FIVE CASES OF ADDISON'S DISEASE WITH SO-CALLED ATROPHY OF THE ADRENAL CORTEX

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In the past few years, the publications of a number of investigators have demonstrated a growing interest in those cases of Addison's disease in which the adrenal cortex is found at autopsy to be affected more or less selectively by a destructive process which is evidently non-tuberculous. The pathological lesion in the adrenal glands in such cases has been designated variously as atrophy (1), cytotoxic contraction (2), primary contraction (3), or as selective destruction of the suprarenal cortex (4). Although this peculiar lesion of the suprarenal gland ranks second only to tuberculosis as a cause of Addison's disease (3), its etiology is entirely unknown.

The literature from 1900 to 1929 on the subject of Addison's disease has been fully reviewed by Guttman (3). His analysis of 403 cases collected from this literature, pathological reports of which were available, shows that "primary contracted suprarenal gland" occurred in 65 cases or 16.13 per cent of the series. This proportion of the total, as Guttman remarked, probably gives a false impression of the relative frequency of this type of lesion, for the reason that cases of Addison's disease in which it was present have been reported frequently in recent years, while many cases of Addison's disease due to tuberculosis of the adrenal glands have probably failed to find their way into the literature. The tendency toward reporting these relatively rare cases of Addison's disease has continued to be in evidence. Since 1929, there have appeared in the literature reports of no less than 24 cases of Addison's disease in which an anatomical diagnosis of "atrophy" of the adrenal glands was reached after microscopic examination of the tissues (4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14). This seems to be a remarkably large number in comparison with the 65 cases reported in the preceding

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thirty years. However, a number of these cases were collected from autopsy records reaching back sometimes for long periods. This fact, considered together with the obviously increasing interest in this particular lesion of the adrenal glands, renders it impossible to be certain that this large number of recently reported cases offers any substantiation for the impression recorded by Wells (4) that Addison’s disease due to “atrophy” of the suprarenal cortex is becoming more frequent.

Regarding this question, the significance of the experience in this laboratory is difficult to evaluate. During the past seven months, four cases of Addison’s disease with “atrophy” of the adrenal cortex have come to our attention; during the same period no cases due to tuberculosis have been encountered. However, only two of these patients came to autopsy here. The other two died at home and reports of the autopsies with material for microscopic study were sent to Dr. G. A. Harrop, under whose care the patients had been in the Johns Hopkins Hospital. Examination of the records of this department showed that, prior to the occurrence of these recent cases, there had been, in a total of 12,342 autopsies, 12 cases of Addison’s disease. Of these, ten showed tuberculosis of the adrenal glands and one presented dense scarring in the suprarenal region which, however, was not demonstrated to be tuberculous. The remaining case, which came to autopsy in 1901, showed typical “atrophy” of the adrenal cortex. It is not to be inferred that the recent cases of Addison’s disease represent an increase in its incidence here. These cases have come to our attention primarily because of the interest of the clinicians in the disease and in its treatment. Even the fact that all of the four recent cases mentioned proved to be cases of “adrenal atrophy” may be no more than mere coincidence. However, it is suggestive of a possible increasing incidence of this rare lesion of the adrenal gland.

It was felt that the five cases of Addison’s disease due to “atrophy” of the adrenal cortex formed a series worth reporting. Four of them are perhaps of added interest in that they had been treated with extracts of suprarenal cortex. The clinical features exhibited by these four patients have been discussed fully by Drs. Harrop, Weinstein and Marlow in a recent publication (15) and to them we are indebted for the clinical information preceding the pathological reports. Our cases 2, 3 and 4 correspond to those of the same numbers in their arti-
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cle, while our case 5 corresponds to their case 8, the patient having died since their paper was written.

The case reports have been condensed as much as possible, only positive findings being recorded and detailed descriptions of commonplace lesions being omitted. However, some mention is made of all of the pathological conditions found in a careful study of all the material available. The limitations upon the study of each case are clearly indicated.

Case 1

Clinical history. F. W., a white boy 14 years of age, was admitted to the Johns Hopkins Hospital on July 23, 1901, suffering from typhoid fever, and died on July 29, 1901. He had been seen on three previous admissions to the hospital but prior to any of these he had had measles at the age of 2 years, whooping-cough at the age of 5 years, scarlet fever at the age of 7 years, and chills and fever at the age of 8 years. On his first admission to the hospital in April, 1896, he complained of chills and fever, and a diagnosis of double tertian malarial fever was made. At that time, an extraordinary pigmentation of the skin was noticed. The skin was described as being of a dusky hue with definite bronzing over the backs of the hands and wrists. The mother stated that the peculiar colour of the skin had appeared about 1893, when the patient was 6 years old and at least two years prior to the appearance of any symptoms of malaria. However, a diagnosis of Addison's disease was not made until the second admission in February, 1897, when the patient came into the hospital suffering again from tertian malarial fever. On this occasion the colour of the skin was about the same as on the previous admission. The mother said that the boy had always been active and had experienced no symptoms of gastric or intestinal irritation. The patient was seen again in September, 1899, when the skin was described as being of a uniform light brown colour. On the final admission in 1901, the patient had symptoms and signs typical of typhoid fever which had a fatal outcome within a few days. The pigmentation of the skin was generalized over its whole surface but intensified over the neck, the hands, the scrotum, and the legs just below the knees. Pigment was seen also on the mucous surfaces of the lips and on the gums about the upper and lower incisors. The final clinical diagnosis was typhoid fever and Addison's disease.

Autopsy (No. 1768). A complete post-mortem examination was made one hour after death by Dr. Eugene L. Opie.

The anatomical diagnosis was as follows: Addison's disease; so-called "atrophy" of the adrenal cortex, with lymphocytic infiltrations in the cortex and medulla; pigmentation of the skin. Typhoid fever; hyperplasia and beginning ulceration of Peyer's patches and the solitary follicles of the ileum; hyperplasia of the mesenteric and retroperitoneal lymph nodes. Acute splenic tumor. Typhoid necroses in the liver. Early biliary cirrhosis of the liver. Tuberculosis of mediastinal lymph node.
The following notes were made from the autopsy protocol and from a microscopic study of fresh sections cut from the tissues of this case which were found to be quite well preserved after more than thirty years. Unfortunately, the thyroid gland was not available for study.

With the exception of the liver and adrenal glands, the organs showed only the lesions usually associated with typhoid fever.

Sections of the liver showed, in addition to typhoid necroses, a considerable increase in the fibrous tissue about the portal areas and these regions were infiltrated by large numbers of lymphocytes and large mononuclear cells.

The thymus gland was not enlarged and it was normal microscopically.

**Adrenal glands.** The adrenal glands were found at autopsy only after the most careful search, which revealed a small mass of atrophic adrenal tissue on each side. These together weighed 2.2 grams. They were flattened triangular bodies, the left measuring 2.5 × 1.5 × 0.3 cm. and the right 3.5 × 2.0 × 0.2 cm. Both of them were almost wholly grayish in colour and fibrous in consistency but on their surfaces were a number of small rounded grayish-brown nodules the largest of which measured 3 mm. in diameter. On section the tissue was tough and grayish-white in colour except for the brownish nodules described which were all that could be identified as cortical tissue.

Numerous microscopic sections cut from the two adrenal glands presented very similar pictures. In all of them the histological structure of the medulla was well preserved, although in several sections it contained a few scattered focal accumulations of lymphocytes. Large areas of the cortex had disappeared completely, leaving only a thin layer of loose fibrous connective tissue which thus formed an encapsulating sheath for the medulla. This layer was quite thin and delicate and apparently was composed of the collapsed framework of the cortex. It contained a moderate number of lymphocytes, diffusely distributed. The few remnants of cortical tissue that were seen in the sections presented a variegated appearance. In some areas a vestige of the normal structure of the cortex could be made out through the presence of groups of cortical cells arranged in small rounded clumps simulating the appearance of the zona glomerulosa. Sometimes a few shrunken cells were seen within this zone but in none of the sections were the fasciculate or reticular zones left intact. Further evidence that the outermost layer of the cortex was the last to disappear was furnished by the observation that cortical cells in fairly typical glomerular arrangement were often seen separated from the medulla by a thin layer of loose, vascular fibrous tissue which was taken to represent the collapsed framework of the inner zones of the cortex. Other groups of cells in similar positions in relation to the medulla were arranged in an apparently haphazard manner. In such areas there were marked cellular changes. Some of the cells were large and swollen in appearance, sometimes with large deeply staining nuclei, while other cells were small and shrunken with granular cytoplasm and very palely staining nuclei. The supporting tissue in the neighborhood was very vascular and infiltrated with considerable numbers of lymphocytes. In still other situa-
tions larger groups of cortical cells were seen arranged in clumps interposed between the layers of the delicate fibrous sheath which surrounded the medulla. These masses of cells were rounded in outline and had the appearance of islands of regener-
tated tissue which had grown and expanded in an outward direction so that they formed small nodular protuberances on the periphery. The cells composing these nodules were packed in a solid mass bearing no resemblance to the normal archi-
tecture of the adrenal cortex. The individual cells varied considerably in size, some being quite large, but they seldom showed any degenerative changes. Lymphocytes, though often numerous in the supporting tissue about the regener-
ated nodules, were never present in large numbers among the cells composing them. In every instance, the capillaries and fine vessels in these nodules were widely di-
lated and packed with red blood cells giving the appearance of great vascularity.

Case 2

Clinical history. M. S., a white married woman, 37 years of age, was first seen in the Johns Hopkins Hospital in February, 1930. At that time she complained of weakness of two years’ duration. She had experienced a gradual loss of energy for four or five years before the onset of definite symptoms. Her systolic blood pres-
sure was reported to have been 95 mm. of mercury in 1928 and during that year her skin had begun to darken. On examination in 1930, there was found a moderate dif-
fuse brownish pigmentation of the skin in typical distribution with pigmented areas also on the gums and buccal mucosa. Her blood pressure was 98 systolic and 65 diastolic. A diagnosis of Addison’s disease was made. Treatment with extract of suprarenal cortex was commenced in July, 1930 and continued until November, 1930, with definite subjective but not much objective improvement. The patient was not seen again until April, 1931. During the interval she had experienced in-
creasing weakness and the pigmentation of the skin had become decidedly deeper. The blood pressure was 70 systolic and 50 diastolic. She was admitted to the hospital and shortly afterward passed through an acute attack of suprarenal insuffi-
ciency followed by two milder attacks in May, 1931. All of these were successfully treated with injections of cortical extract and intravenous glucose. After dis-
charge from the hospital at the end of July, 1931, the patient was given an injection of cortical extract twice a week and continued in excellent condition with the excep-
tion of one relapse of moderate severity in October, 1931. She came to the dis-
pensary on January 15, 1932, for her bi-weekly injection of cortical extract. Her general condition was good; the blood pressure was 76 systolic and 54 diastolic. The following day she ate a rather heavy mid-day meal which was followed by a mild gastric upset. During that night she complained of some shortness of breath and pain about her heart. She was drowsy the next morning and remained in bed where her husband found her dead at noon.

Autopsy (No. 12380). The post-mortem examination was performed five hours after death under conditions of peculiar difficulty in the bedroom of a private house. Permission to examine the cranial contents was withheld.
The anatomical diagnosis was as follows: Addison's disease; so-called "atrophy" of the adrenal cortex; pigmentation of the skin. Lymphocytic infiltrations in the adrenal medulla, thyroid gland and kidneys. Enlargement of Peyer's patches and the solitary follicles in the ileum and of some retroperitoneal lymph nodes. Atrophy of the ovaries. Fresh fibrinous pericarditis. Small pleural scars at spiccs of both lungs; old pleural adhesions (right).

The visceral and parietal surfaces of the pericardium were covered by a thin layer of fresh fibrinous exudate which contained a few polymorphonuclear leucocytes and lymphocytes. Sections stained to demonstrate bacteria failed to show any organisms.

The thymus gland was not enlarged.

The thyroid gland was normal in its general features but it contained numerous dense, rounded accumulations of lymphocytes, some of which resembled lymphoid follicles with definite "germinal centres." These encroached upon and partly replaced the acinar tissue in their immediate vicinity. In addition there was a more diffuse scattering of lymphocytes throughout the gland.

The kidneys were found microscopically to contain numerous dense clumps of lymphocytes in the interstitial tissue just beneath the capsule and a few accumulations were seen deeper in the cortex. The tubules in the neighborhood were usually small and shrunken and their basement membranes were often thick and hyaline. In one kidney a dense focal accumulation of lymphocytes was found in the wall of the pelvis.

The ovaries were small and shrunken and there was a complete absence of Graafian follicles.

Adrenal glands. At the time of autopsy the adrenal glands were not to be seen. However, a careful dissection of the retroperitoneal tissue after fixation, revealed a small body on each side, which on microscopic section proved to be adrenal gland. These masses were of about equal size and after Zenker fixation each one measured about 15 × 8 × 2 mm. They were both flattened bodies of slightly irregular outline consisting of a central mass which became thinned out at the margins to a mere membrane. They were of a dark brownish-gray colour, both externally and on the cut surface. Neither of them contained any tissue suggestive of adrenal cortex.

Numerous microscopic sections were made from these bodies and all of them presented a similar picture. The medulla was clearly recognizable and well preserved in its histological structure but the branching strands of medullary cells were separated by a connective-tissue network which was distinctly denser than normal. Here and there in the medulla were small focal accumulations of lymphocytes arranged in rounded groups. In a few small areas the lymphocytic infiltration was present in a more diffuse distribution. Cortical cells were completely lacking in all of the sections. The medulla was surrounded only by a thin and delicate sheath composed of flattened cells. In many of the sections, this sheath extended for some distance beyond the margins of the medulla at either end as a thin membrane. Fine blood vessels were numerous between its layers, but it contained no cortical or medullary cells.
In this case the masses of tissue which proved to be the remains of the adrenal glands were dissected rather closely and it seems possible that a few cortical cells might have been found if the sections had included more of the surrounding tissue. However, if such were the case, they must have been extremely few in number since there was nothing in the gross examination to suggest that any part of the adrenal glands had been missed in dissecting them out.

**Case 3**

Clinical history. E. S. B., a white married man, 34 years of age, was first seen at the John Hopkins Hospital in April, 1931. He complained of a generalized weakness which had developed insidiously since August, 1930. Darkening of the skin had been noted first in February, 1931. On examination in April, the skin was everywhere of a pale brown colour which was intensified over the face, the backs of the hands and forearms, and over the ventral surface of the torso. A triangular area of deeper pigmentation was present over the lumbo-sacral region and the perineum was also deeply pigmented. The blood pressure was 105 mm. of mercury systolic and 55 diastolic. A diagnosis of Addison's disease was made and the patient was admitted to the hospital. Shortly afterward he had an acute relapse with severe nausea and vomiting, general abdominal pain, marked weakness and falling blood pressure. He was treated with extract of suprarenal cortex and intravenous glucose and showed marked improvement within a few days. He was kept under treatment and observation in the hospital until July, 1931, and then was allowed to go home. During the summer he received one injection of cortical extract daily and continued in excellent condition. He returned to the hospital for observation for a short period in October, 1931. The pigmentation of the skin was if anything a little paler than before. The blood pressure averaged 88 systolic and 55 diastolic. He returned to his home apparently in good condition. However, ten days later he developed anorexia and irritability, and although he was reported to have improved somewhat after injection of larger doses of cortical extract, he died on the fifth day (November 13) in an attack of coughing and dyspnoea which the attending physician thought similar to asthma and which was relieved somewhat by injection of adrenalin.

**Autopsy.** The post-mortem examination was performed by Dr. Earl Clarke of Providence, R. I., to whom we are indebted for the information regarding his findings and for microscopic sections of the organs examined. The autopsy permission limited the examination to the abdomen.

None of the abdominal organs, with the exception of the adrenal glands, showed any gross lesions. Microscopic sections of the liver were not available for study but of the other abdominal organs only the kidneys were remarkable.

Small areas of the kidney cortex just beneath the capsule were seen to contain interstitial accumulations of lymphocytes which were sometimes quite dense. The tubules near these areas were curiously shrunken in appearance and their basement membranes were often conspicuously hyalinized.
Adrenal glands. At the time of autopsy the retroperitoneal tissue was carefully searched but the adrenal glands could not be found. However, in microscopic sections of tissue removed from the suprarenal region, one adrenal gland was identified. There was a complete absence of cortical cells and only the medulla remained intact. Throughout its extent there were numerous thin fibrous strands interposed between the groups of medullary cells. The tissue was infiltrated here and there with dense clumps of lymphocytes. In one area the lymphocytic infiltration extended for some distance in a narrow zone along the periphery of the medulla. In other situations lymphocytes were present in smaller numbers and were more diffusely distributed. However, large areas of the medulla were entirely free from lymphocytes and except for the increase in the density of the stroma these areas appeared normal.

Case 4

Clinical history. R. M. C., a white married woman, 36 years of age, first noticed weakness six months after her first pregnancy in 1923. Early in 1927 her blood pressure was reported to have been 95 systolic and 62 diastolic, and in September of the same year a diffuse brown pigmentation of the skin was observed. From that time until June, 1931, she experienced recurrent attacks of weakness and nausea and there was a steady loss of weight. The patient was then admitted to the Massachusetts General Hospital where she suffered a rather severe relapse. However, she showed marked improvement after treatment with large doses of extract of suprarenal cortex. The injections were discontinued on September 23, and for a time she did well without them. On October 28, 1931, the patient was transferred to the Johns Hopkins Hospital. At that time there was a typical diffuse brownish pigmentation of the skin and slight buccal pigmentation. The blood pressure was 100 systolic and 60 diastolic. A relapse occurred shortly after admission to the hospital but subsided under treatment with cortical extract and after the removal of two badly infected teeth. On November 9, jaundice was first noted and this steadily increased. The patient had a series of episodes, each lasting for several days, in which there was severe nausea, anorexia, vomiting and stupor. There was marked hypotension and a considerable secondary anaemia developed. During the last days of life, oedema of the legs and ascites appeared, and there was bleeding from the gums. The patient died December 29, 1931. The final clinical diagnosis was Addison's disease, mediastinal tumour, and subacute "yellow atrophy" of the liver.

Autopsy (No. 12343). A complete autopsy was performed two hours after death.

The anatomical diagnosis was as follows: Addison's disease; so-called "atrophy" of the adrenal cortex and partial destruction of the adrenal medulla; pigmentation of the skin. Lymphocytic infiltrations in the adrenal glands, kidneys, pancreas, voluntary muscle, thyroid gland and meninges. Partial destruction of the hypophysis, with round-cell infiltration. Atrophy of the ovaries. Peculiar cirrhosis
of the liver; jaundice; anasarca. Mediastinal tumor in the thymus region with cyst formation.

The mediastinal tumor formed a flattened mass which lay over the anterior wall of the pericardium. It measured 10 × 9 × 4 cm. In it there were a number of cyst-like cavities which were filled with dark brown fluid and caseous material. Microscopically, it was composed largely of lymphocytes and there were condensations of cells which resembled germinal centres. However, no Hassal's corpuscles could be identified. The capsule was thick and fibrous and there was a great deal of fibrous tissue in the tumor itself. The large cystic spaces were filled with an amorphous caseous material in which cholesterol crystal clefts and fat-laden cells were numerous.

The liver was scarred and shrunken, weighing only 800 grams. Microscopically, it showed a most extensive and apparently progressing cirrhosis which was most pronounced in the periportal areas where regenerating bile-ducts were frequently seen. The liver parenchyma was greatly reduced, often being represented only by scattered islands of tissue. Even these were frequently the site of fresh necroses which were infiltrated by numerous lymphocytes and large mononuclear cells.

The cortex of both kidneys, while showing no structural change, contained frequent interstitial accumulations of lymphocytes.

Small scattered aggregations of lymphocytes were found also in the interstitial tissue of the pancreas and in the rectus abdominis muscle.

The thyroid gland was normal for the most part but one good-sized collection of lymphocytes was found in the interstitial tissue just beneath the capsule.

In the meninges there were scattered accumulations of small round cells, especially near the blood vessels.

The hypophysis contained a small focal area of atrophy in the anterior lobe, in which large and small mononuclear cells were numerous.

The ovaries were somewhat scarred and only a very few Graafian follicles could be found.

Adrenal glands. The adrenal glands were not to be seen at the time of autopsy, but they were subsequently found in tissue removed from the suprarenal region. Both of them were very small flattened bodies of rounded outline which together weighed approximately 5 grams. That on the left side measured about 2.3 × 1.2 × 0.1 cm. and that on the right, about 3.5 × 2.5 × 0.1 cm. No cortical tissue could be identified in the gross but a central mass of dark brown friable tissue suggested adrenal medulla.

Numerous microscopic sections were cut for study. In both adrenal glands a good proportion of the medulla remained intact. In many places the cells were plump and the medulla did not appear to be greatly altered, but in other situations the fibrous connective-tissue framework was definitely denser than normal. Many areas were densely infiltrated by large and small mononuclear cells and in these localities the medullary cells were shrunken and many had disappeared. Other parts of the medulla were reduced to a thin strand composed largely of loose vascu-
lar connective tissue in which only occasional medullary cells remained. In the right adrenal gland, no cortical cells were found. The medulla was surrounded only by a loose fibrous connective-tissue sheath in which there was a moderate number of lymphocytes. Many sections of the left adrenal gland presented a similar picture, but in some of them remnants of the cortical layers could be clearly distinguished. Sometimes all three zones of the cortex could be recognized but more frequently the reticular layer had disappeared and only the fasciculate or the glomerular zone remained. Remnants of the zona glomerulosa were perhaps most frequently spared, although the fasciculate layer sometimes persisted after the other two had disappeared. In other areas, small groups of cells remained but were too much distorted to permit of identifying them as remnants of any single layer of the cortex. The majority of the cortical cells which could be distinguished as such were normal in appearance. However, some of them about the periphery of clumps of normal-looking cortical cells were shrunken, the cytoplasm was very granular, and the nuclei stained poorly or not at all. In such areas lymphocytes were very numerous and indeed all parts of the cortical remnants were more or less densely infiltrated by large and small mononuclear cells, the latter predominating. The sections showed no evidence of regeneration of cortical cells.

Case 5

Clinical history. M. D., a white unmarried woman, 35 years of age, was first seen at the Johns Hopkins Hospital in July, 1931, and at that time complained of weakness, loss of weight, pigmentation of the skin, anorexia and urticaria. Pigmentation of the skin had been noticed first four years prior to her admission to the hospital, but weakness and loss of weight had become marked only in the last fifteen months before admission. During the last six months of this period the patient had been confined to bed because of marked asthenia. Nausea and vomiting had occurred daily for about two months. Her temperature had been very low and her systolic blood pressure was reported to have fluctuated between 60 and 90 mm. of mercury. Loss of weight and anorexia continued and the pigmentation of the skin became deeper. On admission to the hospital the patient was very emaciated. There was a diffuse reddish-brown pigmentation of the skin intensified about the eyes and over exposed areas, along the skin folds, about the nipples and over the knees. There were also large areas of leukoderma over the neck, abdomen, back and legs. The blood pressure was 92 systolic and 70 diastolic. Treatment with extract of suprarenal cortex was instituted, but three weeks after admission a severe relapse occurred which, however, finally subsided after treatment with large doses of cortical extract and dextrose, administered intravenously. From that time onward the patient received injections of cortical extract twice daily. She was discharged in October, 1931, and was able to carry on restricted activities. She returned to the hospital for observation in January, 1932, and appeared to be in good condition, but the weight, blood pressure and pig-
mentation were unchanged. She returned to her home and continued to receive supplies of cortical extract. Detailed information is lacking regarding the events leading up to her death which occurred on May 1, 1932.

Autopsy. The post-mortem examination was made by Dr. H. H. Plowden of Columbia, S. C., to whom our thanks are due for a report of his gross findings and for blocks of tissue from the organs mentioned below. Only the abdominal contents were examined.

Several mesenteric lymph nodes were reported to have been somewhat enlarged, but none of the abdominal organs with the exception of the adrenal glands showed any gross lesions.

Microscopic sections of the mesenteric lymph nodes revealed no lymphoid hyperplasia.

In the sections of spleen the Malpighian bodies were well developed but the organ was essentially normal.

The liver showed marked shrinkage and atrophy of the liver cells about the efferent vein of each lobe.

Sections of the pancreas and of one kidney revealed no abnormality.

Adrenal glands. The right adrenal gland could not be found at autopsy, but the left adrenal was discovered and was sent to us intact. It measured 2 × 0.9 × 0.2 cm. It was enveloped in a loose fibrous capsule which enclosed a central mass of dark brownish-gray tissue. The appearance of the latter suggested adrenal medulla but no cortical tissue could be definitely identified.

Numerous microscopic sections were cut. In all of them the medulla was intact but its cells were rather shrunken in appearance and there was a definite increase in the density of the fibrous connective-tissue framework. It contained numerous rounded accumulations of lymphocytes. In many places the medulla was in direct continuity with a loose vascular fibrous connective-tissue sheath, but in other areas small numbers of cortical cells separated the two. These cortical cells were usually isolated or in groups of two or three so that it was impossible to determine of which cortical zone they were remnants. Many of these cells were swollen and granular with pale-staining nuclei and some groups were completely necrotic. The areas in which these cells persisted always were infiltrated more or less densely by lymphocytes and sometimes small haemorrhages were present with a few scattered granules of iron-containing pigment. In each section a few larger clumps of cortical cells were seen interposed between the medulla and the capsule. However, the arrangement of these cells bore no resemblance to the normal architecture of the adrenal cortex. They were packed in solid masses of rounded or oval outline which appeared to be islands of regenerated cortical tissue. There was great variation in the size of the cells and the largest of them often possessed very large hyperchromatic nuclei. Such nodules of cortical cells were often surrounded by a moderate infiltration of lymphocytes, but their central parts were remarkably free from infiltrating cells.
DISCUSSION

All of the cases here reported, and particularly the last four, lend support to the now generally accepted idea, that it is chiefly the deficiency of the adrenal cortex rather than any change in the medulla which is responsible for the clinical syndrome of Addison’s disease. Nevertheless, there still remains the possibility that the relatively minor alterations in the medulla may be partly responsible for some of the clinical manifestations of the disease, and especially for the lowering of the blood pressure. However, the existence of such a relationship is not supported by the evidence gathered from this study. Cases 2, 3 and 5 exhibited hypotension of a degree quite common in Addison’s disease, although the adrenal medulla was only slightly altered histologically. Case 4 showed much more severe damage to the medulla than did any of the others and yet the patient’s blood pressure, as recorded during the period of observation here, did not differ appreciably from the pressures recorded in the other cases. A relationship between the severity of the symptoms and the amount of remaining adrenal cortical tissue is not evident among the last four cases, nor can it be said that the presence of cortical regeneration in Case 5 had conferred any advantage upon this patient as compared with Case 4 in which no evidence of cortical regeneration was found.

On the other hand, in Case 1, cortical tissue was much more abundant than in any of the others and the symptoms of the disease were proportionately mild; cortical regeneration was active and the time interval between the appearance of skin pigmentation and death was several years longer than in the other four cases. Indeed, the patient evidently had suffered no disability and eventually died of typhoid fever. Probably the patient’s age of 14 years was of some importance in relation to the activity of regeneration and to the longer survival period.

The pathological changes in the adrenal glands corresponded very well with those which have been described by others and which are well summarized by Guttman (3). Only in Case 1 was cortical tissue clearly distinguishable in the gross examination and then it was present in the form of regenerated nodules. Microscopic examination showed either complete loss of the original cortical layers or such widespread destruction that they were represented only by small remnants.
Study of the sections showed distinctly that the zona reticularis disappeared first. Of the other two layers, the zona glomerulosa usually persisted longer, although the cells of the fasciculate layer sometimes were present after the other two layers had disappeared. When regeneration of cortical tissue was in evidence, the islands of regenerated cells always formed the major portion of the total cortical tissue. The process of destruction of cells consisted of a progressive diminution in the depth of staining of the nuclei with accompanying granulation of the cytoplasm until the cell outlines were lost completely. In one case there were small haemorrhages in the cortex in the areas undergoing destruction. The apparent increase of fibrous tissue in the cortex was no more than could be readily accounted for by the collapse of the supporting fibrous framework. The medulla usually showed some increase in the density of the fibrous stroma and sometimes the medullary cells were slightly shrunken in appearance. More or less dense and abundant infiltrations of lymphocytes were always present in the adrenal medulla and among the remnants of cortical tissue. This process of necrosis of cortical cells with slight relative fibrosis and the presence of lymphocytic infiltrations in the cortex and medulla have been almost constant findings in the experience of others.

Other than the lesions in the adrenal glands and the pigmentation of the skin, no changes were found constantly in other parts of the body. Even the lymphocytic infiltrations in various situations were not always present except in the adrenal glands themselves. In only two cases was the thyroid gland available for study and although numerous dense lymphocytic infiltrations were present in one instance, only one comparable accumulation of lymphocytes was found in the other. In three of the five cases, interstitial lymphocytic infiltrations were present in the cortex of the kidneys often associated with changes in the neighboring tubules. The small accumulations of lymphocytes found in case 4 in the pancreas, voluntary muscle, meninges and hypophysis, were not repeated in any of the others. Hyperplasia of lymphoid tissue was not by any means a feature of our cases. Excepting case 1, in which the lesions of typhoid fever were present, there was found a slight enlargement of Peyer's patches and of some of the retroperitoneal lymph nodes in only one case. The thymus gland was examined in three cases and in two of them it was not enlarged. The
tumor in the thymus region in the remaining case was believed to be of no significance in this connection. No lesions were found in the last four cases which could be attributed to any deleterious effect of the treatment with extract of suprarenal cortex. The same has been true of other cortin-treated cases, pathological reports of which have appeared recently (11, 12, 14).

As we have already stated, the cause of the lesions in the adrenal glands is quite unknown. There was no evidence in our cases that tuberculosis had played any part in the process. There was nothing to suggest a syphilitic origin and, moreover, in the last four cases the Wassermann reaction was negative. In spite of the cellular infiltrations the pathological picture was not characteristic of a chronic inflammatory reaction. In none of the cases were the adrenal vessels narrowed or occluded and it is quite evident that the process was not one of true atrophy. On the other hand, all of the evidence is consistent with the conception that some destructive agent, acting more or less specifically upon the adrenal cortex, was responsible for the necrosis of cortical cells, a process which continued in spite of regenerative efforts until the surviving cortical tissue was too scanty in amount to support life. The nature and origin of the destructive agent is a matter for speculation. Kovács (2) believed that a cytotoxin elaborated through faulty metabolism might be responsible, and the toxins of infectious diseases have been suggested. Wells (4) compared the lesions in the adrenal glands with “acute yellow atrophy” of the liver, and suggested the probability that unknown toxins of a similar nature were responsible for the necrosis in both instances. In this connection it is interesting that one of our cases presented widespread cirrhosis and fresh necrosis of the liver, while another showed a definite increase in the fibrous tissue about the portal areas of the liver lobules. However, the presence of liver damage in cases which show the adrenal lesions under consideration is too rare an occurrence to permit of placing much significance upon their association. All things considered, it seems most likely that the adrenal lesions are due to a circulating toxin, but up to the present time, its origin and nature have remained obscure and its very existence is still hypothetical.

It was thought that a search of autopsy material might bring to light some cases in which a similar process of destruction in the adrenal
gland might be found in its early stages or in a state of quiescence. We were able to find four such cases (nos. 9123, 12097, 12318, 12557), which clinically had shown no symptoms or signs of Addison's disease but in which the adrenal glands were altered in a most interesting way. In all of them, one or both of the adrenal glands had presented more or less marked thinning out of the cortex in localized areas. Microscopic examination showed a loss of the reticular layer in these areas and in three of the cases the fasciculate zone had disappeared also in many places so that the zona glomerulosa was all that remained to represent the cortex. In the fourth case, the reticular and the glomerular zones were the ones most widely affected, while the fasciculate zone was left for the most part intact. However, in all of the cases, there were some localized areas where the whole thickness of the cortex was disorganized, leaving only a few distorted cortical cells lying in the collapsed stroma, and in one case, one end of the adrenal gland was reduced to a thin vascular fibrous sheet in which there were only occasional shrunken cortical cells. In no instance was there any cortical regeneration. The process of destruction did not appear to be particularly active. Necrotic cells were seldom seen and lymphocytic infiltrations were not so dense nor so abundant as in the cases of Addison's disease here reported. However, small accumulations of lymphocytes were frequently found in those parts of the cortex in which destruction was most advanced. Larger collections of lymphocytes were scattered here and there in the medulla, but apart from the presence of these infiltrations, the medulla never showed any alteration from the normal.

The lesions in the adrenal glands in these cases differed in no essential respect from those found in the cases of Addison's disease, except in point of degree. Careful study and comparison of the microscopic sections left no doubt in our minds that the process of destruction was identical in the two series of cases. In the one instance the lesions had progressed to the point of producing adrenal insufficiency and death, while in the other cortical destruction was not so widespread nor advancing so rapidly that clinical signs and symptoms had appeared. The findings in these latter cases indicate clearly that the primary lesion is in the adrenal cortex, for in all of them the medulla appeared to be normal. It seems to be also the case that the zones of the cortex differ in their susceptibility to damage, the reticular zone being the
most liable to destruction and the glomerular zone the most resistant. Such a conclusion was suggested also by the study of the adrenals in the cases of Addison’s disease. That these differences in susceptibility indicate differences, as yet unknown, in the function of the three zones of the cortex seems probable. No lymphocytic infiltrations could be found in the thyroid gland or kidneys in these four cases. This fact indicates that the infiltrations seen in these organs in the cases of Addison’s disease were associated with the state of adrenal insufficiency rather than with the peculiar destructive process in the adrenal glands. The presence of similar infiltrations in cases of Addison’s disease due to tuberculosis of the adrenals makes this quite evident.

Unfortunately, these cases of early adrenal damage offered no better clue to the etiology of the disease than did the more advanced ones. Nothing in their histories or in the associated lesions of other organs suggested a relationship which would point to a common etiological factor. However, a further study of such cases cannot but assist in the elucidation of the process and enhance our knowledge of this peculiar lesion of the adrenal gland.

SUMMARY

Five cases of Addison’s disease, four of which had been treated with extracts of suprarenal cortex, are reported. All of them showed more or less complete “atrophy” of the adrenal cortex.

The destructive process in the adrenal glands consisted of a progressive necrosis of cortical cells with collapse of the stroma. In two cases there was regeneration of cortical tissue. The medulla was affected to a much lesser degree, usually showing only a slight increase in the density of the fibrous framework and some shrinkage of the medullary cells. Lymphocytic infiltrations were constantly present in the adrenal medulla and among the remnants of cortical tissue. Lymphocytic infiltrations in various situations constituted the most constant findings in association with the adrenal lesions. Marked hyperplasia of lymphoid tissue was not present in any of the cases. No lesions were found for which the treatment with extract of adrenal cortex could be held responsible.

The relation of the pathological findings to the clinical observations are discussed briefly. A consideration of the possible factors in the
etiology of the adrenal lesions leads to the conclusion that a circulating toxin of unknown origin and nature is probably the causative agent.

A brief account is given of observations upon four cases which showed the early stages of destruction of the adrenal cortex but which presented no clinical evidence of Addison's disease. The findings indicated that the adrenal lesion is primary in the cortex and that the three zones of the cortex differ in their susceptibility to damage.

REFERENCES