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DISEASES OF THE SUPRARENAL GLAND.

Senior Thesis.

University of Nebraska College of Medicine.

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D. L. Coffman.

(Date)

DISEASES OF THE SUPRARENAL GLANDS.

The Suprarenal glands are two, small, roughly triangular shaped organs which sit closely on top of the kidneys. They resemble very much flattened "cocked hats" which are tipped toward the midline. The average weight of a single organ is from ten to twelve grams and each measures about five by three by one centimeters.

EMBRYOLOGY.

A study of the development of the suprarenal glands, from a comparative anatomy standpoint, shows that the glands were originally of two parts, each distinct and separate. In the lower vertebrates, especially in the fish, this arrangement is especially well demonstrated. The cortical substance, which is of mesothelial origin, never unites with the medullary substance. Rather it assumes a position medial to the medullary substance and remains there as a distinct and separate unit. Since these organs occupy the area between the urinary organs in these animals the term "Interrenal Organs" has been given the tissue.

As the vertebrate scale is ascended, up to the amphibia, reptiles, and birds it is seen that the two parts lie closer together, and finally in mammals they have united to form a single gland. The process can be traced in mammals by a study of the embryo. Here

again is seen the two parts which gradually approach each other and finally unite into one structure.

THE CORTICAL SUBSTANCE.

The cortical substance originates from mesodermal tissue. The mesothelium, at the level of the cephalic one-third of the mesonephros in embryos of five to six millimeters, proliferates and sends buds, or sprouts, into the mesenchyme at each side of the root of the dorsal mesentery. Before long these sprouts lose their connection with the parent tissue and become joined together to form a rather compact mass of epithelial-like cells ventro-lateral to the aorta. Not infrequently these masses fuse across the midline ventral to the aorta. These masses are the anlagen of the cortical substance of the two suprarenal glands, and from the intermediate position in lower vertebrates they are termed Interrenal Organs.

THE MEDULLARY SUBSTANCE.

Shortly after the anlagen of the cortical substance appears there is noticed a beginning differentiation of some of the sympathetic ganglia which lie in the region of the mesonephros. This differentiation produces two types of cells, (1) the so-called Sympathoblasts which become the sympathetic ganglion cells, and (2) the Phaeochromoblasts which later give rise to the phaeochrome or chromaffin cells. From this it is seen that the medullary substance has an ectodermal origin since the parent sympathetic ganglia originate in the

nervous system which arises from ectoderm.

Soon the chromaffin cells become detached from the ganglia and migrate to a position in the region of the cortical anlagen. Once there these cells penetrate the cortical mass in cord-like masses which finally form a single compact mass. Some sympathoblasts are also carried in with the chromaffin cells and they go to form the sympathetic cells within the gland. Thus, these two types of cells go to form the medullary substance. Since, in lower forms, these masses do not unite with the cortical anlagen but remain distinct over the cephalic part of the kidney they are called the Suprarenal Organs. However, in mammals, the two sets of anlagen unite to form the Suprarenal Gland.

As the two parts of the gland unite there is another important change going on in the same area. The mesonephros is becoming atrophied and the suprarenal gland is becoming more closely associated with the cephalic end of the kidney, and by the time the third month is half gone these glands have practically reached their adult position. For the next month then the glands become relatively very large, even larger than the kidney. However from the fourth month on they grow less proportionately than the surrounding and by the sixth month they are about one-half as large as the kidneys. At birth they are about one-third the size of the kidney, and in the adult they are but one twenty-eighth the size of the kidney.

Not all the gland tissue is found within the gland capsule or even above the kidney. Accessory parts of the glands may arise from cells which have been caught before they had a chance to unite with the rest of the gland. This is especially true of the cortical substance. Sometimes both cortical and medullary substances are found embedded within the kidney, in the retroperitoneal tissue near the kidneys, in the walls of the neighboring bloodvessels, or associated with the internal genital organs, the rete testis, epididymus, or broad ligament. These may be extra glands or parts of the main gland which were carried down by the descent of the genital glands.

Baily and Miller⁵ further note some other small masses of tissue which remain in the gland and go to make up part of it. These are permanently associated with some of the prevertebral and peripheral sympathetic ganglia.

HISTOLOGY.

The picture presented to the microscope is one of a series of layers which are divided into two main types of cells, cortex and medulla. They are all arranged in a definite manner with the outer division placed in a series of zones, the characteristics of each being more their relationship to the bloodvessels rather than a difference in cell structure. This is especially true in the cortex.

Cortex.

The outermost layer of the cortex is quite narrow

and lies just inside the capsule. It has been given the name of zona glomerulosa. The cells are small, columnar, closely packed, in ovoid or spheroid groups or in small arcs which surmount the straight cells of the zona fasciculata, the next group or zone. Normally no lumen is found within the glomerule, although a pseudo-lumen may develop through degenerative disease as diphtheria. In most cases the outer, free end of the cell is in contact with a bloodvessel. The nuclei stain quite deeply and the cytoplasm, which is rather scanty in amount, also takes a nuclear stain. The cells usually contain an amount of lipid material proportional to the amount of lipid present in the cortex. When present the lipid is present in the cytoplasm between the nucleus and the capillary.

The widest part of the cortex is made up of the next or middle layer, called the zona fasciculata. The cells here are quite large, polyhedral, rich in lipid, and are much larger than those of the glomerulosa layer. The cytoplasm is practically replaced by lipid droplets, remaining as only very narrow projections between the droplets. When the tissue is fixed in the ordinary way the fat is dissolved out leaving a very spongy appearing cell with many vacuoles in it. The nuclei in these cells are centrally placed and quite often there are seen two nuclei instead of one. This area is much more vascular than the other and in the

outer transitional part especially numerous mitotic figures are seen.

The inner zone of the cortex is made up of irregularly anastomosing cords which have become so arranged that they may conform with the sinusoids which have taken the place of the rather straight capillaries of the preceding layers. The cells are quite similar to those of the fasciculata zone except for a decreased lipid content. However, near the medulla the cells gradually merge into two distinct types which are new. From their staining characteristics they have been called "light" and "dark" cells.

The "light cells" are well rounded, are larger than the "dark" ones, and have a granular, pale staining cytoplasm which is sometimes shrunken from the membrane. The nuclei are smaller and vesicular. The smaller "dark cells" have an excavated outline which is compressed. The cytoplasm is deeply staining and homogeneous, while the nucleus is shrunken and takes an even deeper stain. These cells are quite rich in lipid droplets with also many clumps of yellowish or brownish pigment while the "light cells" have very little of either lipid or pigment. Some of the dark cells are so markedly shrunken that they appear almost triangular or fusiform in cross-section, and they contain so much of the pigment that they have been termed "chromatophores". Also, within this zona reticularis are a number of cells which

appear to be degenerating or dying.

Medulla.

The line separating the medulla from the zona reticularis is, in the adult, quite indefinite because of the irregularity which is the result of the long masses of cortical cells which project into the medullary area. These medullary cells are arranged in several different ways, chiefly in rounded groups or short cords which are in direct contact on all sides with the sinusoids. These cells have a peculiar affinity for chromic acid, or its salts, and when stained with this material there results a yellow or yellowish-brown stained picture. Various methods of staining bring out various properties of the cells but they all have the same general coloration. The origin of this yellowish color is the action of epinephrin, or possibly an antecedent secretion, which reacts with the chromium compound to produce chromium-dioxide, and this material, the epinephrin, is secreted by the suprarenal medulla. When this same tissue is stained with ferric-chloride a greenish color is produced, for the same reason.

Also within the medulla many single or grouped sympathetic ganglion cells are found whose axones end around the chromaffin cells.

In addition to the cells described, there are still others in large numbers, small round cells which have a deeply staining nucleus and a small amount of cytoplasm. In the fetal gland cells, which are very similar to these

are found and they are the forerunners of the sympathetic and medullary cells, called sympatho-chromaffin cells. However, in the adult gland it has been decided that these are lymphocytes.

In all the suprarenal cells mitochondria are demonstrable but they take on different appearances in the various layers. In the zona glomerulosa they are seen as long threads at both ends of the columnar cells; in the zona fasciculata they are round granules and lie in the narrow cytoplasmic partitions between the lipoid granules; while in the light cells of the zona reticularis they are very small granules and rods restricted to an area close to the nucleus, and in the dark cells they are large and irregular in shape. In the medulla they are seen as spherical granules scattered throughout the cell.

The Golgi apparatus has been described only in the cells of the zona glomerulosa and medulla of the guinea pig, hedgehog, and bat. In those it forms a circular net-work between the nucleus and nearest capillary.

BLOODVESSELSandNERVES.

The suprarenal glands have a very rich arterial supply in proportion to their size. There are usually three arteries to the glands and they probably bring more blood to these organs, proportionately, than is supplied to any other organ in the body. The superior suprarenal artery is a branch of the inferior phrenic artery, which is directly off the aorta. The middle

suprarenal artery arises directly from the aorta, and the inferior suprarenal artery arises from the renal artery. Upon entering the capsule there are usually three or four successive systems of branches before they leave that structure. The smaller vessels finally turn at right angles and go into the capillaries of the cortex. Some of the larger arterioles may pierce the cortex completely and go directly to the medulla. The sinusoids then enter into the venules which go to the central veins, which, in turn, all unite into a single central vein. This vein emerges from the capsule through a small indentation in the anterior surface, which is called the hilus. The right suprarenal vein empties into the inferior vena cava, while the left joins the left renal vein.

The central vein, and larger tributaries, are all completely lined with endothelium. In the wall many smooth fibers running in both longitudinal and obliquely circular directions are found. The longitudinal fibers make irregular indentations into the lumen of the veins, since they aren't evenly distributed throughout the walls.

In the cortex the sinusoids are lined by endothelium and also by mature histiocytes, which store lithium carmine, and in heavily stained animals their number is increased. The structure of the sinusoids is very similar to that of the liver.

The lymphatic drainage is arranged in a series of three plexuses, a superficial plexus which is retroperitoneal and continuous with one similar to it in the kidney; there is also a deep capsular plexus and, in addition, a plexus which drains the medulla. All these plexuses empty into the paraortic group of lymph nodes. Only those about large veins have been demonstrated to be endothelial lined within the gland.

Each gland is supplied by twenty to thirty nerves which arise chiefly from the celiac sympathetic plexus, but they also arise in part from the greater splanchnic nerve and possibly from the vagus. The fibers mainly terminate in claw-like endings around the individual cells of the medulla. However, a few end in relation to the cell groups in the cortex, especially in the zona reticularis, but these don't encircle the individual cells. These fibers enter the cortex from the network in the capsule and course along the capillaries.

Regeneration

The cells of the suprarenal glands appear to have a comparatively short life cycle. They are replaced by active mitotic cell division in the outer part of the zona fasciculata, and gradually move toward the medulla. As these cells degenerate large macrophages, or histiocytes, remove the debris. It is quite probable that the "dark" and "light" cells of the zona reticularis are senescent cells and are soon to degenerate, differing from the dying cells only in degree of

morphological change. Other observers believe that these "dark" and "light" cells represent different degrees of the secretory cycle but no direct evidence supporting the idea is presented.

The process of proliferation and destruction of the cells is hastened by acute infections, toxemias, or prolonged narcosis. The cells of the cortex show an especial susceptibility to this type of injury. It may be that this hypersensitivity of the cortical cells to infection is the result of a relatively long exposure to the toxic substances, because of the large blood supply which flows so slowly through the sinusoids. However, repair always takes place in two to three weeks if the damage is not so severe as to cause scar formation and death to the individual.

The medullary cells show little damage except for the presence of the presence of colloid degeneration vacuoles which contain a protein substance.

HISTOPHYSIOLOGY.

Medulla.

The medulla secretes epinephrin, the rate of which is accelerated by the stimulation of the splanchnic sympathetics. The depth and amount of the chromaffin staining is roughly proportional to the amount of epinephrin in the gland. However, the presence or absence of chromaffin granules is no index to the activity of the gland, because the speed of output

must be considered as well as the speed of formation. The chromaffin reaction is abolished by anesthetics, morphine and similar drugs.

Epinephrin has been found to act as a powerful vaso-constrictor and sympathetic stimulator and is also of great value in the control of hemorrhage, to increase the blood pressure and combat shock. However, normally it may not have the same physiologic function, because it is formed in small amounts and is quickly destroyed in the blood stream. Some think, since it is secreted in larger quantities in nervous excitation, that it makes the body more efficient for necessary response (Emergency theory). Others think it is only a waste product of protein metabolism since it is probably destroyed before it reaches the blood stream (Excretory theory). Young and Lehman⁵¹ did an experiment which revealed little, if any, fall in blood pressure following ligation of the adrenal veins, although it is clear that adrenalin is constantly being formed and poured out into the veins.

Abelous and Langlois⁵¹ sponsor the toxic theory of function of the gland. This theory holds that toxic effects of certain substances are counteracted by a product found in these organs. A. Marie⁵¹ found that in vitro adrenin exerts a powerful neutralizing action upon tetanus toxin but when dried powder is used this effect isn't obtained. The exact significance of this in the living organism hasn't been clearly demonstrated yet.

In addition to the theory that epinephrin is a powerful vaso-constrictor and sympathetic stimulator many other actions have been attributed to its presence. This action in any particular part or organ varies, depending on the location and type of tissue there. The cardio-vascular system- it stimulates the heart rate and elevates the blood pressure by contracting peripheral vessels. Smooth muscle reacts differently also in various parts of the body. It causes the coronary vessels of the heart to dilate while the bronchial and intestinal muscles relax, but a violent contraction of the uterus is produced. The pupils are extremely sensitive to the extract, even in small amounts. When injected it produces dilation of that part.

It has been noted that this organ (suprarenal gland) is associated very closely with the other organs of internal secretion, especially the thyroid gland and pancreas. The antagonistic action of epinephrin to insulin causes a ready mobilization of glycogen which produces a rise in blood sugar. It has been noted also that persons who are suffering from hyperthyroidism are very sensitive to the action of epinephrin, much more so than the average person.

Various observations have been made on the action of epinephrin when it is injected in varying amounts. Studies by Gruber⁵¹ indicate that in small doses

epinephrin causes dilation of the blood vessels in the muscles, while others report that it also increases contractions of excised intestinal muscle, especially in very minute amounts. When it is introduced rapidly into the circulation a rise in blood pressure is noted due to the constriction of unstriated muscle in the arterioles, and it was further shown by Addis, Barnett and Sheoky⁵¹ that subcutaneous injection in rabbits results in increased renal activity, while Gunning⁵¹ found that intravenous injection causes a decrease in urine flow. In hypotonic individuals Loeper and Verpy⁵¹ found an increase in both free and total hydrochloric acid in the stomach and food taken in at that time is hastened through the stomach, but where there is a state of increased contraction, both in intensity and frequency, there is produced a sedative effect on that muscle.

Many other experiments have been made in an attempt to determine the physiologic function of the substance but the results have added little to the knowledge of the glandular function.

Cortex.

It is known that the suprarenal cortex is essential to life. Its loss produces a syndrome of progressive weakness, loss of appetite, frequent vomiting, falling of blood pressure and body temperature, and a deeply pigmented skin.

There are two theories as to the mode of action

of this substance:

(1) That it detoxifies metabolic poisons. This view is favored but the chief substantiation is the fact that the cells are so easily damaged.

(2) That it secretes into the blood a hormone which is essential to life. Evidence in favor of this opinion is that completely adrenalectomized dogs have been kept alive by injecting cortical extract.

The Lipoid.

This is a mixture of cholesterol esters, fatty acids, mainly oleic, and phospholipids. Many are doubly refracting to light, especially in the outer part of the zona fasciculata. It is not known whether these are excreted in the blood stream, elaborated in the cortical cells, or merely stored in the cells. However, the quantity increases when the total amount in the blood stream increases, as in pregnancy. There is a decrease in the acute infections but not in starvation, even when nearly all the other body fat is gone.

The pigment in the zona reticularis is only present after puberty and it increases with age. It takes fat stains and is similar to the "lipochrome" pigment in cardiac muscle and nerve cells in old age. It is probably not a product of secretion but is just concomitant with age.

Interrelation of the Cortex with other glands.

This relationship is very important, especially

with the thyroid and sex glands. It has been shown to hypertrophy during pregnancy. Increased sexual development causes increase in the size of the adrenals. Also in rabbits, thyroidectomy causes two or three times the normal size hypertrophy of the normal gland.

Sprunt⁵⁵ has presented the knowledge of the function of the cortex in about as concise a manner as any when he sums it up as being a probable catalyst in maintaining the normal blood chemistry, with probably a specific action on renal function. He believes the chief action to be detoxication, since destruction or removal of the glands causes accumulation of toxins in the body, and death. However, there is no experimental evidence to support that view. It is more likely that the products are not excreted because of the inability of the excretory organs to get a proper blood supply due to a circulatory failure.

Quite recently, however, Swingle and Pfiffner,⁵⁶ after a long series of experiments with the suprarenal cortical extract, the method of preparation of which they perfected and announced in March, 1930, have come to the conclusion that the function of the suprarenal cortex is unknown. This view is supported even more recently by Rowntree and Ball.⁴⁸ All the theories which are advocated by the various observers are as yet unsubstantiated by actual, positive experimental evidence.

Classification of the Diseases of the Suprarenal Glands.

Rowntree and Ball⁴⁸ have noted that, in general, overactivity of either cortex or medulla is the result of a tumor of some type, while hypofunction is the result of destruction of the tissue by atrophy or some destructive disease, as tuberculosis.

Since the suprarenal gland is made up of two types of tissue which differ both functionally and morphologically, and, since the function of these glands is so complex, it is to be expected that there is a large variety of clinical syndromes due to diseases of these glands.

The clinical picture in each case depends on whether there is under or over-activity, the age of onset, and the extent and nature of the disease of the cortex or medulla, one or both.

The classification used here is from those presented by Rowntree and Ball,⁴⁸ and by Sprunt.⁵⁵ Neither of these seemed to be applicable in its entirety to this paper, so portions of each have been chosen with some occasional headings or subdivisions which seem better to satisfy the material as found.

CLASSIFICATION.

Cortical Hypofunction.

1. Addison's Disease.
2. Hypoadrenia.
3. Other manifestations of apparent hypofunction.

Cortical Hyperfunction.

1. Congenital form.- Pseudohermaphroditism.
2. The early post-natal form.- Infantile pubertas praecox.
3. The late form.- Adult virilism and hirsutism.

Medullary Hyperfunction.

1. Neuroblastoma. (Clinical types characterized by):

- a. Metastasis to the liver and lungs or the abdominal lymph nodes. (Pepper type)
- b. Metastatic involvement of the orbit, skull and long bones. (Hutchinson type.)
- c. Severe anemia suggesting the pernicious type. (Goldzieher.)

2. Ganglioneuroma.

Rare; usually found incidentally at autopsy.

Metastasis rare.

3. Paraganglioma, may cause:

Intermittant hyperfunction,

Continuous hypertension, sometimes with diabetes.

Medullary Hypofunction.

Other conditions which appear to be associated with

Suprarenal dysfunction.

1. Relation to neoplastic tumors.
2. Peripheral arterial disease.- Buerger's Disease and Raynaud's Disease.
3. Evidence of endocrine interrelation.
4. Vitamins.

ADDISON'S DISEASE.

Sprunt⁵⁵ defines this condition as being "A state of insufficiency of the suprarenal glands associated with the clinical features of marked asthenia, with marked feebleness of the heart's action and low blood pressure, with irritability of the gastro-intestinal tract, and with pigmentation of the skin".

The disease is relatively quite rare. In 1924 there were 363 cases reported in the United States registration area out of 1,173,990 deaths. There was a similar incidence in 1923, giving a death rate of 0.4 per 100,000.⁵⁵

In 1855 Addison first recognized that the cause of the peculiar syndrome, which had been noted for some time before that, lay in the suprarenal gland. In this case he found that the suprarenal glands were extremely hard and about the size of hen's eggs. He originally attributed the cause of the disease to be tuberculosis, but since that time various observers have seen that there are also numerous other causes, but tuberculosis is by far the greatest. Sprunt cites a series of 402 cases reported by Guttman at autopsy, in which he found 70% of the cases to be due to tuberculosis of the glands, 20% were associated with primarily contracted glands, (atrophy), and 10% resulted from a variety of conditions: pyogenic infections,

amyloidosis, vascular diseases, and neoplasms. Only one case in this series was reported as being due to syphilis.

In a second series reported by Guttman and cited in a paper by Ball, Greene, Camp, and Rowntree,⁷ 566 cases were studied and in this series he found 69.72% due to tuberculosis. He again noted that amyloid disease, atrophy, vascular changes, neoplasms, fatty degeneration, and pyogenic infections with a much rarer incidence of syphilis, metastatic lesions, pressure atrophy, hypoplasia, trauma, metaplasia of the bone marrow, etc. According to Ball and his co-workers,^{b-7} a series of 34 cases studied at necropsy showed 83% to be the result of tuberculosis, while Wells⁷ estimated that 90% of cases result from the disease. From these figures it is easily seen that the chief factor in the etiology of Addison's disease is tuberculosis. Most often when the disease is reported there is found evidence of tuberculous processes elsewhere in the body, as the lungs, bones, or urogenital tract. These other infections are usually of such a slow developing nature that cases of Addison's disease are seldom reported from the tuberculosis sanitoriums.

It isn't to be gathered, however, that all cases of tuberculosis develop Addison's disease or even a tuberculous involvement of the suprarenals. This is brought out very well when a study of tuberculosis in the negro is made. In that race tuberculosis is not at all uncommon, in fact it may be considered quite common, but it is rare to find a case of Addison's

disease among them. Hübschmann⁵⁵ reported a series of these cases of pulmonary tuberculosis in negroes and he found tuberculosis of the suprarenal gland in only 2%, while in a similar series of Ophills⁵⁵ 5% showed the complicating gland involvement. There are many theories as to why the glands are involved so infrequently but there is as yet nothing tangible to work on. It may be that there is some peculiar predilection of the tissue in certain individuals for the tuberculous organisms. Some victims of the disease show evidence of the infection only in these glands and no other part of the body, while others may show a massive involvement of the body but none of the suprarenals. It has been hinted that this may be a peculiar strain of organism which involves only the suprarenal gland, in a manner similar to the involvement of the mitral valve of the heart, or certain joints as a sequel to rheumatic infection. Lowenstein⁵⁵ has suggested an allergic basis because it is noted that there is rarely only one suprarenal gland involved. He believes that one gland is involved first and that infection results in sensitizing the second gland so that it is more susceptible to the disease. However, as was noted above, these are all just theories and are without anything definite to substantiate them.

A study of Addison's disease resulting atrophic suprarenal glands shows that the process is one of true atrophy and not one of just simple shrinking of the gland. Osler⁴⁴ considers this condition the only other cause of the disease which may be considered as not rare. The other causes noted are just mentioned. The cortical substance shrinks from a degenerative necrosis and leaves only a thin outer shell around the medulla. The essential cortical cells are atrophic in appearance with a relative increase in the stroma of the gland, with sometimes an actual thickening of the capsule. When this process is noted there is found an increase in connective tissue between the cells with some lipoid infiltration into the gland.

It is interesting to see the changes, in trend of ideas, of the cause of the disease from an anatomical standpoint. The early idea was that it resulted from the destruction of the medulla along with certain lesions of the sympathetic ganglia elsewhere. As more study was given this idea was changed to the belief that the disease resulted from the destruction of the whole gland. Even now some observers still cling to this theory. However, since 1930, when Pfiffner and Swingle succeeded in producing an extract of the cortical substance, which is relatively pure, and by using this extract on animals which have been suprarenalectomized, the popular trend,

of those actively engaged in the study of the effects of its administration, has swung to the belief that the cause of the disease lies wholly with the destruction of the cortical substance. These workers completed a large series of experiments with the extract on a great many different types of laboratory animals which were carefully controlled, and the extract was also supplied to others at the Mayo Clinic for use on patients suffering from the disease, and in each case, where adequate treatment was given early enough, both in animals and humans, the results were exceedingly gratifying. By these experiments they showed that proper treatment made possible a disappearance of all symptoms of the disease, except for the pigmentation of the skin, and the resuming of the normal activities of the body functions.

Studies of other organs of the body have been made in an attempt to discover constant lesions which are associated with the disease. Many were found but not often enough in any organ to be diagnostic. One condition, noted by Ball and Rowntree in a discussion by Guttman, was that there is usually a lowered basal metabolic rate which usually rises with the administration of cortical hormone.

Addison's disease, clinically, is presented in two different forms: acute and chronic, depending upon the rate with which the symptoms appear and the course is run.

Clinical course.

The usual course is chronic and often extends over a number of years. It begins quite gradually in an insidious manner, often extending on a slow downward course for two or three years, until it is precipitated by some acute infection or illness. Not uncommonly the patient will date the onset of his illness to some acute febrile state as pneumonia or a cold, or some injury or accident from which he didn't recover as he had previously. Instead he remained weak and unable to do his accustomed work. Rowntree and Ball⁴⁸ call attention to the frequency with which the upper respiratory tract seem to usher in the symptoms of Addison's disease. They suggest that it may be a part of the picture if the disease, as an acute febrile phase, since many of the patients never regain their strength until pigmentation is seen weeks, months, or years later.

The gradual downward trend is occasionally interrupted by crises in which all the symptoms are increased. During one of these crises he may die or gradually recover to be as strong as he was before the crisis.

Always, at some stage during the disease, there is noted a marked asthenia. In fact it may be the chief symptom of which the patient complains and may be present at all times. The weakness is noted, not only

physically but mentally in that he is unable to concentrate well. He is usually too weak to even have a desire to work; he has a weak, hoarse voice and Sola and Jacobi⁵⁵ called attention to the fact that some of the negro patients experience a choking sensation. Hartman, Thorn, Lockie, Greene, and Bowen²⁶ point out that the ergometer has been selected as the instrument for measuring the degree of muscular weakness reached in the disease. By its use over an extended period on the same individual a fairly accurate idea can be obtained as to the severity and stage of the disease.

The asthenia extends further than the voluntary system. The cardio-vascular system is also involved, as is shown by weakness of the heart action accompanied by palpitation and dyspnea on even the smallest exertion. Further evidences of change in this system are shown by blurring of vision, fainting spells, soft weak pulse, and usually a low blood pressure. However, the low bloodpressure doesn't always appear, as is noted by Rowntree⁵⁵, who observed patients with hypertension carry a pressure of 140mm. and over untill shortly before death. A systolic pressure of 80 is considered by Rowntree as a danger signal, and one of 70 or below is critical.

Along with this change in cardio-vascular system there appears, usually in the acute crises, a rather

definite, but constant, blood chemistry change. This study has been done chiefly with experimental animals but is comparable to the human and is found to occur in rather definite sequence. The first change noted is a rise in blood N.P.N. and urea, which either precedes by a few hours, or is co-incident with, the refusal of food. However, it definitely precedes the constant drop in respiratory metabolism. No change in creatinine is found until the animal is quite ill but a steady increase in serum potassium is noted. where the animal refuses food there is seen a suppression of chlorides and inorganic phosphates. The blood pressure begins to drop at the time of nitrogen in the blood and there is also noted a marked drop in oxygen consumption, even to a point 20-25% below normal values in animals which later recover.

Associated with these findings are also definite urinary findings of diminished output with suppression of urinary nitrogen and urea, as well as creatinine, creatine, and P.S.P. excretion. A marked muscular weakness is also observed with a lowering of body temperature, as would be expected with the decreased basal metabolic rate.

In a report of three cases of Addison's disease, Benham, Fisher, More, and Thurgar^a noted one case in which there was a urinary suppression for 16 hours before death and in this case there was noted a blood

pressure which ranged between 36-50mm. Hg. systolic during that time. They attributed the suppression to the extremely low blood pressure, and in support of this belief they pointed out that physiologists have found the critical level for urinary secretion to be between 40-50mm. Hg., and that when a pressure of below 40mm. is reached total cessation of urinary secretion occurs. To further support their contention they reported another patient in this group who had cessation of urinary secretion when the pressure was below 50mm., but with adequate cortical therapy the pressure was raised to a point above 50mm. and urinary secretion was re-established. They account for the infrequent complete urinary suppression in Addison's disease by pointing out that the blood pressure rarely goes below the critical point. However, as the blood pressure approaches the critical point, no doubt, the secretion of urine is decreased.

Another set of symptoms which are seen to accompany the disease are the gastro-intestinal disturbances. These are not seen with equal intensity in each case, but to a greater or less degree all are present. Usually the first noted is the lack of desire for food, which may continue to a positive aversion for it. At intervals, and especially during the crises, stages of nausea and vomiting appear and these may be the most distressing to the patient, as well as the most serious of all the symptoms. Along with these findings there results a

loss of weight, but usually the appetite and weight will recover. Rowntree and Ball⁴⁷ give the utmost importance to the appetite and weight curve in the prognosis of any case of this disease by saying, "Only those who eat and gain weight recover". At times there is abdominal pain and gaseous distension which is commonly associated with constipation, but occasionally diarrhea is seen, especially in crises.

One of the most outstanding signs in this disease from the standpoint of observation and diagnosis is the pigmentation of the skin and mucous membranes. this pigmentation may appear early and persist for years before any other symptoms are noted. Rowntree and Ball⁴⁸ believe that marked, prolonged pigmentation, which develops as the sole manifestation of the disease, indicates, as a rule, a favorable prognosis.

This peculiar pigmentation resembles the tan given to the skin after a sunburn, and is most prominent on the exposed surfaces, as the hands, face, and especially is it prominent on those surfaces which are normally pigmented, as the eye lids, nipples, genitals, and points of friction. The palms and soles may escape but the creases look dirty and can't be cleaned. Along with the rather uniform discoloration there is quite often found various sized black freckles. The mucous membrane lining of the mouth, lips, and tongue also show this coloration, and here it may be in the form

of dark spots or streaks. Rowntree and Ball⁴⁸ believe that dermal, buccal, and labial pigmentation, along with the dark spots on the skin, are almost pathognomonic of the disease.

The intensity of the pigmentation varies in different individuals, and also in the same individual, and is described variously as an amber hue tinged with blue, grey, yellowish-green or olive. More important than the shade of pigmentation is the observance of a change in color in the person over that which is normal for him. This is especially true in those persons who are inclined to normal pigmentation, as pronounced brunettes and the dark races.

There are many theories as to the source of the pigmentation but as yet nothing definite is known. Sprunt⁵⁵ notes that Black believes it is due to a specific oxydase in the skin which forms melanin from di-oxy-phenyl-alanine which is, in his opinion, one of the normal precursors of epinephrin. When the epinephrin can't be formed in the gland the substance collects in the skin and is converted by the oxydase into the pigment. Others believe that there is a connection between the Hexuronic acid in the cortex, which was isolated by Szent-Gyorgyi in 1928. Its exact connection isn't known but Rowntree and Ball point out that this substance is connected with phenol color reactions in vitro and probably in vivo. Consequently they believe

the pigmentation in Addison's disease is probably connected in some manner with this material.

Quite often in Addison's disease certain nervous and mental manifestations occur, principally those of mental asthenia, insomnia, irritability, querulousness, apprehension, and depression. Commonly paresthésias and abdominal pain are seen, and several authors note a terminal muscular twitching, occurring just before death. The cause of these symptoms isn't known. Special mention of the muscular twitching is made by Benham, Fisher, More, and Thurgar⁹. In a report by Hartman, Greene, Bowen, and Thorn²⁵ the theory is raised that they may possibly be the result of the use of a toxic extract in the treatment of the condition.

Some other findings which are usually seen with the disease and which have been in part referred to previously, are summed up by Sprunt as:

Decreased temperature, which is usually in keeping with the decreased metabolism, however, as was pointed out by Rowntree in the report of a series of 41 cases in which the average metabolic rate was well within normal limits, not all cases show the decreased metabolism. There may be a terminal fever, Biot respiration, arterial hypotension and a change in bloodpressure with a change of position of the body. Probably of less importance is the evidence of anemia, as indicated at times by a

decreased red cell count and hemoglobin. It is only in crises that any particular change in blood volume is noted, at which times it is reduced and assumes a higher than normal viscosity. In three cases reported by Rowntree and Snell⁵⁵ there was creatinuria which they interpreted as indicating a fundamental disturbance of metabolism and probably it was incidental to muscular wasting. Gastric analysis usually shows an achlorohydrria, which is usually accompanied by a decreased basal metabolic rate.

Clinical Course.

Clinically this disease usually takes one of two courses, depending on the rapidity of onset of symptoms which progress to a termination. These two courses have been termed "acute" and "Chronic".

From the foregoing discussion of the symptoms a fair idea of the clinical manifestations of the disease may be gathered to be quite insidious in the chronic case. The first thing noticed may be the pigmentation which may appear a very long time before the onset of any other symptoms. One case is reported by Guttman⁵⁵ in which this discoloration was present for 15 years while increase in other symptoms only appeared 18 months before death.

However, even though the pigmentation may be present for a long period the patient may attach no particular significance to it. Instead he may date the onset of his illness to coincide with that of an

acute upper respiratory infection, as a severe cold, influenza, etc. After considerable study, Rowntree and Ball have concluded that this febrile state is one of the phases of the disease rather than merely a co-incident. The patient doesn't get back his normal strength after the febrile stage and from that time on the course is progressively downward, being broken at times by crises in which all symptoms appear with much greater force. In these crises the patient may be so weak that he is unable to even raise his head from the bed. After a time the severe stage of the crisis has past and the patient begins to gain in weight and strength as he is able to eat more food. He may recover his strength to a point equal to that which he had before he entered the crisis. The course continues in this manner until death intervenes from exhaustion.

The acute type of Addison's disease goes through very much the same course as the chronic, but it extends over a period of time measured in days, weeks or months, rather than years. Sprunt reviews a case reported by Schlesinger in which the entire course, from the onset of the first symptoms until the patient was dead, extended over a period of only 11 days. This was a case of a woman 36 years of age, who was apparently well in every respect until she suddenly became prostrated with extreme weakness, hiccoughs,

nausea and vomiting, and diarrhea so severe that she had to go to bed on the first day. The vomiting and diarrhea deminished on the second day and on the fifth day pigmentation of the skin appeared with insomnia, a great thirst and a systolic blood pressure of 85mm. of mercury. the asthenia continued and increased until the blood pressure failed, delirium appeared, and death on the 11th day. At autopsy the suprarenals were seen to be extremely atrophied. Schlessinger⁵³ attempted to explain the acuteness by considering that there was sufficient cortical tissue present to maintain the patient in a semblence of health until 11 days before death, when some additional injury to the remanents of the gland precipitated the disease in an unusually fulmant form.

*of course
misplaced*

Prognosis.

Before the discovery of the cortical hormone the prognosis of all these cases was almost uniformly bad. Occasionally a case would recover but this was rare. There was always the danger of death in a crisis, and the average duration of life after the onset of symptoms was probably not over two or three years.

Since the announcement by Pfiffner and Swingle of their cortical extract in March, 1930, the outlook for patients suffering from Addison's disease is much more promising. True, it wont cure 100% of the cases but from the reports of its use on large numbers, both on

experimental animals with total suprarenalectomies, and human cases with well advanced symptoms, it is shown that where the hormone is used, and continued to be used, in sufficient quantities, the individual may live indefinitely, very comfortably and entirely free from symptoms, excepting possibly the skin pigmentation. They have been able to continue normally, in every respect, their usual activities, physical and mental, and they may even become active sexually to the extent of normal reproduction. In nearly every case reported, in which the patients haven't survived, the death may be attributed to failure to begin hormone therapy soon enough, or inadequate dosages were given, the supply of hormone available was not sufficient, or the patient failed to obtain more extract after his symptoms disappeared.

Rowntree and Ball consider the grave indications to be extreme asthenia, lowered body and surface temperature, collapse, prostrated vomiting, extreme loss of weight, systolic blood pressure less than 70mm. of mercury, concentration of blood urea more than 60mg. per 100cc. of blood, a short, rapid course without much pigmentation, poor response to treatment, and active tuberculosis elsewhere in the body. They consider a most important index to prognosis to be the body weight when they say that only those who eat and gain in weight recover.

Diagnosis.

The diagnosis is made chiefly from the symptoms which are noted above. The presence of tuberculosis elsewhere in the body may be considered to confirm it. It is necessary that a very careful history, physical examination, including roentgenograms of the chest be taken. Bone lesions or the presence of red blood cells or tubercle bacilli in the urine are other valuable aids in diagnosis.

It was considered for a long time that radiographs of the suprarenal glands were of comparatively little value in diagnosing the disease, since it was so seldom that the glands were sufficiently calcified to produce a shadow on the plate. However, in numerous studies on this subject by Ball, Greene, Camp, and Rowntree,^{7, 8, 12} they have come to the conclusion that the X-ray may be of great value in the early diagnosis of some cases and that it should be attempted in all cases of suspected Addison's disease. The fact that there isn't a shadow in every case has led many to doubt its value, but there isn't in every case, even tuberculosis of the suprarenals, sufficient calcification to cast the shadow. They call attention to the description which Addison gave of his original case in which he described the suprarenal glands as being extremely hard and about the size of hen's eggs. From this the authors believed that if the X-ray had been perfected at that

time he would, undoubtedly, have been able to demonstrate the glands by that method. Thirty-four cases which came to autopsy with a diagnosis of Addison's disease or Tuberculosis of the suprarenal gland were examined by these men. The suprarenal glands were studied and these which they believed were sufficiently calcified to have cast a shadow in life were called positive, while those, even though they contained areas of calcification, were considered negative if the observers felt they were not grossly enough calcified to have been demonstrated before death. Out of this series of 34 cases, 11 or 32.3% were considered positive. Three types of calcification were recognised in this study:

1. Gross calcification of the entire gland.
2. Homogeneous increased density of the whole gland, suggesting a diffuse deposition of lime salts, such as would be expected in a high grade of caseation.
3. Multiple, discrete areas of calcification throughout the gland.

These features were confirmed by histologic and chemical examination of the tissue.

The diagnosis of Addison's disease, as may be seen, is relatively very easy if the whole clinical picture is fully developed.

The differential diagnosis, which must be made,

lies chiefly in those diseases or conditions which produce a pigmented skin. Occasionally certain tendencies toward the dark races, as mixtures of races, will give a color which may be mistaken for the pigmentation of Addison's disease, as will also undue exposure to sun and wind. Pathological conditions which are at times confusing are seen in those suffering from hemochromatosis, acanthosis nigricans, scleroderma, parasitic malanoderma, exophthalmic goiter, pellagra, carotinemia, pregnancy, arsenical dermatitis, and argyria. It is of utmost importance that it be determined whether or not there is any increase in pigmentation over that which is normal for that individual. Occasionally persons who have received heliotherapy will show an increase in the pigmentation of the skin.

Probably the best diagnostic method, especially in doubtful cases, is the therapeutic test with cortical hormone extract.

Treatment.

Before the isolation of the cortical hormone extract the treatment was notoriously ineffective no matter what was used. Some of the patients seemed to improve for a time but sooner or later they failed with the recurrence of the crisis.

The treatment of Addison's disease is of two kinds, both of which are essential to the recovery

of the patients. These are (1) general care, including diet, rest, preventing exposure, etc., and (2) organo-therapy.

General care.

In every case this phase of the treatment is of exceeding importance. The physical exercise must be limited to such an extent that the patient does not over exert, because with the already weakened state he is in danger of being thrown into a crisis. He also has a much decreased resistance to changes in temperature, exposure to wet weather, excitement, etc., so these must all be guarded against.

During the interval between the crises the diet should be sufficient for maintaining weight, and should consist of just enough protein to prevent a negative nitrogen balance. It seems that excesses in the protein diet tend to bring on the acute exacerbations.

According to Hartman, Greene, Bowen, and Thorn²⁵ the best place to treat a patient with Addison's disease is in comfortable surroundings where he can get plenty of rest.

In the crises probably the condition which is the most difficult to combat is the dehydration incident to the nausea and vomiting which is one of the characteristic symptoms. This may be done by introducing fluid in any manner the patient can

tolerate it, intravenously, subcutaneously, or by rectum. From three to five liters a day are needed to cover all that is lost. A 10% glucose solution is excellent since it provides food as well as fluid. However, contrary to the apparent great necessity for large amounts of fluids, Benham, Fisher, More, and Thurgar,¹ in their report of 3 cases, concluded that it made very little difference whether their patients received large amounts of fluids or not as long as they did receive adequate amounts of cortical extract. Under those conditions they found that the gastro-intestinal symptoms disappeared and the patient was able to take sufficient fluids by mouth.

Organotherapy.

Since the time it was discovered by Addison in 1855 that the cause of the disease, which bears his name, lay in the destruction of the suprarenal gland there have been attempts at organotherapy. Hartman, and others,²⁶ in a review of the literature, noted a previous review of the literature by Kennicutt in 1897, in which he reported 28 out of 44 cases to show improvement with that form of therapy. In the light of the present knowledge the reviewers were very skeptical of the accuracy of these results. They chose rather toward the opinion that remissions were, in part at least, responsible for the apparently good results.

Previous to the isolation of the cortical hormone the best glandular therapy was along the lines suggested by Muirhead and which process bears his name. It consisted in giving epinephrin to the point of tolerance of the patient by any route possible: by mouth, both as the extract and dried gland; by rectum and subcutaneously. The dried gland was found to be irritating to the stomach at times making it impossible to retain it. When given subcutaneously different patients react differently, some tolerating it quite well and others poorly. It is usually started in doses of 3-5 minims of the 1/1000 solution and it is increased as the patient is able to tolerate it. When given rectally the dose is from 3-8 minims in about 90cc. of physiologic salt solution. If any benefit is to come from the Muirhead treatment it will be seen usually in about a week. About one-half the patients respond well to it and about one-third show good results at once.

Occasionally X-ray therapy is of value, especially if it is known that the damage has been the result of tuberculosis. The rays may tend to stimulate the remaining tissue to increased function. However, if there is any doubt as to whether or not there is an atrophic gland present the X-rays should not be used, because of the great danger of further damage to the atrophic gland.

Cortical hormone therapy.-- Since the announcement by Pfiffner and Swingle in March 1930, of the discovery and successful isolation of the cortical extract of the suprarenal gland there has been a very large amount of work done on the use of this material in the treatment of Addison's disease, as well as its use in the treatment of conditions of deficiency of the gland in conditions other than Addison's disease. The results vary but they all point to a conclusion that when it is given soon enough, and in adequate amounts, recovery from the symptoms may be expected. All the studies have been greatly hampered because of a lack of a sufficient quantity of the hormone. The process hasn't been developed as yet to the point where it can be produced as fast as the demand. Often the study of a particular patient is interrupted because the supply of hormone was exhausted and the patient died.

In order that there might be a definite strength of the hormone in the extract it was decided to concentrate it to a point where one cubic centimeter of the extract contained the active principle of 40 gms. of cortex.

According to an article which appeared in the Journal of the American Medical Association,¹⁷ they hadn't had a definite means of standardizing the extract, so at that time it was decided to use the resistance which it gave to white rats, in aiding them to overcome the toxic effects of histamine, as an index of its potency.

It has been known for some time that suprarenalectomized rats have a much decreased resistance to the toxic effects of histamine or typhoid vaccine. In experiments, six days after suprarenalectomy in adult white rats, a dose of 100-200mg. of histamine per kilo body weight was fatal. But by giving one cubic centimeter of the extract, equal to 40gm. of cortex, daily the rats were able to withstand doses as high as 500mg. per kilo body weight. On that basis a method has been worked out by which, on the 5th and 6th days after suprarenalectomy the hormone is given intraperitoneally and on the 6th day 200mg. of histamine per kilo body weight is given. One unit of potency of the cortical hormone is described as that quantity required to raise the resistance of the suprarenalectomized rats to that amount of histamine.

Cortical hormone extract may be given, apparently, with effectiveness by mouth⁵ subcutaneously, or intravenously. Probably the intravenous route is more rapid in its action than the others. The route which has been used most often in the various studies is the subcutaneous one. In crises the intravenous method is used for the purpose of obtaining a more rapid action. However Perkins⁵ reports a case in which it was given by mouth and the patient went through a normal pregnancy and labor without any difficulty. Herman¹⁷ also reports

a case in which the subcutaneous preparation was taken successfully by mouth. Hoskins and Freeman¹⁸ have developed a glycerine extract which is made up in pill form which, in the treatment of 9 cases of schizophrenia, has proven to be quite potent.

The treatment in a crisis, or in any exacerbation of symptoms, differs from that of the chronic condition mainly in amount and intensity of administering the hormone. Hartman, Greene, Bowen, and Thorn²⁵ concluded from a series of cases that if the crisis was severe it was best to begin treatment with the injection of 5-10cc. of the extract intravenously to be followed in an hour or two by a similar amount subcutaneously. They further considered that large amounts of fluids should accompany the hormone to obtain the greatest benefit. However, contrary to this view, Benham, Fisher, More, and Thurgar⁹ found that there was little difference, apparently, whether the extract is accompanied by large amounts of fluids or not if the hormone is adequate because the gastro-intestinal symptoms disappear and the patient is soon able to take sufficient fluids by mouth. Two to five days was found to be the average interval between the starting the hormone and a response, but after that time, if adequate dosage was maintained, the patient felt better, gained weight and appetite, and improved until he lost all symptoms, excepting, perhaps, the pigmentation. And Hartman,

Thorn, Lockie, Greene, and Bowen²⁰ found that following each relapse there was a widespread desquamation of epithelium which was especially marked on the anterior abdominal wall and forehead. Also in cats these same men noted that the hair became quite loose but it tightened again upon cortical therapy.

During the stage following the crisis it was found that the treatment didn't need to be as intensive as during the crisis but the injections might be given at the rate of one or two or more a week. The size of the individual dose, or the frequency of administering it couldn't be set at any definite figure as a blanket statement, but rather it is necessary to find that amount required by each patient to maintain him in health.

If the patient is allowed to progress too far along in a crisis, or in each succeeding crisis, it is more difficult to bring him back to normal. Finally a place is reached where even massive doses of the hormone are unable to restore health.

It has been noted by many observers that a supra-renalectomized animal will often react much better in a crisis than will a person who is in crisis from Addison's disease, espacially if the animal is just entering the first crisis. Rowntree, Greene, Ball, Swingle, and Pfiffner attempt an explanation of this

phenomenon by saying, "The bilateral suprarenalectomy produces an acute suprarenal deficiency in an animal with normal reserves of strength and previously unimpaired vitality. The conditions for the recovery of the patient with Addison's disease are very different, for the latter suffers from a chronic ailment characterized by marked exhaustion and greatly reduced vitality. The recuperative power may well be greatly reduced under these conditions and it is not surprising that treatment may occasionally be without avail. Swingle has also noted that if treatment is postponed unduly in experimental animals, it, likewise, becomes more difficult". They further observe that tuberculosis is usually the cause of the disease and there are nearly always tuberculous processes in other parts of the body to be overcome as well as in the adrenals.

Complications of Addison's Disease.

It was long known that individuals suffering from Addison's disease were much more susceptible to toxic insults and infections than other persons, and that a very minor infection in a normal individual would quite probably prove very serious, or even fatal, to the one so affected. However, with the beginning of the use of the cortical hormone astonishing results have been seen in patients who were able to withstand severe infections without much difficulty. Rowntree and others,⁴⁹ report a case of acute broncho-pneumonia, which came on

following a sore throat from which streptococcus veridans and hemolyticus were cultured. He was given 85cc. of the hormone and on the 6th day he was free from symptoms. This is most remarkable since it is a severe infection for one otherwise normal.

Pregnancy may complicate Addison's disease, as is shown by Perkins.⁴⁵ His case was able to become pregnant, carry the fetus to term and deliver a normal, healthy baby, by taking adequate doses of cortical extract by mouth.

Hartman, Greene, Bowen, and Thorn²⁵ report a case in which the patient successfully withstood a diphtheria infection along with active tuberculosis.

These are only a few of many instances but they suggest that the hormone is of great importance in aiding the patient to resist infections.

Conclusions:

With as much experimenting as has been done on the suprarenal gland it would appear that some rather definite conclusions as to the function might be in evidence. However, when we turn to Swingle and Pfiffner's⁵⁶ lengthy report, which covers more work on the gland than probably any other of the later experimenters, we find this interpretation:

" In the present state of our knowledge of the adrenal cortex, it is impossible to draw any definite

conclusions regarding function. We have pointed out several times in this paper that the real functional significance of the adrenal cortical hormone is unknown. All of the changes reported as occurring in the organism following bilateral adrenalectomy, we regard as secondary to some, at present unknown, underlying derangement of the animal. To our knowledge no one has yet succeeded in presenting definite, clear-cut unequivocal evidence of cortical function. The literature is filled with theories and hypotheses of adrenal function- on the relation of the cortex to lipid, carbohydrate, tissue metabolism and mineral metabolism. However, it is our candid opinion that none of these theories or hypotheses withstand careful scrutiny and experimental test, nor do they throw any new light on the mystery of cortical function. The function of the adrenal cortex is a subtle and intriguing one, but the solution is not yet at hand".

A very interesting experiment was done at the Mayo clinic in which the experimenter, Kendall,³¹ produced experimentally the same condition in a dog that is seen in the human in Addison's disease. During 81 days following the suprarenalectomy the dog was allowed to go into coma eight times. After the maintenance dose of the extract was discontinued it was seen that the blood urea climbed much more rapidly than other reports in the literature. He found that on the following day

the blood urea rose to 50-100mgs.; the second day it was 200mgs. and over and on the third day the condition was so serious that it was only by using relatively very large doses of hormone that the animal was able to return to normal. All phases of Addison's disease, as it is seen in the human, were noted here and all except the skin pigmentation disappeared upon the use of cortical extract alone.

HYPOADRENIA.

It has been very much discussed as to whether or not there is such a condition as hypoadrenia, and many investigators flatly deny that there is such a disease. Rowe⁷⁷ in 1932, says that he has never seen a case of so-called hypoadrenia, as defined by Sajous which is, " A little bit of Addison's disease".

Rather he believes that it is a symptom presented in the early part of Addison's disease, because, as he notes, the early stages of Addison's disease often present symptoms slightly different from those later on but the difference is chiefly one of degree rather than a departure from the normal, or the average symptoms. Also he notes that there is quite often a color index which is positive, approaching a plus one and it is occasionally mistaken for primary anemia.

During the war Sprunt notes many cases reported as Addison's disease in the men in active service, but even in the most active cases it tended to subside. The most prominent symptom presented in these cases was extreme asthenia, more mentally than physically, and occasionally was so marked that the patient was unable to even write a letter, read a paper or answer a question which required any thought. Many others who had just spent much time in the trenches showed a sub-normal temperature, weakness, depression, and a marked dyspnea. All of these cases recovered after a period

of rest and quiet.

Rowntree and Ball⁴⁸ also admit the doubt as to the difference between hypoadrenia, as such, and Addison's disease. They noted certain patients who presented symptoms of exhaustion, chronic fatigue, emaciation, low basal metabolic rate and blood pressure, and loss of libido and potentia. Although these symptoms were attributed to suprarenal insufficiency, the authors believed that the diagnosis is often made without a definite foundation, since there is little demonstrated reason for it. They cite two cases who had marked symptoms as described, and in whom the clinical diagnostic test of treatment with cortical extract was given, but the results showed no improvement in either case, which strongly suggests additional reason elsewhere for the condition.

Still another type of patient, at least occupational, was noted by Mills³⁹ in China, and his observations pointed toward a medullary, rather than a cortical, deficiency. This conclusion was reached because the administration of epinephrin by mouth to these cases brought about rapid improvement. In these cases the symptoms appeared following a change in climate, and most often appeared during the very hot season which was associated with a very high relative humidity of the air. The temperature often went as high as 114F in the shade with a relative humidity of 92%. He believed that the high temperature

and humidity caused poor function of the epinephrin secreting cells, which later led to lack of function, and the animal experimentation which has since been done supports the theory. However, treatment of cases in this country by Rowntree and Ball using the same methods described by Mills, failed to produce the same results which he obtained. Consequently the subject continues to remain a theory and is not actually supported by experiment or pathological findings.

OTHER CONDITIONS (which indicate hyposuprarenalism or suprarenal destruction in the presence of disease, and symptoms other than those of Addison's disease.)

There have been reported numerous cases in which an acute, infectuous disease is suddenly complicated by symptoms of rapid onset with fever, pain in the hypochondrium radiating to the loin, convulsions, vomiting and diarrhea, tympanites, collapse and death, usually within 48 hours from the onset.

The conditions, in which this chain is most frequently seen as a complication, are chiefly the infectuous diseases as diphtheria, typhoid, pneumonia, meningitis, erysipelas, etc. Trauma may be a factor in etiology, as may also various blood dyscrasias or the hemorrhagic diathesis. Apparently the symptoms are caused by hemorrhage into the suprarenal cortex, which condition of hemorrhage, in any part of the body, is often seen to accompany the acute infections. Occasionally it is seen in bilateral tuberculosis of the gland in which the symptoms take this form rather than Addison's disease. There is usually no pigmentation but there is the pain and rapid death. Just why the course is along this line rather than the typical course of Addison's disease isn't explained unless there is the difference of acuteness and chronicity. However, the acuteness could hardly be considered a factor, as is shown by the rapid course of the patient reported by Schlesinger. Also the matter

that pigmentation is essential before a diagnosis of suprarenal insufficiency may be made is gravely questioned by Herman²⁷ in which he believes that there need not always be a disturbance of the hexuronic acid metabolism, which is considered to be the basis of the pigment formation.

Goldzieher²⁰ notes the frequent occurrence of symptoms of hemorrhage into the adrenal glands in children, especially in the newborn. In these cases he terms it "Pseudo-pneumonia neonatorum" and the symptoms are: rapid respiration with negative chest findings, high temperature which may be accompanied by petechial hemorrhages into the skin, a low blood sugar and high blood urea. He has noted similar symptoms in adults, even with rapid destruction of the gland. Occasionally he believes that there is a partial destruction of both cortex and medulla which introduces a more complicated picture. In these cases a very careful study of all the symptoms must be made which in any way point to an adrenal insufficiency, most particularly those of asthenia, loss of weight, gastro-intestinal pain and functional disturbances, anemia, low blood pressure, hypoglycemia, and increased sugar tolerance. There may be no change in the basal metabolic rate, but there will usually be a higher blood urea nitrogen and creatinine. Probably the best diagnostic method is to test the

sensitization to adrenalin, or other drugs, to determine a possible abnormal response.

Berkow¹⁰ has noted the frequent occurrence of symptoms of acute suprarenal insufficiency with sudden death several days following an extensive burn or scald. Both human cases and experimental animals presented at necropsy findings which were most striking in the suprarenal glands. These findings indicated that there was thrombosis of the vessels of the gland with hemorrhage and destruction of tissue, and they appeared both grossly and microscopically. The symptoms in these cases were of a sudden death any time from about the end of the 10th day to 3 weeks after the burn and after a time when the recovery seemed assured. Explanation of the phenomenon on the basis of shock, reflex, or anaphylaxis were not satisfactory, since these appear immediately following the injury. Neither did the loss of the excretory surface of the skin with the absorption of altered proteins, ordinary uremia, or circulatory or blood element changes explain the latent death. Rather he says, " There is evidence of the culpability of the suprarenal glands, or rather of suprarenal deficiency, in the production of many of the outstanding phenomena observed in extensive burns and scalds including the abrupt death we are discussing". As evidence he offered (1) suprarenal pathology in extensive superficial burns

and scalds; (2) similarity between the destructive signs and symptoms, including the manner of death, following experimental adrenalectomy and after extensive superficial burns; (3) clinical evidence. There is an outstanding lack of shock in burns which he attributes to the rapid outpouring of the secretions of the medulla. As further evidence he points out that often in experimental suprarenalectomy there occurs acute gastric and duodenal ulcers, the same being found following burns. This observer, however, tends to believe that the cause of the syndrome lies with the medulla rather than the cortex and cites the apparent improvement of patients treated with medullary extract.

Robbins⁴⁶ reports a case of acute streptococcic sore throat which developed symptoms of acute suprarenal deficiency that progressed to a grave degree. He believes that the tendency for the suprarenals to be injured in infectious processes is probably the same thing as that which causes renal damage in the same conditions, because the blood supply to the suprarenals is relatively much greater, and in part is derived from the same source as the kidneys, so any material affecting the kidney would be practically certain to also involve the suprarenals. In the particular case which he reported excellent results were obtained with suprarenal cortical extract. It was necessary to continue treatment for only a short time, indicating a temporary toxic state rather than

any permanent damage to the gland.

Dr. Roy G. Hoskins²⁸, of Boston, in an abstract discussion of the paper by Rowntree, Greene, Ball, Swingle, and Pfiffner, believes that there may be some connection between suprarenal deficiency and dementia praecox. At that time there was not sufficient extract available for study along those lines but he hopes to do so when the supply is adequate. Since making the above observations he, along with Freeman and Linder,^{19,29} has completed a series of careful experiments, using a specially prepared glycerine extract and nine patients who were suffering from dementia praecox. They report that the patients derive marked benefit from the treatment. In summary they offer: (1) There is conclusive evidence of the potency of the extract. It definitely raised the blood pressure in 9 patients studied, during three periods of medication, respectively systolic 34, 24, 22, mm. of mercury, and diastolic 20, 11, and 20 mm. of mercury. (2) The cardiovascular reactivity of the patients to environmental excitement, to change of posture, and to exercise was increased during the medication period. Other findings were not constant but there seems to be a relation between the suprarenal gland and schizophrenia, and it represents a wide variety of possibilities in treatment of the condition.

With the knowledge in mind that the suprarenal glands are often attacked by acute infections, rendering

an acute suprarenal insufficiency, Scott, Bradford, and McCoy⁵³ attempted to fortify a series of laboratory animals against these symptoms of deficiency by injecting doses of cortical extract during the period of infection. The suprarenal glands were not removed. However, they were unable to demonstrate any appreciable increase in the life of those animals so "protected" when compared with those that didn't receive the injections.

CORTICAL HYPERFUNCTION.

Hyperfunction of the suprarenal cortex is nearly always associated with some type of tumor in the glands, and they generally produce, or are associated with, changes in the sex glands accompanied by striking changes in the secondary sex characteristics. Rowntree and Ball⁴⁸ report all types of tumors as having been found at autopsy and operation, and they vary from small, benign, adenomatous growths which were accidentally discovered at autopsy, to large, infiltrating and metastasizing neoplasms. Some reports showed these tumors to be highly malignant with early metastasis, while others showed no extension at all.

The most frequent sites of metastasis of these tumors is to the lungs, liver and bones. Consequently, when such a tumor is suspected it is always well to first examine these regions with the roentgen ray to determine whether or not surgery would be of value. Where the liver is involved there results a retention of bromsulphthalein out of all proportion to the extent of the involvement or the number of growths. Usually when death results following surgical removal of one of these tumors, it is quite soon after the operation and no evidence is found as a rule. However in these cases is frequently observed that the opposite gland¹⁵ poorly developed, atrophied, or absent altogether, a condition

which is in marked contrast to that found in experimental removal of the gland, when the opposite gland hypertrophies. The fact that there is atrophy of the second gland indicates that death is the result of acute insufficiency of the suprarenal hormone, and as such, the use of cortical extract will quite probably be of value in future treatment.

Cortical tumors appear somewhat oftener in females than in males, but in each sex there seems to be a tendency for a change to the secondary sex characteristics of the opposite sex.

In the female the tendency is to change to the masculine type presenting an increased amount of hair on the face and body, deep voice, and a change in the external genitala especially marked by an increase in the size of the clitoris. The malignant tumors may be accompanied by a loss of weight but more commonly there is an increase which may go to a definite obesity. This may be confusing since the increased weight is a rather constant association with benign tumors. However, in these individuals, instead of assuming the masculine characteristics there may be, especially in young girls, a tendency to early menstruation with the other developments of secondary sexual characteristics early.

In males, Rowntree and Ball noted five cases, four of which tended to become more masculine in characteristics, while the other showed a feminine form.

The degree of change in an individual depends largely on (1) the age of onset, the greatest being seen in those which started during fetal life, and (2) the type of tumor present. As for the age difference it might be stated, as pointed out by Goldzieher,²⁰ that in childhood there is a precocious sex development, while in the adult there is an inversion of the secondary sex characteristics, as well as those of primary nature.

The Congenital Form- Pseudohermaphroditism.

Probably the best review of this condition has been made by Sprunt. He notes cases of this type in which the internal sex organs are normal, or reduced in size, but the external organs resemble very closely those of the opposite sex. Cases of female pseudo-hermaphroditism have been seen in which the ovaries are present, but the clitoris is much enlarged so as to resemble a penis, and a masculine type urethra is associated with it. The vulva is slitlike and more or less closed to resemble a scrotum. Conversely, males show just the opposite condition, with the external genitals resembling those of the female but in this case testicals are found. From this it would indicate that the true sex would be difficult to determine. Socially, the sex is accepted to be as the external genitals indicate, but actually it is only determined by the internal sexual organs.

The real cause of this condition is somewhat theoretical. A study was made by Gunther⁵⁵ in which he was unable to give a cause definitely. However, he believes the cause of these phenomena is determined, either genetically or on a hormonal basis, the hormonal regulation being due to disturbances in the genito-interrenal system. Some think it to be the result of interrenal overactivity, but Gunther concluded that this is more likely just an associated condition, since it is quite frequently found in conjunction with other conditions, as anomalies. These individuals seem to be especially prone to develop hernias, malignant tumors, especially tumors of the sex glands, and certain infectious diseases, most particularly sepsis and tuberculosis. No reason is advanced for this tendency.

The Early Post-natal Form.- Infantile Pubertas Præcox.

At least a part of the cases of premature puberty are associated with this condition of suprarenal cortical hyperfunction. Often times a child will appear quite normal at birth and continue to develop as such until the fifth or sixth year. At this time, or even earlier, he may show an excessive accumulation of fat and abnormal growth. These changes in physical shape may be accompanied by changes in character as unusual activity and strength, which condition has been described by various French workers as, "enfants herculeans". The external genitalia

go through changes similar to those seen at puberty. In the girls this may assume the form of increased size of the labia, development of the mammary glands and early menstruation, or it may appear as a tendency toward the male type of development with indications of virilism. Several such reports are seen of cases who, before the age of puberty, show an increased growth of the body and a male type distribution of hair, hypertrophy of the clitoris, deepening of the voice and masculine bodily conformation.

Freedman¹⁸ reports a case of a child six months old who complained of recurrent blood in the stools and an inability to retain fatty foods. Examination showed positive findings of protruding abdomen, definite hypertonicity of muscles, fuzz on the face and body, hair on the upper lip and pubes, a visible and palpable clitoris, which measured 1cm. in length, hypertrophy of the labia majora, much brownish pigmentation on the face and back and left leg, and blood which didn't clot coming from the vagina. Since that time she menstruated several times at intervals of about every four weeks which lasted two to three days. Under a dietary correction she showed improvement with no further spread of the pigment, but no mention was made of a cessation of mensis or change in the pubic hair. No operation was done because of improvement but the question of differential diagnosis was discussed. In his opinion the diagnosis lay between

tumor of the pineal gland, tumor of the gonads, and tumor of the suprarenal gland. Pineal tumor was decided against because those cases usually show a rapid growth which was absent here. Ovarian tumor was discredited because of the early onset of menses and because of the close relationship known to be present between the suprarenals and the gonads, the case here just didn't fit the picture of ovarian disorder. He finally decided on suprarenal disorder, but at that time surgery didn't seem to be indicated so it wasn't done.

Harris and Plemmer⁵⁵ reported a case of hypernephroma accompanied by virilism in a girl three years and eleven months old. In this case the tumor was found and removed surgically. At the time of reporting the authors believed it to be the second successful case of surgery on this type of tumor, 11 cases having been reported with 2 surviving. These authors also reviewed 25 other cases in the literature of which 20 were females and 5 males. The symptoms and findings were, collectively, : ages- birth to thirteen years old. Duration of symptoms before death- six months to 14 years and six months. The greatest age attained was 16 years in which case the symptoms were present for 6 years. All cases showed pubic hair and 12 showed hair on the face. 11 cases showed obesity. 3 of the 5 boys showed great muscular development. 15 of the girls and 5 boys showed a sexual development indicated by (girls) a definite hypertrophy of the clitoris in 6, precocious development in 5, and normal in 3. (Boys) 1

showed a definite hypertrophy of the external genitals, 2 were precocious and 2 normal. Pathological reports were obtained on 19 and they were all reported as some sort of hypernephroma, most of which were malignant. Surgery was attempted in 11 cases with 9 deaths. The other to survive was one in which the tumor was encapsulated. Upon its removal the abnormal hair growth disappeared, the clitoris was less markedly enlarged but the voice remained hoarse, even after 2 years. 15 of the cases came to autopsy and 5 showed metastasis to the liver, 3 to the lungs, and 2 metastasized to both liver and lungs. 1 case showed invasion of the suprarenal vein, while 4 cases showed on metastasis.

Rowntree and Ball noted many cases of precocious sex development in young girls who were studied at the Mayo clinic, but the clinical evidence in most of them was insufficient, so that a positive diagnosis in them of suprarenal dysfunction was not possible. Along this line of early menstruation, etc., they say, "Some authors claim that in conditions of this sort, in which a suprarenal tumor has been found, there has been marked change either in the pituitary body or the ovary, which would account for the precocious menstruation. In any event the interrelationship is important".

From the reports, the prognosis of these cases is usually quite grave. As was seen in the prenatal types

of tumors, these also show a strong tendency to be malignant.

The Late Form of Suprarenal Hyperfunction,- Adult Virilism and Hirsutism.

This is a syndrome which develops when the tumor appears after the individual is past puberty. Here the changes noted in the prenatal form can't take place because the external genitals, and other primary sex characteristics have become established in their true state. Also the disturbances in the secondary sexual characteristics don't appear here because they have become normally established, that is, in the female the menstrual cycle has already reached its normal periodicity, and the breasts and genitals have developed, and in the male the beard has appeared, the voice deepened, and the genitals have reached the increased size and adult functional capacity. However, there is a definite group of symptoms which do appear and when they do they are practically diagnostic of cortical tumor.

Here, as in previous reviews, it is seen that the sex incidence is most commonly in the female. The onset may be manifested by irregular menstruation, or amenorrhea, accompanied by nausea and vomiting. They may show unusual muscular strength, some even being able to lift greater loads than men who are considered to be quite strong. There may be some mental changes accompanying the disease, shown as egotism, overbearing tendencies,

irritability, and features which have been interpreted as a kind of mental hypersthenia. Associated with this is the characteristic appearance of hair over the body, noted especially on the face as mustaches and long beards, and long hairs over the body and extremities, the picture of hirsutism. About the only change in the genitals seems to be an enlargement of the clitoris. Later in the course of the disease dark spots, or a generalized pigmentation, may develop, and after several months, if untreated, symptoms of Addison's disease may intervene which terminate in death.

Sprunt cites as evidence of etiology one case in which all symptoms disappeared upon removal of a tumor by operation but they re-appeared when the growth returned.

In contrast to the female picture, Sprunt notes a case which occurred in a man 44 years old. Previous to the onset of symptoms he had been normal in every way, and he was the father of two normal children. He first noticed a change when his breasts enlarged and became painful. The nipples rapidly became pigmented, he lost his potency, and a large amount of fat became deposited on the abdomen, face and breasts. There was no change noticed here in the normally deposited hair, on the head, face, axilla, pubes, etc. This patient was operated on and a large, encapsulated tumor of the left suprarenal gland was removed, with a complete disappearance

of symptoms. He became sexually potent and one year after operation he had remained free from any recurrence.

There are many cases of cortical tumor reported in the literature but Murray and Simpson⁴¹ were able to find the reports of but two cases of successful surgical removal of these tumors before 1925. These were reported by Holmes at that time from a review of the literature, who at the same time reported another case. Two cases of tumor of the cortex of the gland were reported between 1925 and 1927, both of which died, but an operation was done on only one.

Murray and Simpson⁴¹ report a very interesting case of a woman whom they observed. The patient was 36 years old, in good health up until 2 or 3 years before when she had several severe attacks of abdominal pain which recurred at intervals of a few weeks and were accompanied by anorexia. These gradually disappeared. Nine months before the operation the patient missed her regular period. This fact was more striking because she had always been quite regular in her periods. Later she noticed changes elsewhere in her body. These were an increase in weight, the hands and feet became larger, there was a falling out of the hair of the head with a coarsening of the skin of the face, and an increase in the amount of hair on the face, chin, and lips. Also she became very much depressed mentally. Five months after menses stopped a tumor was discovered in the right

loin and at that time it was suspected to be renal in nature but later it was diagnosed to be hypernephroma, because of the changing features. There was a blood pressure of 200/120 and the symptoms continued to increase in severity until operation. Following operation there was a marked change in the symptoms, all but the blood pressure showing a marked improvement. After two months she was able to return to her home and at that time definite changes were noted in her skin, which were much exfoliating and scaling, and the hirsutism was less marked. Also the scalp hair began to grow again. Before the operation she had a ravenous appetite and had gained markedly in weight, but since the operation these had both returned to within normal limits for her. Gradually the other characteristics of hirsutism disappeared and she assumed her former normal features. Most interesting is the fact that she began menstruating exactly 36 weeks to the day after her last period, the day on which she would have expected it had there been no intervening trouble. The blood pressure was lowered to about 130mm. of mercury systolic, but was very easily raised to 190 to 200 with the slightest excitement.

Dr. H.H. Gleave made the pathological examination of the tumor removed in this case, and following his report he gave a very good review of adrenal cortical tumors. He calls attention to the fact that the term

"Adrenal cortical hypernephroma", has been suggested for this type of tumor. They arise from the cells of the adrenal cortex and are clearly distinguished from the paragangliomas and neuroblastomas arising from the medulla. These may be of all grades of malignancy, cases having been reported in which the symptoms extended, in one case, 14 years and another about 16 years with the removal of a 12 pound encapsulated tumor. Another case was noted in which the symptoms began eight months before death and metastasis was found to the vena cava. It is his observation that, "The tumors which more closely resemble the adrenal cortex are the more benign". Also he finds that even the malignant tumors may remain localized for a much longer time than other types of tumors, thus giving a slightly more favorable prognosis.

Kennedy and Lister³² report a case of hypernephroma in a patient 13 and one half years old which was apparently started by a fall 5 months before. She showed the marks of hirsutism, and at operation a tumor was removed. However, in a very few hours she died, and at autopsy it was found that the right gland, the one which was left, was present in only a small amount and that was much atrophied. The authors pointed out that in cases of this kind it isn't at all uncommon to find the opposite suprarenal gland very poorly developed. A similar observation was made by Rowntree and Ball in a patient from whom a right sided tumor was removed. In

this case there was no gland found on the left side at all.

Rowntree and Ball also note that occasionally suprarenal carcinoma is associated with, as a case reported from the Mayo clinic records, enlargement of the thyroid gland, nervousness, tremor, tachycardia, hyperhidrosis, intolerance to heat, dyspnea, choking sensations, precordial distress, increased appetite and basal metabolic rate, and hypertension. There was also a skin pigmentation, weakness, fatigue, alopecia, suppression of menstruation, change in voice and increase in weight, all suggestive of perverted function of the suprarenal cortex. Death followed operation and it was such as to suggest suprarenal insufficiency, which was borne out at autopsy by the finding of only a small gland remaining on the opposite side.

A case of apparent overactivity of the suprarenal cortex was reported by Rowntree and Ball without finding any pathological basis for it at operation. However, all the symptoms were relieved by unilateral suprarenalectomy so it points to the occurrence of cortical hyperactivity without morphological change of the gland.

Treatment.

This is primarily a surgical problem. However, if the case is one in which malignancy appeared very early with metastasis, so that it is inoperable, X-ray is then indicated. The tumor cells are usually quite susceptible to X-rays while normal gland tissue is very resistant.

MEDULLARY HYPERFUNCTION.

As was seen in cases of cortical hyperfunction, the etiology lay with tumor tissue of some sort. The same is true of medullary tumors. There are primarily three types of tumors, which are differentiated from the others by the type of cells from which they arise.

Neuroblastoma.

Although all three types of neuroblastoma are mentioned the only one which is given much consideration in the reports is the Hutchinson variety, the one which involves by metastasis the orbit, skull and long bones. At Mayo clinic, Rowntree and Ball found seven cases had been examined, all of which were children. Only one case was studied through and came to autopsy, but the symptoms and findings of all were very similar and they all died very early.

Case Report: ⁴⁸ A boy, aged 13, apparently had been well until about six months before his examination at the clinic, when it was noticed that small lumps were appearing under his scalp, and he had begun to lose strength and had become increasingly pale. He had been taken to a physician, who had examined his eyes and had said that he had choked discs. Since that time he had grown gradually weaker. His vision had become progressively poorer, and the lumps on his head had continued to increase in size. For about a month before his admission he had been complaining of attacks of pain in his knees

and hips. He had not complained of headaches or vomiting.

When the patient was examined at the clinic pallor was striking and his skin had a slightly greenish tint. The entire vertex and forehead were covered with nodules varying in size from 2 or 3 to 6 or 7 cm. in diameter. Some of these nodules were rather soft and others were very hard. The veins of the scalp were greatly dilated and there was moderate exophthalmos. He was extremely emaciated and his skin was hot and dry. There were hard, rapidly throbbing vessels in his neck. The liver and spleen were palpible and there was marked tenderness over the sternum. Ocular examination revealed choked disks.

The patient was hospitalized and grew gradually worse during the month he was under observation. He then contracted influenza and died. Necropsy disclosed malignant neuroblastoma of the left suprarenal gland with multiple, extensive metastasis to the bones of the skull, vertebra, sternum, and regional lymphatic structures; bilateral hypostatic bronchopneumonia, also was present.

Ganglioneuroma.

This type of tumor is quite rare. Usually they are small, benign tumors which are accidentally found at necropsy without having given any symptoms during life. Occasionally they are seen to reach some appreciable size, but this is usually before the person reaches the

twentieth year. Rowntree and Ball found a report by Gallerstedt and Helm, in 1928, of a boy six years old, by X-ray a coral like calcification in the suprarenal region. At autopsy it was found to be a calcified ganglioneuroma of the suprarenal medulla.

Paragangliomas (Chromaffin cell tumors)

Clinically, these are the most significant of all tumors of the suprarenal medulla. Rowntree and Ball noted that Berdez first described the condition in 1892. In 1929 Rabin reviewed the literature and found 30 authentic cases reported in all literature of tumors of this type.

These tumors are found, not only in the suprarenal medulla, but also in other parts of the body wherever chromaffin tissue is found, notably in sympathetic ganglia, and carotid body or Zukerkandl's organ. The tumors are usually benign and do not produce a cachexic state.

Sprunt found that Rabin in his review noted more women than men were affected, there being 18 women and 6 men. The ages usually range from the 4th to the 6th decades, but there was one case reported who was only 2 years old.

The symptoms of this type of tumor are usually quite constant. Goldzieher notes chiefly those of high blood pressure and exacerbations with further increase in the pressure. Sprunt also calls attention to the sudden rise in blood pressure; evidence of peripheral

vaso-constriction; violent heart action and glycosuria. These all suggest an epinephrin reaction. Rowntree and Ball note a series of symptoms which are described in other reports. These are: (1) Changes of sclerosis due to epinephrin in a child 2 years old with this type of tumor. (2) vaso-motor instability in another case. An apparently very healthy man had a tooth extracted under local cocaine anesthesia and in 2 hours he died. At necropsy a large bilateral suprarenal tumor was found which contained much epinephrin. (3) Intermittant, paroxysmal hypertension. This was noted by Labbi, Tinel and Doumer⁴⁸ in 1922 and again in 1927 by Oberling and Jung⁴⁸. Rowntree and Ball saw a similar case in 1926 which presented complaints of paroxysmal attacks of dyspnea, occipital headache, tachycardia, and vomiting. Careful study showed the blood pressure to rise suddenly, in 3 or 4 minutes from the onset of the attack, from a systolic pressure of 80 or 90mm. of mercury to 160 or 180mm. of mercury. Also they further observed that the tachycardia was secondary to the rise in blood pressure, and was accompanied by a moderate dilation of the heart during the paroxysm. This patient was operated on and a left suprarenal tumor was removed. She apparently recovered from the paroxysms and was able to do her normal work.

Pincoff⁴⁸ reported a case with symptoms similar to those stated above. This patient complained of hot,

flushed feeling in both arms followed by a sensation of tightness about the heart with palpitation. There was a sensation of dyspnea and of swelling in the neck as well as nausea which was partly relieved by forced vomiting. During the attack there was some apprehension and a general shaky, nervous feeling. The blood pressure was about 120/80 but during an attack it ranged up to 260 systolic and returned quite slowly. All symptoms were relieved upon removal of a medullary tumor which contained much epinephrin.

A third case was reported by Rowntree and Ball in their paper, in which the patient complained of peculiar attacks accompanied by an unpleasant sensation in the epigastrium, "Similar to, but not exactly, nausea". Most of the attacks occurred in bed, but he found that by assuming a certain upright position the attacks could be brought on at will. The color became ashen, the systolic pressure rose from 110 to 200mm. of Hg. or more in about 90 seconds. In bed the attacks lasted about 30 or 40 seconds but when upright they persisted for 3 or 4 minutes and then disappeared as rapidly as they appeared. A large tumor was found in this case, the removal of which relieved the symptoms.

It has been indicated that it is not in all cases of intermittent hypertension or vascular crises that are indications of suprarenal tumor. Cases have been

reported with symptoms similar to this occurring with mediastinal tumors and pneumonia. They have also been attributed to vagus irritation. In contrast to the apparent nearly constant findings of tumor with the symptoms of increased epinephrinism, Rowntree and Ball report a case in which no tumor was found to indicate the cause of the symptoms.

Goldzieher, along the line of increased symptoms of hyperepinephrinism without tumor of the pheochrom tissue, believes it is logical to assume such to be the case. An excessive blood pressure and arterial changes may be the result. These have been considered for a long time but not accepted because of the inability of the pharmacologists to demonstrate the epinephrin in the blood stream in larger quantities than normal. However, he sees no reason why it might not be present in an altered form which hasn't as yet been identified by the ordinary methods. In upholding the theory the author points out observations which he has made in many thousand gland examinations under the microscope. He noted changes which he considered to be quite characteristic, the most significant of which he found in each case, which was, great hypertrophy of the muscle bundles of the suprarenal veins. The muscles, by contracting, tend to block the lumen of the vessel, thus preventing the regular venous exit from being used by diverting the blood into the collaterals, on the left

side to the diaphragm and kidney and on the right to the liver. In this way the epinephrin is probably inactivated before it reaches the heart and arterial circulation. In hypertension and arteriosclerosis these muscles in the vein walls are extremely hypertrophied indicating an attempt to divert the blood flow. He says that this phenomenon has, since his description, been noted by other observers. He called further attention to the fact that in hypertension there is an increase in the adrenalin content of the glands. About 20 years ago an increase of 50 to 100% over the normal was noted. Later he noted small nodules in the glands, similar to, but much smaller than, the pheochromatic tumors observed in paroxysmal hypertension.

Treatment.

The treatment for medullary tumors, as was seen in those of the cortex, is primarily surgical, but X-ray or radium may be used. Sprunt notes that Vaquez suggests the use of insulin to counteract the effects of epinephrin on the blood sugar.

Suprarenal Tumors and Hypertension.

There seems to be a very definite relationship between tumors of the suprarenal glands and hypertension. Rowntree and Ball reviewed the literature on this subject, citing all references, and they found that in a few cases the medullary tumors were surgically removed with a loss of symptoms, while one was reported by Vaquez who refused operation and he finally had a continuous and permanent

hypertension. In the cases which these men studied, 29 in all, they grouped them into three types in an attempt to determine just what the relationship of the suprarenals to the matter of hypertension might be.

1. Paroxysmal hypertension dominates the group (chiefly paraganglioma.)
2. Body configuration and changes in sex characteristics indicate hyperactivity of the cortex as well.
3. Those in which glycosuria and hyperglycemia are prominent clinical findings.

These authors also note that there are several features of the disease of these glands which have a bearing on bloodpressure:

1. Hypotension results from the destruction of the gland.
2. A potent principle which raises the blood pressure has been isolated from this gland.
3. Tumors often lead to intermittent or continuous hypertension and removal of the tumor restores normal blood pressure.

From their studies the authors (Rowntree and Ball) came to the conclusion that, "We are forced then, we believe, to accept either the view that there is a small and special group of cases of hypertension of which the cause is in the suprarenal gland, or that the suprarenal glands participate directly or indirectly in the pathogenesis of hypertension".

Thus from the studies it can be seen that the subject of suprarenal tumors is a very complex one. Some cases present symptoms which are very clearcut and in which the diagnosis is relatively easy. Other cases present symptoms of involvement of both parts of the gland and they may even resemble very closely some other endocrine dyscrasia.

MEDULLARY HYPOFUNCTION.

When the medullary tissue fails to produce sufficient epinephrin, or other substance whatever it may be, there are apparently very few symptoms which are definite. Little mention is made anywhere in the literature of a hypofunctioning medulla except as theoretical cause of a condition, as that described by Mills which produced "hypoadrenia". However, the only evidence he had for the belief was the fact that his patients responded well to epinephrin therapy and similar results were not obtained in this country.

Goldzieher believes that medullary insufficiency may be a factor in producing a low bloodpressure with a low blood sugar which is commonly found in infections. He believes that this is a picture of decreased sympathetic tonus accounted for by medullary injury. Further, he believes that many cases diagnosed as "heart failure" in diphtheria, pneumonia, and other acute infections are the result of peripheral circulatory

failure caused by medullary insufficiency.

In Berkow's study of the glandular injury resulting from burns, he finds that patients treated with medullary extract seem to get along much better than those who do not get this substance. He believes the syndrome seen in those cases may be the result of a sudden depletion of hormone which affects a part of the nervous system, or a sudden rise in the nitrogen products of the blood due to a loss of excretion through the kidneys or a lack of detoxifying processes.

However, it may be seen that the evidence isn't sufficiently large, as yet, to definitely establish a state of medullary insufficiency.

OTHER CONDITIONS, which appear to be associated with
the suprarenal dysfunction.

In addition to the various syndromes which have been above, certain other writers have pointed out the possibility that these glands may be the cause of other conditions, or that other pathology elsewhere in the body may result in definite reactions in the suprarenal glands. These conditions, as would be expected, are still hypothetical in nature and are much in dispute.

According to Bischoff and Maxwell⁵⁵ There has long been the idea that the origin and extension of neoplastic tissue is due to the lack of, or imbalance in, the growth regulating hormones. Working along those lines Coffey and Humber⁵⁵ prepared an extract of sheep suprarenal glands and by its use they found that it caused sloughing and ultimate disappearance of malignant tumors in man. Injections in graduated doses, subcutaneously at regular intervals, caused marked necrosis of areas of malignancy followed shortly by sloughing, where it was anatomically possible. When these patients came to autopsy it was found that necrosis had taken place in metastatic areas, even if they were no larger than a lead pencil point. Clinically, these patients treated with the extract said that they felt, slept, and ate better. A very striking observation was that very soon the weight began to increase and a large part of the pain disappeared. The patients were given the extract subcutaneously, beginning with one minim twice a week and increasing it to twelve

minims. They could show nothing that would indicate that the extract was of value as a substitute for the suprarenal hormone.

In contrast to the claims of Coffey and Humber, Harris³⁴ reports a study of 415 cases of malignancy of all parts of the body who were treated by the Coffey-Humber method. The studies were made under the Kellogg Foundation and as far as was humanly possible it was done without prejudice. They reached the following conclusions :

"1. The benefits of use of the suprarenal cortex extract experienced by patients with malignant tumors in relation to gain in weight and relief from pain did not occur uniformly or in the majority of the patients observed by us.

2. The extract administered to these patients had no selective influence on the growth, necrosis or sloughing of malignant tumors.

3. Necrosis and sloughing of malignant tumors were not beneficial, but were detrimental to these patients, producing hemorrhage, anemia, distressing fistulae, perforation with abscess or peritonitis and other serious consequences.

4. Cure of malignant diseases in patients with advanced carcinoma or sarcoma, in view of the experience of the patients of this series, cannot reasonably be expected to occur as a result of the use of the suprarenal

cortex extract.

5. The benefits to be expected from use of suprarenal cortex extract lie principally in improved appetite, improved muscle tone and better feeling of general well-being of patients who are ambulatory or who are not too far advanced toward a fatal termination of the disease".

Arterial Hypertension.

This subject has been partially discussed under the heading of Medullary tumors, but some other phases are found which are considered here.

European clinicians⁵⁵ have been interested in this condition, especially in regard to the hypertensive cases. One of these writers discusses hypertension at menopause. Women at menopause present sometimes a picture of vagotonia in which there is precocious hair growth, slight pallor, normal or subnormal blood pressure with a marked tendency to urticaria, asthma, pseudo-angina, and other anaphylactic phenomena and with neuromuscular and vascular hypotonia. As contrasted with this type there is presented the sympathicotonic syndrome of stout, plethoric appearance, highly colored or congested face with a fresh skin even during summer, with a tendency toward virilism, appearing younger than their real age, no tendency to anaphylaxis, neuromuscular or cardiovascular hypotonia, but rather to a hypertensive state. One such patient had a unilateral suprarenalectomy with a marked drop in blood pressure,

which amounted to a drop in systolic pressure of from 50 to 100mm. of mercury. However too little is known and the results are as yet too incomplete to draw any definite conclusions from the studies.

Peripheral Arterial Disease, - Buerger's, Raynaud's disease.

Sprunt noted that Oppel⁵⁵ believes both conditions are due to the same cause, that of spasm of the arteries brought about through the sympathetic nervous system and that the presence of hyper-thrombocytosis and hyper-glycemia with increased central arterial pressure and lowered peripheral pressure were all dependent upon hyperfunctioning of the suprarenal glands. He claimed good results from unilateral suprarenalectomy. He reported one case of Buerger's disease in which the progress was stopped, pain disappeared and the patient could use his foot. Another case the gangrene stopped, the pain stopped and the foot was useful again.

Along with surgery radiotherapy may be of value. But Crile¹⁴ reports 3 cases of unilateral suprarenalectomy in Raynaud's disease in which there was no relief of symptoms. Allen and Brown³ also studied the effects of treatment of Raynaud's disease but they used glandular extracts. They found the extracts to be valueless in their studies.

Some Evidence of Interaction of the Various Endocrines.

Dr. Crile¹⁶ has been very much interested in the actions of the suprarenal gland for some time and he has done much work on the subject. In his studies he has noted the great similarity of the conditions of hyperthyroidism, neurocirculatory asthenia, and peptic ulcer. They all occur in individuals, "Most active, most strizing, most worrying men and women". He believes that this may be due to the control which the frontal lobe has obtained over the suprarenal-sympathetic-thyroid system and quite often the syndrome is set off by an emotional excitation as excessive worry and work, or by infection, and since the adequate defensive mechanism and general body activities can't be carried on properly without the system, he sees no reason why, by disconnecting the system from the propelling action of the brain, that it can't overcome a large part of the distressing symptoms. Working on that theory he has performed many operations on the suprarenal glands, since these are probably the most vulnerable point in the chain. He finds good results in this type of treatment with, in many cases, almost complete loss of symptoms of the exophthalmos and neurocirculatory asthenia, and those in peptic ulcer were quite promising. The cortex is just denervated in the treatment of neurocirculatory asthenia and he believes it is almost a specific treatment.

He reserves the operation in peptic ulcer for those who respond poorly to any other form of medicine or surgery and tend to recur.

The operation for recurrent hyperthyroidism is usually a unilateral suprarenalectomy, and he finds a noticeable quieting of the patient. He believes the results are obtained this way because, in the normal gland there is a large reserve in tissue so that the removal of a gland only causes hypertrophy of that tissue which remains. But in diseased glands all the tissue is being used, and so the removal of one gland decreases the supply by half. He reports that the symptoms have been very well controlled in his studies and he is very enthusiastic over the possibilities it presents.

As further studies are made on Peptic ulcer Crile notes the presence of gastric hyperacidity in both that and hyperthyroidism, while in myxedema there is a decreased or absent acidity. He reasons that the thyroid controls gastric acidity and the adrenals control the thyroid through the sympathetics. Hence, if the adrenals are controlled the thyroid and ulcer symptoms should be controlled. His experiments have been promising but not conclusive as yet.

Other Glands.

Pancreas in diabetes. An European experimenter, Ciminata,¹³ believes that diabetes can be controlled very

well by attacking the suprarenal gland. He has shown by denervating the adrenals of a pancreatectomized dog that the blood sugar level dropped markedly; similarly it reacted the same in a patient who was suffering from diabetes. The patient was markedly improved and the blood and urine sugar levels were much lower. The patient was more sensitive to insulin, shown by obtaining the desired reaction from smaller doses. This interpretation seems reasonable since the epinephrin is the antagonist of insulin and when the inhibitory action of insulin is removed the sympathetic system tends to react by stimulating the adrenals to further epinephrin secretion, which releases more sugar. Thus by severing the sympathetic control the excessive epinephrin secretion would be checked.

Gonads.- In gonadectomy.

Anderson and Kennedy⁴ made a study of the effects of gonadectomy on the adrenals and other endocrines. After a rather exhaustive search they concluded the study of the rat by saying, "The adrenals of animals spayed before maturity resemble those of the controls of the same age until the latter have become mature. The adrenals of the operated animals then retain, in part, the structure of those of the immature animals. In the case of gonadectomy after maturity there is a temporary increase of lipoid in the fasciculata, more marked in the females, with congestion of the inner third of the cortex. In the

male 3 weeks after castration the adrenals appear similar to those in normal animals. The process of regression is the female with degenerative changes in the inner portion of the cortex and marked congestion of the capillaries". They further believe that the glands increase in size by an increase of the cortex and not the medullary tissue.

Pituitary Gland.

In a study of the relations of the suprarenal and pituitary glands, Moehlig and Bates^{H^o} noted the not uncommon association of polycythemia with suprarenal tumors. But they believe that this is due to a malfunctioning pituitary rather than suprarenal gland. Their ideas are based on the conclusions reached by various foreign writers and they quote one, "Schweizer believes that the suprarenals influence centers which have a hemopoetic influence. If the suprarenals are defective, the central regulating mechanism is defective. He bases this conclusion in part on the observations of defects of the brain associated with suprarenal defects".

Some men have had good results in increasing the red blood cell count in various diseases, according to Moehlig and Bates, by administering cortical extract. This has even been obtained in the treatment of pernicious anemia.

According to one reporter, the degeneration and

necrosis of the suprarenal cortex results in the liberation of a toxin which stimulates the bone marrow. Also he believes that there is a very close relation between the suprarenal cortex and the reticulo-endothelial system. Others, however, have reported several times that there is a polycythemia with excision of the suprarenals in animals. Further, Rowntree and Snell note the not uncommon polycythemia in Addison's disease but they also say that except for the crises there is usually a normal blood volume.

According to Barker,⁸ in Addison's disease there is a marked decrease in the number of basophilic cells of the pituitary gland.

As a conclusion to their study Moehlig and Bates have decided that the suprarenal cortex reflects the state of the pituitary gland. They believe that the primary disease of the suprarenal cortex, resulting in either hypo- or hyper-function, produces a variable but definite change in the pituitary as a secondary factor. And since the change occurs they believe the pituitary gland is responsible for many of the changes attributed to the suprarenal gland. It has been shown by injecting pituitary extract that it is possible to produce suprarenal cortex hypertrophy. Also in persons predisposed to suprarenal deficiency there has been shown a pituitary hyperplasia. But others have shown a hyperplasia with adrenalectomy so on that track we are undecided.

Vitamins

From studies made by Lockwood and Hartman³⁴ there appears a definite relationship between the suprarenal cortex and vitamins B and C. In 1928 Szent-Gyorgyi³⁴ isolated hexuronic acid from the suprarenal cortex and in 1932 King and Waugh³⁴ pointed out that the vitamin C which they isolated from lemon juice was identical with it. Later it was shown that vitamin C deficiency can be prevented by feeding the raw suprarenal cortical substance.

SUMMARY.

Of all the various syndromes attributed to the suprarenal gland deficiency, Addison's disease is the only one upon which all the writers agree to be the result of a lack of function of the organ. Further, it is the only condition for which a specific treatment has been developed. If the cortical extract therapy is instituted early enough, and in sufficient quantities over a long enough time, the patient may be restored to health and he may continue his normal activities without symptoms, excepting a pigmentation of the skin.

The other conditions of so-called "Hypoadrenia", or other forms of adrenal insufficiency, remain more or less in the class of the theoretical. Opinions have been presented both in favor of, and against, the existence of such a condition. However, conclusive evidence of its presence hasn't as yet been given. It is quite likely that it is some other condition, since the treatment with the hormone is usually ineffective.

The suprarenal cortex appears to be actively connected with the sexual development. A condition of hyperactivity of this substance, usually in the form of a tumor, causes, in the congenital form, pseudo-hermaphroditism; in children before puberty, precocious development of secondary sex characteristics; and in the adult, the development of virilism and hirsutism, with also a tendency toward a reversion of sexual characteristics.

These tumors are usually malignant but often they can be entirely removed by surgery, which is the best form of treatment.

Medullary discrasias are less definitely defined than cortical disturbances. Tumors, which have a tendency to metastasize to bones, lungs and liver, seem to be the chief disturbing factor. Apparently they secrete some substance which increases the body activity. It appears that there is a definite relationship between hyperactivity of the medullary substance and hyperthyroidism and hypertension, but this condition is also much in dispute. It remains for further work to be done before any definite conclusions may be reached.

Medullary hypofunction remains a theory which has no definite clinical or experimental backing. The same may be said of all the other conditions attributed to the suprarenal gland. Until more conclusive evidence is offered supporting the ideas they must remain in the speculative field.

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