A CASE OF ADDISON'S DISEASE WITH SIMPLE ATROPHY OF THE ADRENALS.*

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PLATE XXVIII.

The study of simple atrophy of the adrenal bodies in Addison's disease may prove of considerable importance in explaining more thoroughly the process underlying this group of symptoms. The lesions in simple atrophy of the adrenals afford a much better opportunity of investigating the gradual death of the parenchyma than the gross destructive changes in tuberculosis of the glands, most commonly associated with the disease. The histological examination of the comparatively early phases of the atrophic lesions in the present case possesses considerable interest, for the subject has received but little investigation. Very few cases of simple atrophy of the adrenals in Addison's disease are recorded, and of these hardly a single one has been given thorough histological study.

I am indebted for the following clinical notes to Dr. D. H. McAlpin, Jr., Visiting Physician to the City Hospital of New York.

F. N., male; aged 42; admitted to City Hospital August 10, 1897, died February 17, 1898.

Family history: Negative.

Previous history: During childhood the patient had measles. At 20 years of age he had an attack of rheumatism, after which he was well until his 28th year, when he had some affection of the skin. Patient denied alcoholic excess and syphilis.

Fourteen years ago, he says, he began to "turn yellow," but he was well for seven years after the first appearance of the discoloration, when he

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had another attack of rheumatism in the legs, from which he soon recovered. In 1895 he had a similar attack of "rheumatic" pain in the legs, accompanied by acute bronchitis, loss of flesh, and profound weakness, but he recovered and was apparently well until June, 1897. Six weeks before admission, he had an attack of weakness, diarrhœa and polyuria, without headache or pain in the abdomen. The feet became swollen and he had pains in the legs and ankles.

Status on admission: The entire body is of a yellowish-brown color, deeper in tint where protected from the sun, and especially dark over areas pressed upon by the clothing, waistband, collar, suspenders, etc. Ocular conjunctivæ pearly white. Mucous membrane of tongue and mouth pale and free from pigment. The patient's mental condition is dull. He says he has a fair appetite, sleeps well, but has pains in the knees and ankles. The bowels move three to four times daily. He complains also of epigastric pain and slight cough.

Physical examination of lungs revealed high-pitched and rather prolonged respiration at inferior angle of left scapula. Blood examination, September 6, by Dr. Reilly; hæmoglobin, 20 per cent; reds, 1,490,850; whites, hypoleucocytosis. From the stained specimens, I made the following observations: Differential count of 500 leucocytes gave: adult cells, 55 per cent; young cells, 41 per cent; eosinophiles, 4 per cent; myelocytes absent. There are a few microcytes and poikilocytes but the blood does not indicate severe anæmia.

September 11. Patient complained of severe darting pains from the neck to the occipital region and of pain in the left hypochondrium. For the past 18 days he has had frequent stools. At this time examination showed impaired resonance over both infraclavicular regions with fine moist rales, heard especially posteriorly.

September 13. On ophthalmoscopic examination, retinæ and optic disks were extremely pale, but otherwise normal. The following week the patient seemed much improved. The cough became less frequent and severe, the stools less numerous and he appeared to be brighter mentally. On September 22, diarrhœa recurred with frequent bilious vomiting, watery stools, cough, pain in the abdomen and legs. This condition persisted except at intervals of a few days during which the patient would feel fairly comfortable. On October 26, ptosis of the right eyelid developed, but disappeared after a few days.

On physical examination, November 5, bronchial breathing, coarse mucous rales, friction, etc., were heard over the right infraclavicular region, but there was no evidence of cavity formation.

The patient remained in this condition until January 15, 1898, after which date he began to grow much weaker. The diarrhoea and vomiting continued with severe abdominal pain and at times delirium. He died February 17, 1898. The temperature was irregular and atypical and at no time above 101° F. The urine was examined weekly. The specific gravity varied from 1018 to 1022. Neither albumin nor sugar was found.

The *autopsy* was performed a few hours after death. I have prepared the following notes from Dr. McAlpin's protocol.

Body extremely emaciated; eyes and cheeks sunken; panniculus adiposus absent. Skin of entire body of a brownish mulatto color, pigmentation being especially pronounced over upper anterior part of thorax, scrotum, glans penis, dorsum of hands and feet, and either side of spinal column, especially in lumbar and sacral regions. No pigmentation of buccal mucous membrane or sides of the tongue. Conjunctivæ generally white, but tinged with yellow where exposed to the air. Peritoneum smooth and glistening. Stomach and large intestine distended with gas. Lower edge of right kidney 1½ inches below last rib; left kidney same, slightly movable. Vermiform appendix small, its lumen patent and filled with impacted hard fæcal matter. Bladder distended. Edge of liver above free border of ribs; gall-bladder distended.

Right lung: Oedematous; a few old adhesions over middle lobe; cut section of lower lobe yellowish pink, with small, elevated, pale, dry, granular areas exuding a creamy fluid on pressure; upper lobe grayish yellow, with moderate anthracosis, and a few apical caseous nodules from 1 to 6 cm. in diameter.

Left lung: Oedematous; old adhesions over upper lobe; tubercular nodules at apex and a few in lower lobe, surrounded by firm, pinkish granulations. Bronchial glands enlarged and the right calcified.

Heart: About 20 cc. clear serum in pericardial sac. Heart of average size; epicardial fat absent; right ventricle collapsed; right auricle distended with ante-mortem clot; cavity of left ventricle dilated; walls thin, pale brown; endocardium normal; aortic and mitral segments practically normal; no myocarditis; right ventricle normal; tricuspid and pulmonary valves normal, save some yellowish discoloration of segments; also some atheroma of coronary arteries.

Liver: Small, reddish-brown, firm; lobules distinct, with dark centres; vascular walls thickened. Gall-bladder distended with two ounces of dark greenish, thick bile, containing many small, pultaceous masses; gall-ducts patent; mucous membrane normal.

Stomach: Small, mucous membrane normal.

Pancreas: Pale, very firm, evidently the seat of interstitial hyperplasia.

Small intestine: Extremely pale, distended with gas; mucosa pale, covered with mucus; no increase of adenoid tissue.

Mesenteric glands small, firm.

Spleen: Somewhat enlarged, firm, reddish-brown.

Bladder distended with eight ounces of dark urine, mucosa normal.

Kidneys: Enlarged; finely granular surface, in places cystic; cortex thickened; pale yellowish, striæ obscure, small, grayish, tubercle-like bodies on surface.

Adrenals: The left measures 2 in. in length by $\frac{3}{4}$ in. in width and less than $\frac{1}{4}$ in. in thickness; the right has about the same dimensions; their general appearance normal, except somewhat atrophic; surface smooth and pale; consistence normal; no evidence of tubercular disease.

Celiac sympathetics easily removed and apparently normal.

Brain: Small, fresh hæmorrhages on under surface of dura, especially on right side. Pia mater very œdematous, opaque and thickened; in region of both Sylvian fossæ, dusky pigmentation, seen also over pons. Brain small, symmetrical and very pale; sulci deep, convolutions thin.

Spinal cord: Normal.

Anatomical diagnosis: Chronic miliary tuberculosis of lungs; tuberculosis of bronchial glands; passive congestion of liver; chronic interstitial pancreatitis; chronic catarrhal enteritis; chronic interstitial nephritis, and simple atrophy of adrenal bodies.

Microscopic examination: Unfortunately as the central nervous system was not preserved and the dissection of the sympathetic was incomplete, the microscopic examination is restricted to the only available material, the adrenal bodies and the semilunar ganglia.

Pieces from both *adrenals* were hardened in formaldehyde solution (4 per cent), in absolute alcohol, and in Müller's fluid. The entire gland of either side was cut and stained. The sections were variously stained in Delafield's hæmatoxylin and eosin-blue, lithium carmine, Van Gieson's mixture of picro-acid-fuchsin, by the Heidenhain-Biondi method, etc. The microscopical findings being similar in both adrenals, one description will suffice. On casual observation the appearance of many sections is that of normal tissue, but on closer examination and by careful comparison with a series of sections taken from normal adrenals distinct morbid changes can be demonstrated. The periglandular fat is decreased in amount and the seat of serous atrophy. The remains of the adipose tissue are seen as a richly cellular mass, in which appear fully formed fat

cells. The intercellular substance is a homogeneous finely granular material, in places fibrillated, which encloses small, round, deeply stained nuclei. The fibrous capsule, with the septa, does not appear thickened and is free from evidences of inflammation and of tuberculosis.

The zona glomerulosa is present in some part throughout all the sections, the individual glomeruli varying greatly in size and appearance. In places they are represented by only one or two small cells, with round, deeply stained nuclei, and at times they appear to lie in the outer capsule. In places, however, this zone appears two or three times the usual thickness and is composed of four or five layers of glomerular acini, and again in other areas it is entirely absent, the cells of the zona fasciculata being in contact with the fibrous capsule.

The part of the gland represented by the zona fasciculata shows many interesting as well as uncommon conditions. The most striking change consist in the irregularity of the columns in this portion. The cells, instead of being arranged in definite columns, running more or less vertically from the zona glomerulosa to the medulla, compose branching masses and columns, having an irregular course and being intimately mingled with cells from the zona reticularis. The cells vary greatly in size and appearance, their nuclei being small, round, deeply stained dots. The cytoplasm is finely granular and stains a delicate pink with a watery solution of eosin-blue. The walls of the individual cells cannot be distinguished, so that the general appearance is that of finely granular, branching masses, in which lie small, round nuclei. The small cells, which are arranged in tubules in this region, have protoplasm resembling in every way that of their enlarged associates. The fatty condition of the cells, normally present in this region, is absent or noticeably diminished and in only a few sections was I able to demonstrate the large, clear fatty cells, so common in the normal organ.

Especially in specimens hardened in Müller's fluid, are seen in the fascicular zone circumscribed areas composed of large, pale acini, containing a peculiar colloid material of crescentic and other shapes. These colloid masses, when stained by eosin, contrast by their brilliant red color with the pale pink cytoplasm. With picro-acid-fuchsin they are colored a brownish-purple. They have sharp borders and are striking objects in the sections. Auld describes cylindrical bodies with highly refractive index between, or more often in, the medullary cells of adrenals hardened with chromic salts. Colloid masses similar to those described, however, I have never seen in any other sections from a series of at least fifty adrenals studied during the past year.

Adjacent to the swollen areas of the zona fasciculata are seen tubules made up of small cells which have been pushed aside and evidently compressed. Such a condition is commonly seen in the normal gland just at the side of a small area undergoing fatty metamorphosis.

The most prominent departure from the typical structure, is seen in the region immediately adjacent to and including the upper medullary portion or in the zona reticularis (Plate XXVIII, Fig. 2). In specimens hardened in alcohol, there is an evident increase in the normal content of pigment, of a bright, brownish-yellow hue, both in the cell bodies and free in the intercellular substance. So great is the accumulation of pigment granules that sections stained with Delafield's hæmatoxylin and eosin-blue do not reveal the nuclei in this region. Potassium ferrocyanide and dilute hydrochloric acid fail to give evidence of iron in the pigment granules. The cells of the zona reticularis, instead of appearing in small anastomosing columns, remain more or less distinct in clusters of two or three. This appearance is to be interpreted as evidence of simple atrophy.

The intercellular spaces are large and prominent and appear as finely granular areas, in which delicate threads of the normal reticulum are distinct.

The polymorphism of the cells of the zona reticularis is very noticeable. They vary from one-third to twenty times the size of the typical cell in this situation. Many large homogeneous cells of giant size are seen (Plate XXVIII, Fig. 1). Each of these possesses a single large, deeply stained nucleus, usually about the centre of the cell. Many of these nuclei have a diameter ten times that of those in adjacent cells. The cytoplasm appears almost homogeneous, stains with eosin a delicate pink and, without definite limits, shades off insensibly into the surrounding intercellular substance. These I take to be hypertrophic cells undergoing necrobiosis. Many of the smaller cells in this zone also show evidences of degeneration and necrosis. Many are polychromatophilic with indistinct fragmented nuclei; others appear swollen, granular and devoid of nuclei, while in places the original cell is represented by nothing but a small mass of pigment.

In this region, as already mentioned, the intercellular substance and fibrous reticulum, are especially prominent, less apparently from actual new formation, than on account of the atrophy and disappearance of the columns of cells. Sections treated with picro-acid-fuchsin, fail to show any definite increase of the fibrous stroma. The reticulum is throughout rich in round and fusiform, deeply staining nuclei and especially so about the smaller capillaries.

The blood-vessels of the adrenals show in many places a pronounced perivascular infiltration with small round cells. The walls of the larger vessels present in areas peculiar nodular thickenings, not unlike those first described by Kussmaul, as periarteritis nodosa. There is a moderate nodular fibrous thickening of the intima of the vessels, but not so marked as to encroach materially upon the lumen.

The medullæ of both adrenals show but little microscopical evidence of disease. Here and there are seen, embedded in the medulla, portions of the cortex, a finding not uncommonly met in the normal organ. This portion of the gland is relatively small in amount, but present in all the sections near the hilum. As the edge of the gland is reached, it becomes narrower and ceases entirely about 1 cm. from the free edge. At the junction of the medulla with the cortex, I was able by the Nissl method to demonstrate here and there ganglion cells staining deeply and showing the same picture as that seen in cells of the semilunar ganglia.

Sympathetic ganglia: The right and left semilunar ganglia were hardened in absolute alcohol. Sections were stained by the Nissl stain, Van Gieson's method and hæmatoxylin and eosin. With simple stains the ganglion cells appeared numerous, without evidence of atrophy or degeneration. With the Nissl stain, the cells appeared large and fully formed, staining deeply and without evidence of chromolysis. At the borders of many of them were seen dark brownish metaplasia granules, usually appearing as a little irregular cluster on one side of the cell. The Nissl bodies were fully formed, standing out distinctly in the cytoplasm. A few of the ganglion cells contained two well-formed and distinct nuclei. This condition has been observed a few times before in different conditions, but is not believed to have any pathological significance. Nor to the increase of pigment can especial significance be attached. Otherwise no lesion is apparent. There was no small-celled infiltration, necrosis, caseation or any condition even suggestive of simple or tubercular inflammation in the celiac ganglia.

The following facts in this case of Addison's disease seem to me worthy of note: the appearance of the cutaneous pigmentation fourteen years before the onset of the profound constitutional symptoms; the occurrence of severe rheumatoid pains in the extremities, so commonly observed among the early manifestations of the disease; the profound weakness with uncontrollable diarrhoea, epigastric pains and bilious vomiting; the prolonged duration of life (six months)

after the onset of the severe diarrhœa and vomiting; the irregular and atypical temperature; the absence of albumin or sugar from the urine; the characteristic color and distribution of the pigment; the rather severe anæmia with hypoleucocytosis.

The condition of the adrenal bodies found at autopsy was certainly surprising, the only gross abnormality being a simple atrophy of quite moderate degree. The microscopical evidences of this condition may be briefly summarized as follows: diminution in size and number of the glomeruli of the zona glomerulosa; diminution in length with great irregularity in the course and arrangement of the columns, as well as diminution of their fatty contents; colloid degeneration of circumscribed areas in the zona fasciculata; marked atrophy with increased pigmentation of the cells in the zona reticularis and replacement of some of the cells by clumps of pigment; general diminution in size of the medulla associated with the presence of displaced cortical structures; the presence of many mononuclear cells of gigantic size, of cells with fragmented nuclei and cells devoid of nuclei; thickening of the vessel walls with perivascular infiltration, and absence of chronic interstitial or tubercular inflammation.

These conditions warrant the diagnosis of *simple atrophy*, associated, perhaps, with attempts at compensatory cellular hypertrophy.

Assuming this condition, without lesion of the abdominal sympathetics, to be the essential cause of the clinical symptoms in this case, it may be well to call to mind other conditions concerned with the pathogenesis of this disease.

Addison, in his original memoir, considered that any lesion of the adrenal bodies, which interfered sufficiently with their function, could give rise to the disease.

Guy and Fowler, however, found that malignant lymphadenoma destroying the cœliac ganglia, without involvement of the adrenals, was capable of causing the classical symptoms. Rolleston, in the Goulstonian lectures for 1895, gives the following morbid conditions in the adrenals as possible etiological factors: Caseating tuberculosis; simple atrophy; chronic interstitial inflammation; malignant disease; occlusion of the adrenal vein; hæmorrhagic states. To these he adds destructive lesions of the semilunar ganglia.

From this classification, we are to believe that next to tubercular disease of the adrenal bodies, simple atrophy is the most common cause. Examination of the records shows reports of at least 16 cases of atrophy of the adrenals associated with symptoms of Addison's disease.

The cases reported by Osler,* Monti,† and Hadden,‡ respectively, should be classified as degenerative atrophies associated with chronic interstitial inflammation. There thus remain for consideration only 13 cases. Brief citations from the various records may not be out of place here:

Case I. (J. K. Spender, *Brit. Med. Journ.*, 1858.) Female, aged 53. Time of the first appearance of the pigmentation unknown. Attacks of profound prostration, epigastric pain, bilious vomiting and diarrhoea. Skin of entire body of a yellowish-brown color. At autopsy entire absence (?) of both adrenals.

Case II. (J. W. Legge, *St. Bartholomew's Hosp. Rep.*, 1874, X.) Female, aged 37. 18 months before admission noticed dark brownish streak on lip; 6 months ago, face became pigmented and there appeared weakness, shortness of breath and frequent attacks of bilious vomiting. Yellowish-brown color over entire body, especially over face, neck and dorsum of hand. Small patches of pigment on buccal mucous membrane. Symptoms became exaggerated and patient died one month after admission. At autopsy no evidence of tuberculosis in the body. The right adrenal absent but replaced by a mass of fat supplied by the adrenal artery and vein. The left adrenal thin, fibrous, without trace of the normal cortex. Microscopic examination revealed fully formed connective tissue, fat cells but no remnants of the gland. No coarse disease of nerves or ganglia.

Case III. (Goodhart, *Trans. Lond. Path. Soc.*, 1882.) Coal miner, aged 20. Admitted October 7, 1881, on account of increased weakness. Skin had begun to darken two years before. Pigmentation appeared first upon glans penis, then on face, arms, legs, etc. One year before admission attacks of severe epigastric pain with nausea. Skin dry, of a marked brown color, especially on sides of body, buccal mucosa, nipples, scrotum and glans penis. The diarrhoea, vomiting and weakness in-

* *Internat. Med. Mag.*, 1896-7, v, 3.

† *Arch. f. Kinderh.*, 1884-5, vi, 319.

‡ *Trans. Lond. Path. Soc.*, 1885, xxxvi, 436.

creased and the patient died in coma. Aside from the hyperplasia of the adenoid tissue of the gastro-intestinal tract, the principal post-mortem findings were in the adrenals. In the place of each of these bodies was a thin layer of a reddish-brown substance, still retaining the triangular outline of the gland and connected with the large adrenal vein. The glands were so thin, that, when placed between the fingers, they could hardly be appreciated. Microscopically the tissue showed simple atrophy without evidence of tubercular disease or implication of the coeliac ganglia.

Case IV. (Goodhart, *Trans. Lond. Path. Soc.*, 1882.) Draper, aged 44. For twelve years has had rheumatic pains in the knees. Eight years before skin became pigmented. Acute melancholia, necessitating confinement in a sanatorium, appeared for some months, but from this there was entire recovery. For a month before death, emaciation, weakness, nausea, vomiting and epigastric pains were manifested. At autopsy all organs healthy, except the adrenals, which were so wasted as to be scarcely visible. No evidence of suppuration or of caseous material. Apparently there was simple atrophy until each gland was reduced to the size of a split pea.

Case V. (Davy, *Trans. Lond. Path. Soc.*, 1882.) Machinist, aged 25. 3 years before entrance to hospital noticed pigmentation of nose, followed shortly by pigmentation under eyes. Gradually entire body became yellowish-brown. At times profound prostration. Death in coma following alcoholic intoxication. Entire surface of body uniformly pigmented, especially over genitals, flexor surfaces of joints and axillæ. Conjunctivæ pearly white, pupils minutely contracted. Left adrenal very much smaller than usual but of normal appearance except in one place near the middle. Right adrenal presented even less recognizable structure. Semilunar ganglia not found on account of fat.

Case VI. (R. G. Hebb, *Lancet*, 1883, I.) Female, aged 48. Pigmentation of skin noticed four weeks before, preceded by emaciation, attacks of headache, vertigo, nausea, vomiting and constipation. General pigmentation, especially over neck, elbows, areola of nipples and buccal mucosa. At autopsy no evidence of tuberculosis. Adrenals weighed 28 and 19 grains respectively, were of normal shape, of reddish color and soft, medulla apparently absent. No lesion of sympathetic ganglia observed.

Case VII. (Sidney Coupland, *Trans. Lond. Path. Soc.*, 1885.) Stone-sawyer, aged 34, admitted June, 1881. Present ailment began two years ago with loss of appetite, vomiting, weakness and pigmentation of skin, which became deepest on face, dorsum of hands, neck and buccal

mucous membrane. Patient had many attacks as described and was under observation two and a half years. In January, 1884, following over-indulgence in alcohol, he succumbed, but was conscious until the last few hours. Mesenteric glands and Peyer's patches enlarged. No trace of right adrenal—possibly replaced by a small mass of fat. Left adrenal one-third normal size, of usual shape, very thin and almost translucent. Semilunar ganglia normal.

Case VIII. (Thomas Barlow, *Trans. Lond. Path. Soc.*, 1885.) Female, aged 42, admitted July, 1883. Pigmentation of skin began one year before; pregnant for last nine months; attacks of weakness and vomiting. On July 1, birth of a still-born child, followed by great prostration and death, in a typhoid state, a short time afterwards. At autopsy, pigmentation of entire body, deepest over areola of nipples, groins, dorsum of feet, under side of knees, etc. At first it was believed that the adrenal bodies had vanished without a trace, but careful dissection indicated the fibrous investment of the bodies, still preserving their cocked-hat shape and containing the merest trace of pale glandular tissue in each, which on microscopical examination gave evidence of the columnar arrangement of the cortex.

Case IX. (J. W. Legge, *Lancet*, 1885.) Female, aged 29, admitted May, 1884. Six months before had an attack of vertigo with vomiting. One month later noticed pigmentation of the skin, of a tawny brown color, deeper over right eye, xyphoid cartilage and axillæ. Clinical course characterized by fever, vomiting, progressive asthenia, deepening of the pigmentation and death. Autopsy: Lungs normal; right adrenal represented by a small shred of tissue about one-half inch long and one-quarter inch broad, left black, of natural outline, but completely wasted and thin as paper; solar plexus to naked eye normal.

Case X. (Senator, cited from Lewin, *Charité-Annalen*, 1885, p. 648.) Female, aged 53. For past six years attacks of vomiting; six weeks ago black masses of blood vomited, at same time high fever and epigastric pains. One month ago, small dark spot appeared on the gums. Soon entire body became bronzed, the pigmentation being especially marked upon the face. Many dark brown spots on face, arms and groins; skin, especially of fingers, rough and scaly; hair completely gray; iris yellowish-brown, sclera somewhat gray. Albuminuria with hyaline casts and pus corpuscles. Pulse 152. Adrenals markedly atrophic, the cortex being represented by scarcely more than two separate leaflets.

Case XI. (P. Guttman, cited from Roloff, Ziegler's *Beiträge*, ix, p. 344.) Male, aged 20. One year before noticed pigmentation of the

skin, followed by increasing weakness, vomiting, epigastric pains, sopor and death. Autopsy: pronounced brownish pigmentation, most marked upon face, mucous membrane of mouth and lips, genitals, nates and bend of knees. Induration of pulmonary apices. Both adrenals reduced to mere traces of cortical substance. Cervical (? celiac) ganglia normal.

Case XII. (Roloff, Ziegler's *Beiträge*, ix, p. 329.) Male, aged 22. Pigmentation, which increased in intensity, began 13 years previously, after an attack of acute pleurisy. Patient was comparatively well until five days before death. Constitutional symptoms began with loss of appetite and weakness. The day before his death, for the first time had vomiting and epigastric pains. He soon became delirious and died. Autopsy: acute hyperplasia of the gastro-intestinal lymph nodes; chronic pulmonary tuberculosis; right adrenal, 20x12x3 mm., markedly atrophic, left a little larger, but not more than $\frac{1}{4}$ to $\frac{1}{3}$ usual size, without evidence of tuberculosis in either gland, either macroscopically or microscopically. Microscopical examination revealed total absence of fat in the cortical cells. The principal portion of the gland remaining is the medulla. Here and there are small islets of tissue resembling the zona glomerulosa and zona reticularis. Microscopically semilunar ganglia normal.

Case XIII. (Bramwell, *Brit. Med. Jour.*, 1897.) Grocer, aged 37. Typical case of Addison's disease, characterized by profound and causeless asthenia, pigmentation of skin and buccal mucous membrane, pain in neck, occasional vomiting, slight emaciation. Death from influenza. Autopsy: lungs normal; complete absence of adrenals, their place being taken by masses of fat, which on the left side presented appearances suggestive of the remains of the degenerated adrenals. Microscopical examination revealed only a mass of fat cells and blood-vessels without trace of glandular structure.

It is seen that of the 14 cases reported (including my own), tuberculosis was present in the body only three times, being absent in all instances from the adrenals themselves. In none of the 13 cases from the records was the lesion of the glands relatively so slight as in the present case. The adrenals in case XII were apparently the largest of the series, and even the largest was less than 3 cm. in its greatest diameter. In my case they were nearly of normal size.

In two of the cases (I and XIII) the glands were apparently entirely absent, suggesting complete aplasia. Zander and others have noted

such a condition, but always, so far as I am aware, it was associated with defective embryological developments in other portions of the body, and it can hardly be supposed that the patients could have survived so long with actual aplasia of the adrenal glands. Case XII is at least suggestive of hypoplasia. Here the pigmentation of the skin began when the individual was nine years of age and continued for thirteen years, his health remaining fairly good until five days before death. The pathogenesis of this form of simple atrophy of the adrenal bodies is entirely unknown.

In attempting an explanation of this condition, the general causes of simple atrophy may be referred to: (1) pressure; (2) disuse; (3) senility; (4) neuropathic influences; (5) impaired nutrition. The first three need not be discussed. The possibility of defective inheritance may be suggested, but of its participation in the etiology of the disease we have no conclusive evidence.

In regard to neuropathic influences, there is evidence that lesions of the sympathetic may produce indirectly atrophy of the adrenal bodies, and as a result the symptom-complex of Addison's disease. Whether or not the ganglion cells have a trophic influence upon the cellular parenchyma of the adrenals, analogous to that of the anterior motor cells of the spinal cord upon voluntary muscular fibres, is not positively known, but recent physiological experiments fail to strengthen this supposition. von Kahlden and others have shown that a lesion involving the splanchnic nerves without direct lesion of the semilunar ganglia, may produce these clinical symptoms, and Biedl has shown that the secretion of epinephrin is under the influence of these nerves. In our case the splanchnic nerves were not carefully dissected out and examined, but it is certain that no gross or histological changes were present in the coeliac ganglia.

It has been suggested that certain cells in the spinal cord may exercise a trophic influence upon the adrenal parenchyma, but there is only negative evidence to support this hypothesis. The brain and cord of the present case were not obtained for microscopic examination.

Defective nutrition cannot be excluded as a possible causative factor in this case, but no such changes were observed in the adrenal vessels as would indicate serious disturbances in the local circulation.

It must be admitted, therefore, that at present we are as much at a loss to understand the pathogenesis of this condition as was Spender in 1858.

The work of Oliver and Schaefer,* and more recently that of Abel,† has shed light upon the function of the adrenals. The blood-pressure-raising constituent, designated by Abel "epinephrin," has been shown to be derived from the medulla, but the exact rôle that it plays in normal metabolism or in the production of the pigmentation and other phenomena of Addison's disease has not been demonstrated. The medulla in the glands of the case just reported, though as a whole somewhat diminished, is nevertheless present in comparatively fair amount.

It is difficult to believe that the symptom-complex of Addison's disease can be explained by such quantitatively insignificant histological changes as were present in this case. It is well known that certain glandular organs may undergo perversion of function and still present little or no histological evidence of disease. There is evidence that some cases of diabetes mellitus are referable to disordered function of the pancreas without manifest histological lesions of this organ. Recent investigations have demonstrated the vital importance of the adrenal glands and their endowment with a so-called internal secretion. If it were possible to estimate clinically the amount of epinephrin secreted, as we estimate the amount of urea in the urine, we might then be in a better position to explain such obscure case of Addison's disease as the one reported in this paper. Although Addison's disease is undoubtedly due to some interference with the function of the adrenal bodies, it seems probable that, in this case at least, we have to deal with a perversion rather than with a total lack of function.

DESCRIPTION OF PLATE XXVIII.

Fig. 1. From section of adrenal. *A*, large cell with vacuoles; *B*, cells of the zona reticularis; *C*, perivascular infiltration. Zeiss ocular 2, objective D.

Fig. 2. Section of adrenal. *A*, portion of normal zona fasciculata; *B*, simple atrophic cells of the zona reticularis; *C*, atrophic and hypertrophic

* Oliver and Schaefer, *Journal of Physiology*, xvi and xviii.

† Abel, *Bull. of the Johns Hopkins Hospital*, 1897, p. 153, and *Zeitschr. f. physiol. Chemie*, xxviii.

cells in contiguity; *D*, pigmented protoplasmic remains of cell bodies; *E*, connective tissue reticulum prominent on account of degeneration and disappearance of the parenchyma; *F*, normal cells in zona reticularis.

The red masses seen in some of the cells correspond in reaction to the colloid masses described as occurring in the zona fasciculata.

Technique. Hardened in Müller's fluid, stained in Delafield's hæmatoxylin and one per cent aqueous solution of eosin-blue. Zeiss ocular 2, objective D.

FIG. 2.

FIG. 1.