the cells have a fuchsinophil reaction. (17) Servinghaus feels that the syndrome is due to a secretion from the abnormal or atypical cells which are present in tumors of the cortex. (34)

Goldzeiher states that adrenal hyperplasia in the fetus with concommitant production of androgens is the cause of masculine pseudohermaphroditism in the genetic female. That this is actually the mechanism by means of which adrenal changes elicit pseudohermaphroditism was shown experimentally by the treatment of pregnant animals with androgens; the result was sex reversal, that is, masculinization of the females of the litter. The question of pseudohermaphroditism was fully reviewed by H. Young, who conclusively established the pathogenetic connection between adrenal hyperplasia and abnormal development of the genital organs. Adenomatous growth of the adrenals may become an added feature later on in life, and superimpose marked virilism upon the existing anatomic deformity. (11)

It seems probable that the adrenal androgens act directly upon the accessory male sex organs, and not through the intermediary of the interstitial cells of the

testes. In cases of virilization of the female, no tissue is found corresponding to the Leydig cells. In most of the cases of macrogenitosomia precox in boys resulting from adrenal tumors, the testes have been immature, the Leydig cells have not been increased and spermatogenesis has been absent. The familial occurrence of adrenal hyperplasia deserves special emphasis. Wilkens, Fleischmann, and Howard report a family with twelve cases of andrenogenitosomia syndrome. Hermaphroditic sisters have been reported in families. Priesel reports a female pseudohermaphrodite who had a brother with sexual precocity, and Jacobziner and Gorfinkel found a sexually precocious boy and two pseudohermaphroditic sisters in the same family. O'Farrell reported that there were five hermaphrodites out of forty children born to six members of the same family, but it is not certain from his description that the hermaphroditism was due to adrenal hyperplasia. In these families, the sexual abnormalities have occurred in only one generation. In no instance did either parent present definite evidence of an endocrine disturbance. Therefore, there is no reason to suppose that the adrenal hyperplasia in the embryo is brought about by a hormonal unbalance in the mother. (40)

Thus to state that there is an etiological agent

or condition or specific factor that is the cause of such a condition would be far from correct. One must consider a variety of causes and conditions which may or may not be responsible for such a picture, continually keeping in mind the factors at hand and ever on the alert for new points which may arise to be blended into the picture.

SYMPTOMS AND SIGNS

The symptoms and signs of the adrenogenital syndrome may be conveniently broken down into various subjects, and by so doing, it is possible to get a clearer picture of the condition and to keep the material in a more organized sequence.

In the male before puberty, a precocious sexual development is the most frequent finding. There is a definite increase in muscular development, and athletic ability. Hair appears on the face, abdomen, and genitals, and it is of a coarse dark nature.(4) The voice often changes very early in life, and the patient may have a full beard at a very early age. If such a condition is present very early in life, the child may assume the "Infant Hercules" type of body stature which is a marked development of secondary sexual characteristics, as well as marked muscular development.(17) Often the child will have adult genitals, adiposity of the trunk, an acne of the face and shoulders, and a dark red face. There have been cases recorded of children with sexual desire at a very early age.(5)

In the male after puberty, tumors of the adrenal cortex may be asymptomatic, or the patient may notice an increase in masculine characteristics. There may be

hypertrophy of the genitals, increase in weight, and an increase in the amount of hair upon his face and that distributed over his body. (4) Several cases have been reported in which males who have had cortical tumors undergo feminization. They have noticed a swelling of the breasts which in some cases have been painful and in others not. Later, there was a loss of libido, the genitals became smaller, and a pigmentation occurs around the nipples of the breasts and they may or may not give forth a secretion. (33)

In the female before birth or in early infancy pseudohermaphrodism may be the case. The clitoris may hypertrophy until it approaches the size of a penis, and the infant may have the characteristics of a male child. The external genitals manifest male characteristics, even to a distinct scrotum, physical configuration, voice, and hair distribution. However, the internal genitalia are distinctly feminine. (4) Miller and Kenny describe the case of a male appearing patient about the age of ten years, whom the accoucheur stated was hermaphroditic at birth. During his childhood his development had been much more rapid than normal children. He was definitely attracted to women, and had fits of jealousy if someone else paid attention to one of the girls to whom he was attracted. He was very energetic in athletics, and in his studies

and was far ahead of the average. He was found at autopsy to have a complete set of female genital organs, and his so called penis was a greatly hypertrophied clitoris which resembled a hypospadius with a perineal opening of the urethra. (30)

The female after puberty and before menopause may be asymptomatic with an adrenocortical tumor, but the tendency is toward male secondary characteristics. Amemorrhea and hirsutism are the case although there may be headaches at the time of menstruation. There is usually a loss of sexual desire and libido. Primary and secondary sexual organs fail to develop, except the clitoris which hypertrophies. Ovaries are cystic or sclerotic, and there is no menses or it slowly ceases after varying irregularities of several years duration. The uterus and cervix are small and fibrotic. The body contour and boney frame and muscular equipment is verile; thorax is deep, hips small, shoulders broad, larynx masculine with a hoarse voice. Most of these women remain psychologically feminine and may yearn for male attention. In the adult type the most striking changes are hirsutism, general genital regression with hypertrophy of the clitoris, menstrual irregularities finally culmination in amenorrhea and sterility, and gradual disappearance of the typical feminine lineation due to

resorption of characteristic fat pads and to muscular hypertrophy. (17) Suckerman and Struckenhoff described a typical case of masculinization in a normal female, aged forty-nine, who experienced all of the typical symptoms of masculinization. Hirsutism, of a masculine type, fat distribution of the masculine type, alipecia, and hypertrophy of the clitoris were all noted. Upon abdomenal laperotomy, an adrenal cell rest tumor was found, and upon removal the symptoms were relieved. (35)

In another group, symptoms may be classed on a metabolism basis. They frequently resemble the many changes described by Cushing, and are assumed to be associated with basophilic adenoma of the pituitary at times. The changes in the skin are erruption, pigmentation, dryness, and loss of elasticity with striae. In the hair, changes occur in color, texture, and distribution. There are increased deposits of fibrous fat in certain places, particularly the face, neck, and trunk, and depletion of the fat from others, especially the extremities. The fatty deposits are often edematous and painful. Changes occur in the blood, with apparent concentration of volume and cellular contents, with an apparent lessening of the total blood volume in circulation, but with high hemoglobin percentage and red blood counts per cubic centimeter. There is often present a low sugar tolerance and the

blood cholesterol readings have been uniformly high. Disturbances in the emotional field are seen in the well marked metabolism syndromes. Bone changes appear to be less often present in the adrenal syndromes than in the somewhat similar ones due to pituitary changes. Whether such symptoms are caused by adrenal changes alone, or are due to associated disturbances in other glands, a pluriglandular syndrome, appears to be debatable, but they are often seen with definite adrenal tumors. (5)

No clear cut picture of the mental changes have yet been described from the adrenocortical syndrome, probably because no one has paid any attention to such. Many children show precocious mental development, and have the speech of adults, while others are intellectually dull. Many of the adults are bright and mentally active, although depressed by their condition. Langdon Brown described one woman who came to him with the terrible fear that she was turning into a man. Upon examination, it was found that she was suffering from an adrenal tumor which was found and removed. Here the psychological symptoms were recognized long before the physical signs.

Often there is the feeling that they no longer desire the company of men and, in fact, such associations become distasteful to them. Erotic temperament, homosexual trends, and emotional instability are quite fre-

quently the case. Occasionally, the patients have the fear of being poisoned and their food polluted. Jump, Beates, and Babcock described a girl of seventeen who was a bright scholar, and developed an adrenal tumor which was followed by an increase in muscular development and strength. Her mental ability did not decrease in any manner, but she became very affectionate to dolls, and preferred to give caresses rather than to recieve them. Crile described a patient whose uppermost thought was that of suicide. (18)

C. Allen describes the psychosis of a patient who was suffering from an adrenal hyperplasia. She was grossly halucinated, and complained of hearing voices who stated that she smelled bad. She was terribly afraid that someone was trying to poisen her through her food, and was very careful about what and when she ate. She always slept with her head under the pillow because she was afraid that someone would shoot her through the eyes. She had no idea who the persons were who were endeavoring to do her this harm, but only felt that someone was trying to kill her. She experienced no change in intellect, and was able to add and subtract numbers with amazing rapidity.

She took enemas for the satisfaction she received from then, and had the burning desire to urinate while

standing up, and thought that if she were a man, she would be able to do so. She also hated the idea that she had so much hair distributed over her body, and resented her masculine appearance. During her psychosis she had fantacies of immaginary intercourse in which she was the female partner. Thus it would appear that she was conciously heterosexual, and unconciously homosexual, neurologically expressed as partly conditioned to masculinity. (1)

HORMONAL STUDIES

Hormonal studies have been attempted but each author and investigator have obtained varying results, and each has devised a method of his own for the determination of the various hormones which he wishes to determine. However, one method has been fairly well accepted and has been in fairly general use. This is the method of testing for the hormone by the growth of a chicken's comb. The technical points will not here be ellucidated as they are rather laborious and time consuming,but it must be mentioned as this is the method used for the following determinations. In the adrenocortical syndrome, there is an excess excretion of male hormone. Estrogenic material excreted was less than the normal amounts. Other cases have been reported that had no increase in male hormone, but fell within or below the normal range.(18) In some cases with androtropic syndromes, there are excreted large amounts of male sex hormonal substances than normal, and the amounts seems to vary with the degree of masculinization. Some of the patients with small androtropic changes and marked other metabolism changes, excreted smaller amounts of both male and female hormonal substances than normal. Of particular interest has been the demonstration bv Burrows and Simpson, and Joll of

twenty times the normal amount of estrogenic substance in the urine of a male with adrenal cortical tumor and feminism. The large amounts of estrogenic material were accompanied by a moderately high amount of androgenic substance. The tumor was thought by them to have produced the excess estrogens because of the reduction to normal after removal of the tumor and the reappearance of an excess associated with the recurrence as metastasis.

There also has been described a steroid compound isolated by Butler and Marian from the urine of a woman with adrenalgenital syndrome, and an adrenal tumor. It seems to be associated with the tumor syndrome because it is not excreted by men, and by normal pregnant and non pregnant women, and it was not found in the urine after removal. Confirmation of this finding may be of great interest in type diagnosis of tumor. As yet, however, data on these types of tumor cases and investigation as to their hormonal excretions will be required before hormonal studies by themselves will establish the diagnosis of adrenal cortical tumor. (5)

DIAGNOSIS

At present, the diagnosis of this condition is more or less dependent upon the clinical manifestations and x-ray findings, as the chemical tests are somewhat variable and far from dependable. In cases without endocrine symptoms, the tumor as a rule, has been large enough to palpate in the abdomen in the region of the kidney. There is frequently pain and the tumors displace the kidney downward. This may be demonstrated by pyelograms. In the displacement, the upper pole is frequently pushed downward and inward with the hilum of the kidney facing downward. This is the reverse of the usual picture of the nephrototic kidney, and does not resemble the congenital, unascended kidneys in which the kidney, usually unrotated, has the hilum facing anteriorly. In some cases, invasion of the kidney has been demonstrated by irregular compression changes in the pylographic shadows in the upper pole.

When the characteristic syndrome of genitosuprarenalism is present, the diagnosis lies between tumor of the adrenal, hyperplasis of the adrenal, and possibly basophic adenoma of the pituitary. Ovarian tumors, as arrhenoblastoms, are reported to have produced symptoms that might be confused with adrenal cortical tumor.

Tumors and enlargements of the adrenal have been diagnosed by x-ray, either through the density of the tumor shadow itself, or through the tumor displacing some shadow-forming organ, usually the kidney. Carelli in 1921 used CO_2 infiltrated into the perirenal fascia to help in the visualization of the adrenal tumors by x-ray. Since 1930, the method of Carelli has been the most universal in useage. Here it is possible to demonstrate both pathological and normal kidneys and adrenal. The air injected into the perirenal fascial space is displaced by manual pressure around the adrenal areas, then upon x-ray, the air is seen to be infiltrating around the adrenal and upper pole of the kidney. It is possible to outline the adrenals and with the change in size, shape, and position of the adrenal shadows, to have a tentative diagnosis of tumor, and it is possible to determine whether or not there is the presence of a shadow of an apparently normal adrenal on the opposite side. (6)

To consider some of the clinical points which are of value in the diagnosis of this condition. There is a three part syndrome which is the most noticeable, namely; hirsutism, obesity, and menstrual disorders, thus involving the pituitary, the ovary and the adrenal glands.

Hirsutism may be broken up into types, depending

upon the various etiological causes of the abnormality. The pituitary type shows the presence of fine facial hair of lanugo type, usually more conspicuous on the cheeks than the chin. Ovarian hypofunction causes a loss of hair on the pubes and in the axillary region, while hypersecretion such as arrhenoblastoma may cause definite hirsutism. Adrenals, if early in life, causes a precocious development of public and axillary hair. Later in life, after puberty, gives a masculine hair distribution, which is coarse and dark and seen on the upper lip and chin.

The fat distribution or obesity may also be broken down into the types seen with the three endocrinological causes. In pituitary type of obesity, the fat is characteristically a girdle type, conspicious even in general adiposity. Often there is an apron of abdomenal fat which covers the genitals like an apron. The forearms and legs are seldom involved. Ovarian deficiencies often cause a generalized obesity, but there are usually deposits on the thighs and trochanteric regions as well. Excess adrenal cortical secretion causes the fat to be restricted to the trunk and the legs, while the thighs, arms, hands, and upper arms are relatively free and the patients have a characteristic "bull neck" appearance.

Menstrual disorders of the pituitary type have their

onset before puberty, the ovarian by primary amenorrhea and oligomenorrhea. If the luteinizing factor alone is lacking, abbreviation of the menstrual period with excessive blood loss follows. Hyperfunction of the pituitary leads to polymenorrhea and menorrhagia. If the leuteinizing factor prevails, amenorrhea results. Removal of the ovary results in complete amenorrhea. Hypersecretion of the adrenal cortex results in precocious puberty of children and sexual precocity, and virilism in adult women. They show hirsutism, enlargement of the clitoris, atrophy of the uterus, and breasts, and cecession of menses. Also, there is a change or deepening of the voice, which is often the differential point between a pituitary syndrome and the adrenal syndrome. (32)

Children with masculinizing tumors of the adrenals show on radiological examination a marked advancement in the bone age. The fusion of epiphyses and the number of carpal bones which are calcified are greatly increased for the age of the patient. Advancements in bone age of two to four years are common. There is usually a definite indication of advancement of bone age in such cases. (16)

A few studies have been done on the cholesterol levels of the patient with such a syndrome. There is some evidence that a disturbance in cholesterol

metabolism may be brought about by adrenal cortical tumors. It is not known how frequently blood cholesterol levels are altered because observations on this point are not numerous. In the few that have been reported there is some decrease in blood cholesterol. (16)

PATHOLOGY

In consideration of some of the more common pathological conditions of the adrenal cortex, Grollman presents simple hyperplasia, cortical adenoma, and malignant carcinoma.

He considers hyperplasia a response to demands for more cortical hormone, such as infections and toxic irritations. The lesions may be diffuse or circumscribed nodules microscopic to hen's egg size. They show columns of cells similar to the fascicular zone, and at times like the glomerulosa, the peripheral layer of cells. Adenomas differ from hyperplasia by atypical cell formation and malignant tendencies, and are seen as reddish or yellow masses which may deform or destroy the whole gland. Often there are no demonstrable symptoms. Carcinomas resemble adenomas, but have atypical areas of malignant character and metastasize early, especially if it is around a blood vessel. Malignant tumors of the cortex are rare, and often do not give rise to virilism or any abnormality of the genital system. (13)

Goldzeiher and Koster in a review of five cases feel that the enlargment of the adrenal was not equally conspicious in all cases. The storage of lipoid material was evident, but does not vary materially from the adrenals

of cases with no evidence of hyperadrenalism. Microscopic sections of these cases showed a formation of a broad reticular layer of cortex which, heretofore, had not been noticed. Miller, Deansley, Poll, Martin, and Whitehead demonstrated such a layer in the cortex of female rodents, and connected this "x-zone" with the influence of adrenal cortex on the function of the sex glands. (10)

Cahill feels that most of the tumors were of a reddish-yellow color, ovoid in shape with a thin capsule, According to literature, the kidney has been the most frequent organ invaded. Section of the tumor from males without endocrine symptoms showed irregular cells with very large and bizzarre shaped nuclei. These tumors showed a deep fuchsinophil reaction in the cytoplasm with the trichrome stain similar to that described by Broster and Vines in adrenogenital syndromes of their series. In the females without endocrine syndromes, the cells resembled more the renal hypernephroma and and looked most like the fasciculate layer of the adrenal and contained only small amounts of fuchsinophil granules. The androtropic tumor was an andrenocarcinoma with considerable fushsinophil granules in the cytoplasm, and the cells mostly resembled the reticulate or inner layer of the adrenal. In the cases of androtropic

and Cushing type metabolism changes, the tumors were adenomas with uniform cells, or adenoma with large amounts of vacuolated cells or diffuse cellular carcinomas. These did not contain many fuchsinophil granules, and it was not possible to tell from which cell layer the tumors might have been derived. The syndromal cases without tumors that were operated upon had the adrenals carefully explored and in none was found any evidence of small adenomas. Portions of these adrenals were removed, selecting the thickest half of the larger glands in the hope that a small hyperfunctioning adenoma may have been in that portion. No adenomas were found microscopically, and the gland structures were almost uniformly normal. Excess fuchsinophil granules in the cytoplasm could not be demonstrated in the portions removed. (5)

Cahill also states that some cases of virilism vary in pathology from adenoma to carcinoma. The cells of malignant tumors show a relatively uniform picture, but vary in size. They are rather large and irregularly rounded or cylindroid with well defined cell membranes, and a voluminous, faintly staining, acidophilic cytoplasm. Some areas are vacuolate as if they contain lipoid material. (4)

The specificity of the fuchsinophil reaction in masculinizing lesions of the adrenal cortex has been

widely discussed. The vividly red ataining of the inner layers of the cortex of adrenal glands removed for virilism was first described by Vines. He found a positive reaction to a ponceau fuchsin dye in twenty-four of twenty-six glands removed for the relief of the symptoms of masculinization. Further studies with the stain showed that it is also taken up with avidity by the acidophilic cells of the pituitary, the interstitial cells of the testis and the young corpus luteum. Moreover, while the reaction is commonly absent after birth, it is normally positive in both the male and female glands during certain developmental stages of fetal life. The greatest activity is seen during the weeks of sex differentiation, and the development of the pituitary into a solid gland. The period lasts longer in the male than in the female. It is the belief of the majority of workers that the adrenal gland exerts a strong "bisexual" function at this time. This does not completely disappear in later life, as shown by the presence of male sex hormone in the normal adult female, and vice versa. In disturbances such as virilism, the hormone of the opposite sex is seen in excessive amounts. Broster feels that the adrenal cortex is the main source of excess hormones found. (28)

TREATMENT AND PROGNOSIS

The treatment of such cases is more or less confined to surgical means in these cases as there seems to be no medical management at present which produces any aleviation of symptoms or recession of the typical signs which accompany the disease. Authorities are fairly well agreed upon surgical treatment if the diagnosis can be made early enough. Even if these conditions are diagnosed early, the surgical risk is poor, and quite frequently the patient will die soon after from metastatic growths and a return of all the former symptoms due to the metastatic growths. (33)

Upon the removal of the adrenal cortical tumors, the virilism is frequently improved. The body hair and acne disappear, the breasts usually develop and the menses return sometimes to normal. Urinary androgrens which have been increased before operation usually return to normal, and the patient usually enjoys fairly normal health thereafter unless beset by complications of a metastatic nature. (26) It has been found that roentgenological therapy for either the tumor itself or the metastatic growths is entirely unsatisfactory. (17)

The operative technique for removal of such tumors has been more or less divided up into three approaches

which are most frequently described, namely: the extra peritoneal route through the lumbar region, the transthorasic route, and the transperitoneal route.

The lumbar route with an extraperitoneal approach has been quite extensively used, especially by the Mayo group. Many workers do bilateral exposures of the adrenals to determine, first, the diseased side, and second, to be satisfied that there was an opposite adrenal present.

The transthoracic route has been used by Broster and Vines in most of their cases of adrenal genital syndrome. This, they claim, is the easiest approach in view of the fact that the adrenal vascular pedicle allows a slight range of upward movement. It has the disadvantage of creating an artificial pneumothorax. In the transthoracic approach, it was first necessary to do a preliminary laporotomy for exploration of both adrenals by palpation, and then after recover, perform the main operation by the transthoracic approach.

In an approach to an adrenal with a tumor, the ideal method should be ligation of the adrenal vessles, particularly the veins, before any manipulation of the tumor. With the tumor, the adjacent fascia containing the lymph vessels and nodes should be removed. This requires an adequate exposure, especially if the tumor is large, and many prefer to do so transperitoneally. Here it is possible

to palpate the adrenal of both sides and confirm the information obtained by x-ray. A bilateral oblique subcostal incision is felt to give the most adequate exposure. The exposure is facilitated by the use of an elevated bridge on the table, situated so that the costal flare is opened, and the subcostal area projected forward as often used in common bile duct exposure. The posterior parietal peritoneum is opened to the right of the duodenum and across and above the colon. On deflection, this exposes the adrenal and renal area. The right adrenal presents more difficulty than the left because it enlarges to a considerable degree around the vena cava, and its central vein is short, and empties directly into the vena cava. The vessels are first ligated and divided, and then the tumor delivered with its fascia. The ligation of the viens on the left side is much easier, because the central vein empties into the left renal vein, and is directly accessible. (6)

In all operations on adrenal cortical tumors, it should be remembered that the operative risk is great due to shock and trauma produced in reaching the desired point, and thereafter, doing the necessary procedures. The prognosis of such operated cases is fair if care is taken to prevent surgical complications and if no metastasis has occurred. If the latter has taken

place, there is little hope for the patient. In untreated cases, the mortality approaches one hundred percent in the light of tumor metastasis and the symptoms produced by abnormal secretion present. Cases that are properly treated early in the progress of the disease experience almost complete relief from symptoms and metastatic recurrences are less frequent.

SUMMARY

1. The normal secretion of the suprarenal cortex seems to have little or no effect upon the abnormal development of the genitals.

2. The absence of the secretion from the adrenal cortex renders the organism unable to fix glycogen in any degree in the liver, skeletal muscles, or the myocardium.

3. The adrenal cortex is vitally concerned in the regulation of sodium and water balance in the body.

4. Adrenal cortical hormone is of value in combating post operative shock, as well as severe reactions from febrile and toxic diseases.

5. The cause of the androgenic syndrome seems to be a neoplasm or cell rest tumor which produces an abnormal cortical hormone. Such a condition is often familial in incidence.

6. The symptoms include a masculinizing syndrome in women, while in men the reverse is sometimes the case, or there may be an accentuation of masculine features. At times the chain of symptoms is accompanied by psychic changes which are far from constant, and vary from homosexual tendencies to extreme schizophrenia.

7. Hormonal studies show an increase in androgenic substance excretion in some cases, while others show an

increased output of estrogenic substance.

8. The diagnosis is usually based upon the clinical findings in conjunction with x-ray studies of the kidneys and adrenals.

9. Tumors of the adrenals are usually one of three types, namely: simple hyperplasia, cortical adenoma, or malignant carcinoma. Any one of these tumors may produce the androgenic syndrome, but the latter, being malignant, is the condition to be most feared.

10. Treatment is more or less resolved into surgical methods for removal of the tumor; which, if done before metatasis, if the tumor is malignant, results in quite marked alleviation of the symptoms.

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