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ON SIX CASES OF ADDISON'S DISEASE, WITH THE REPORT OF A CASE GREATLY BENEFITED BY THE USE OF THE SUPRARENAL EXTRACT.

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NINE cases of this rare affection have fallen under my observation. In two of these I made the dissection of the nerves and capsules.<sup>1</sup> A third case I reported in conjunction with Dr. J. C. Wilson in volume xiii. of the *Transactions of the Philadelphia Pathological Society*. The additional six cases, which I here give, have not been previously recorded.

Recent studies render it very probable that the original view of Addison is correct,—namely, that the symptoms of the disease are caused by loss of function of the adrenals. The evidence on which this is based is readily available in the elaborate Goulstonian Lectures of Rolleston,<sup>2</sup> in the address of Professor Schäfer<sup>3</sup> on Internal Secretions, and in a paper by Dr. Oliver.<sup>4</sup> On this view the disease is analogous in all respects to myxœdema, and is caused directly by the loss of the internal secretion of the glands. The comparison between these two diseases has frequently been drawn. As far back as 1885, in an article on Addison's disease in Pepper's "System of Medicine,"<sup>5</sup> I used the following words:

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<sup>1</sup> Ross, *Transactions of the Canadian Medical Association*, vol. i., 1877, and Pepper, *Transactions of the College of Physicians*, Philadelphia, Series iii., vol. viii.

<sup>2</sup> *British Medical Journal*, 1895, vol. i.

<sup>3</sup> *Lancet*, 1895, vol. ii.

<sup>4</sup> *British Medical Journal*, 1895, vol. ii.

<sup>5</sup> Vol. iii. p. 947.

“The relation of affections of the thyroid gland to myxœdema and cretinism, and the experimental production of these conditions by the removal of the thyroid, have widened our view of the importance of the ductless glands. It is interesting to note the analogy between myxœdema and Addison’s disease. In both there are distinct histological changes in the tissues—in one an increase in the mucin, in the other an increase in the pigment—and in both marked nervous phenomena: mental dulness, a progressive dementia in myxœdema, a profound asthenia in Addison’s disease. We regarded the thyroid as unimportant to life until the experience of surgeons and extirpation in monkeys by Horsley demonstrated that abolition of its function was followed by a serious train of symptoms; and perhaps the experimental removal of the suprarenals in monkeys—so much more closely allied to man than the animals hitherto experimented upon—may demonstrate that these little bodies are also not without their influence upon health.

“Although the view of disturbed innervation consequent upon involvement of the abdominal sympathetic meets the case, theoretically, better than any other, and is at present widely held, yet there are signs of a return to the old view of Addison.”

The analogy will be complete if it be found that in suitable cases the use of the suprarenal extract cures Addison’s disease in the same remarkable way that the thyroid extract relieves myxœdema. Clinical workers may now contribute their share by carefully studying the effects of the extract in selected cases. Addison’s disease is so rare that every opportunity should be seized. At the same time the greatest caution should be exercised, on the one hand, to select only well-characterized cases, and, on the other hand, to exclude cases in which the condition is a concomitant of widespread tuberculosis.

CASE I.—Failing health for a year; attacks of faintness; bronzing of face and hands; sudden death. (Abstract.)

A. J., aged about forty, lawyer, consulted me in the spring of 1885, complaining of weakness and attacks of faintness. He was a healthy-looking, well-nourished man, of good family history. For about a year he had been overworked and worried, and had had at times dyspepsia. On one occasion, in court, he felt very faint and almost fell. On two or three other occasions he felt very weak and prostrated without any obvious cause. For nearly a year he had noticed a gradual darkening of the skin of the face and of the hands. At the suggestion of his physician he sought an opinion as to the existence of Addison’s disease. The patient’s general condition was so good, without anæmia, loss of flesh, or any signs of tuberculosis, and the pigmentation was so slight and limited, that doubt seemed reasonable. Dr. Pepper saw the case with me, and we agreed that the pigmentation and causeless fainting spells were, to say the least, suggestive, and we advised him to give up business for a year and live quietly abroad. He went home prepared to follow our advice, arranged his affairs, and made preparations for his trip, when one morning he dropped dead in a railway station. There was no autopsy.

CASE II.—Gradual asthenia; progressive bronzing of the skin; attack of syncope; nausea and vomiting. Autopsy: cheesy foci at apex of left lung and in bronchial glands; tuberculosis of the adrenals; very slight matting of the semilunar ganglia and nerves.

Nellie R., aged forty-one; admitted to the Philadelphia Hospital July 2, 1886, with great weakness and bronzing of the skin. Her father and mother both died of heart-disease, one sister of dropsy, and one of heart-disease. She had small-pox when a child; otherwise she has been a very healthy woman until a year ago, when she was attacked suddenly with great pain in the region of the heart and with dyspnoea. The distress lasted for at least three days. Until April of this year she has been in fairly good health, except that she seemed more languid than formerly and felt indisposed to work.

Last November her friends noticed that she was changing in color, and throughout the winter her normally fair complexion has been replaced gradually by a dark bronze. Three weeks before admission she had a sudden attack of syncope, preceded by dizziness in the head. Shortly afterwards she began to vomit after meals, and has done so almost every day since. She has had no pain anywhere.

*Present Condition.*—Small, somewhat emaciated woman. Face, neck, and hands deeply, general surface of the trunk slightly, pigmented. The bronzing of the face is extreme; it is interesting to note that on the forehead the deep small-pox scars are unpigmented. The skin of the abdomen is much darker than that of the thorax; the fingers are not clubbed; the nails are incurved; the pulse is 96, small and thready; the heart-sounds are clear and loud; there is slight flattening beneath the clavicles at both apices, and the percussion note is a little high pitched, and there are a few râles on deep inspiration. The abdomen is soft; no pain on deep pressure in the epigastrium; no tenderness on either side in the renal regions. There is no pigmentation of the mucous membrane of the mouth. The color of the lips is fairly good; no anæmia; temperature 98° F.

The patient had most profound anorexia with great prostration, and once or twice vomited small quantities of blood. She gradually sank and died on the 13th.

*Autopsy.*—Body not emaciated; skin of face, neck, hands, and arms of a light bronze color; marked pigmentation of abdomen. On the inner surfaces of cheeks a dark patch on either side. Vaginal mucosa not pigmented; panniculus over abdomen three-fourths of an inch in thickness.

*Peritoneum.*—Adhesions between the surface of the liver and the diaphragm. The omentum is adherent to the wall of the pelvis. In thorax there are adhesions at the right apex and general adhesions at the left side. The heart contains fluid blood and clots. The valves are normal; the muscle substance is a little pale.

*Lungs.*—The left is crepitant except at extreme apex, and in two or three small areas of anterior margin, which show cheesy foci surrounded by gelatinous infiltration. The right lung is everywhere crepitant. The pleura is thickened, particularly at the apex. The bronchial glands are caseous.

*Stomach.*—Everywhere throughout the mucosa are small white bodies about two millimetres in diameter. There is pigmentation towards the pylorus; no erosions and no other special changes.

The *spleen* is of average size, closely adherent to the diaphragm, and the pulp looks normal.

The *liver* is small, united closely to the diaphragm. There are no tubercles, but in the adhesions on the right border is a small caseous body the size of a pea.

The *intestines* show no special changes except a slight enlargement of Peyer's patches and the solitary glands.

The suprarenals and sympathetic ganglia were dissected *in situ*.

The right splanchnic nerve is large, and a ganglion existed on it opposite the tenth dorsal vertebra. The left nerve is not so large and presents a smaller ganglion. The right nerve enters the semilunar ganglion, which is readily dissected, as it is not specially involved in cicatricial tissue. On the left side the ganglion is large, but also readily separated from the adjacent tissue. The nerves joining the two ganglia and those about the cœliac axis are less distinct than usual, owing to the slight matting of the tissue. The nerves passing to the suprarenals are free.

The capsules are not much enlarged. The right is six centimetres long, very firmly adherent to the liver and to the inferior cava. The left, six centimetres in length, is closely united to the kidney and to the spleen. On section the right capsule presents no trace of normal gland tissue. The lower half is occupied by a large cheesy mass, the central portion of which presents a grayish translucent, fibrous tissue. The remainder of the organ is made up of a similar tissue in which are small cheesy nodules. Behind the *vena cava* there is also a solid caseous mass. The left capsule presents a firm, cheesy nodule just where its main vein emerges. The organ is flat and made up of a gray, translucent, fibrous tissue.

The kidneys are of average size. The left presents numerous small tubercles and one or two caseous masses which are in close proximity to the suprarenal capsules. In the pelvis the broad ligaments, ovaries, and tubes are closely matted together by old peritoneal adhesions.

The dissection of the nerves and adrenals is in the Mütter Museum of the College of Physicians in Philadelphia.

CASE III.—Dyspepsia and occasional attacks of vomiting for two or three years; for some months gradual pigmentation of the skin and mucous membrane of the mouth; attacks of dizziness; extreme prostration and anæmia; profuse diarrhœa; urgent vomiting; death; no autopsy.

William S., aged fifty-nine, longshoreman; admitted June 30, 1887, to the Philadelphia Hospital, complaining of vomiting and great prostration. With the exception of yellow fever, in 1864, he had enjoyed very good health until three years ago, when he began to have dyspepsia and occasional attacks of vomiting. He has, however, kept at work.

For many months past (he does not know the exact time) he has himself noticed, and his friends have remarked, that he was becoming very dark in color. Eight days before admission he had an attack of dizziness, in which he fell but did not lose consciousness. Since then he has been extremely prostrated and the attacks of vertigo have become more frequent.

*Condition on Admission.*—Large, well-nourished man; slight œdema of the feet. Skin of the face, neck, and hands of deep mahogany brown. General surface of the body very much darker than ordinary; sclerotics are pearly. The lips are pale, and there is evidently marked anæmia. Mucous membrane of the lips and inner side of the cheeks deeply pigmented, and a large patch can also be seen on the soft palate.

The lungs are entirely negative: no râles at the apices; no dulness; no sign of old tuberculous disease. The apex-beat is in the fifth interspace. Pulse 96, small. There is a venous hum in the vessels of the neck; no hæmic murmur at the base of the heart.

There is marked pain on pressure over the tenth and twelfth ribs on the left side; none on the right. The blood showed the characteristic features of an extreme anæmia, and the blood drop looked very watery. The count gave one million red corpuscles per cubic millimetre. Proportion of white to red one to four hundred.

The patient sank rapidly after admission; had profuse diarrhœa and urgent

vomiting, and died July 6. The temperature ranged from 98.2° to 101.4° F. So far as could be ascertained from the patient himself and his friends, there had been no tuberculous disease in his family.

This is the only case of Addison's disease which I have seen with profound anæmia, a symptom on which Addison laid a good deal of stress. In a majority of the cases the blood count does not fall below fifty or sixty per cent. A difficulty sometimes arises in the diagnosis of the disease in cases of severe anæmia of the progressive pernicious type which have irregularly mottled pigmentation. I have recently seen a case in which, with the progressive anæmia, there was a degree of asthenia and gradual pigmentation highly suggestive of Addison's disease.

CASE IV.—Gradually developing languor and asthenia; frequent attacks of causeless vomiting; progressive pigmentation of the skin; convulsions; toxæmia; death. Autopsy: sclerosis and atrophy of the adrenals; no tuberculosis.

David A., aged fifteen and a half, a patient of Dr. Mullin's, of Hamilton, Ontario, who consulted me by letter about him, and who very kindly sent me the suprarenal capsules for examination.

The patient's father died at forty-five from pulmonary tuberculosis of four years' duration. The mother is a healthy woman; the brothers and sisters are healthy.

The boy had suffered from no serious illness in early life, and had good health until the onset of the present illness. In March he had a slight febrile attack, in which he was confined to bed for two days. Early in April his mother noticed that he appeared to be sunburned, and she thought it was due to wearing his Scotch cap too long in the spring. He seemed also languid and listless, and did not seem able to apply himself to study. Early in the summer he was taken from school, as he fretted and cried frequently on account of the scoldings. Ever since the attack in March he has had at intervals of three or four weeks attacks of vomiting, in which he brought up greenish and yellow matter, after which he felt better. In the summer the mother noticed that the skin became much more discolored. He was very indolent and took but little exercise and did not engage in any sports. His complexion was fair and his hair of a light color and thin, so that his discoloration, which deepened through the summer, was very marked. He had at times very severe headache, and sometimes acted strangely, as if silly.

His final illness is so graphically described by Dr. Mullin that I give his statement in full.

"On Monday of this week he complained of sickness and headache. On Wednesday he did not rise from bed; that night he slept and did not complain. On Thursday he was languid and stayed in bed; vomited a little green matter; said he had no headache, but had a bad taste; he was dull and heavy; his eyes appeared strange, and he acted as if he did not wish to be disturbed. About 2 P.M. he took a little oyster-soup; this was taken quickly, and he then turned to the back of the bed; later he vomited slightly. About 5 P.M. he would not answer questions; turned to the wall as if he wished to sleep. A little before 6 P.M. a convulsion occurred, not violent; the limbs were fixed; he was quite unconscious, face a little drawn, and slight frothing; the hands jerked slightly. After this he did not speak, except to say 'yes,' 'yes'; he would put out his tongue and open his mouth, and then turned away and moved to the back of the bed. A few minutes after the convulsion he was seen by a physician, who said that the movements were very similar to those of an hysteri-

cal patient. I saw him at nine o'clock the same evening. He was not unconscious, but did not seem able to fully understand. He moved to the front of the bed at my request, but soon turned and moved to the wall. The pulse was feeble and could not be counted at the wrist; the hands were cold; temperature in axilla, 100° F.; it had fallen one degree since taken after the convulsion. The tongue was a little furred, yellow; the breath seemed foul. During the night he was very restless, tossing from side to side and pulling the bedclothes. He passed urine once; at this time he asked for the vessel. The next morning I visited him at ten. The hands were cold, bluish, nails blue; pulse so feeble that it could not be counted at the wrist; heart-impulses, 132 per minute. Occasionally he made a deep sighing inspiration.

"The brownish discoloration of the skin very marked on the face, the shoulders, and anterior part of the thorax; the surfaces of the extremities discolored, but not so deeply; the integuments of penis and scrotum much darker than elsewhere, and the areola around each nipple was discolored as in pregnancy. Along the spinous processes from the level of the scapular spines to the sacrum was a row of ten spots about the size of a quarter of a dollar more deeply discolored than the surrounding skin. No pigmentation of the mucous membrane of the mouth; the breath was offensive; urine free from albumin and sugar.

"Until the afternoon he was very restless, pulling the bedclothes, and tossing about from side to side, and at 4 P.M. one-third grain of morphine was given hypodermically. After this he became more quiet, and when I visited him at 9 P.M. he was sleeping. He continued quiet during the night, and died the following morning about nine o'clock."

Dr. Mullin was kind enough to give me the opportunity of examining the suprarenals, sections of which I showed one evening at the Pathological Society of Philadelphia. Unfortunately, the specimens and sections of both this and the following case have been mislaid. Both capsules were extremely small, not half the normal size, and surrounded by much fat. They were firm, and on section showed no distinction between the medullary and cortical portions. Microscopically, there was a condition of diffuse sclerosis, with here and there areas of fatty degeneration. There was no tuberculosis of the organs.

CASE V.—Attacks of vomiting and indigestion for eight months; gradual pigmentation of the skin; intense prostration; death. Autopsy: tuberculosis of both adrenals; no involvement of other organs.

William B., aged nine, a patient of Dr. William E. Parke, of Philadelphia, Pa. The boy was at Girard College, and according to the doctor's statement he had seen him, on and off, for about eight months, during which time he had been repeatedly admitted to the infirmary with attacks of vomiting and indigestion, occasionally with a mild tonsillitis. His color had changed and he had become very much bronzed, but this was suggested to have been due to a dark ancestor. His last illness was characterized by most intense prostration and weakness, and obstinate vomiting. There was no elevation of temperature; the pulse had been rapid, but on the morning of his death it came down to forty.

I made the autopsy on the 28th of March, 1888. Unfortunately, the notes which I dictated to Dr. Parke at the time were mislaid. The skin was uniformly pigmented and about the color of a mulatto's. There was no enlargement of the lymph-glands; the heart and lungs were normal; no tuberculosis; no involvement of the lymph-glands in the abdomen; no changes in the stomach or intestine. The suprarenal glands alone were diseased. Both looked small; the right was larger than the left, and presented a flattened tuberculous mass about the size of an almond,

the left a smaller mass in the upper part of the gland. There was no thickening or adhesion about the semilunar ganglion in the nerves passing to the glands.

**CASE VI.**—Pulmonary tuberculosis; injury two years ago; dyspepsia; gradual asthenia; pigmentation, deepening for nearly two years; treatment for eight months with suprarenal extract; rapid disappearance of the serious symptoms; marked and persistent improvement in general condition; no change in the pigmentation.

William H., aged forty-six, sail-maker, admitted to the Johns Hopkins Hospital May 3, 1895, complaining of cough, shortness of breath, great weakness, and a change in the color of his skin.

*Family History.*—His father died of cholera morbus and his mother from the effects of a stone in the bladder. He had three brothers and two sisters, all of whom are dead. He does not know of what the brothers died. One sister died in confinement; the other from poisoning by mercury. He knows of no tuberculosis in his family, and none of his relatives have had discoloration of the skin.

*Personal History.*—When a child he had measles, diphtheria, chicken-pox, and mumps, and when about seventeen years of age, varioloid. In his sixteenth year he served on board a man-of-war at Panama, where he had a protracted fever of nearly four months' duration. Shortly after this he had jaundice for a month, since when he has never had a very healthy or natural-looking color of the skin. Ten years ago he had two attacks of severe pain in the hypochondriac and epigastric regions, lasting about five hours. He was doubled up with the pain and had to have morphine. The attack was not followed by either jaundice or chills. In July, 1893, the patient was run over by a wagon, the wheels passing over his abdomen just below the navel. He was laid up for two months, and suffered a great deal of pain in the abdomen. There was no paralysis afterwards, but he has not been very strong since. For two years the skin has been growing darker in color, and his friends have noticed that within the past five or six months the pigmentation has become much more intense. He has had at intervals throughout his life attacks of indigestion, and at times belching, but no vomiting. Twelve years ago he had an attack of diarrhoea, which lasted for a week. During the past two years he has lost very much both in flesh and strength, and for some months has had no ambition whatever for his work.

He is uncertain how long he has had a cough, but five weeks ago he began to have a great deal of cough with much muco-purulent expectoration. He has not had any pain, but he has suffered a great deal with shortness of breath on the slightest exertion, and he has the dyspnoea even when resting quietly in bed. There have been profuse night-sweats. He has been losing flesh rapidly, and has become very weak. The appetite is poor, but he has had no nausea and no vomiting. He has had no palpitation of the heart.

*Present Condition.*—The patient is a small-framed, poorly-nourished man; height about five feet, eight inches; present weight ninety-nine pounds. Temperature on admission was 101° F.; pulse, 136; respiration, 40. The eyes are sunken, and he looks very apathetic. One's attention is immediately attracted by the intense pigmentation of the skin, particularly of the face and forehead, which is of a uniform deep brown with irregular patches of a darker color. The lips and mucous membranes are not anæmic. On the roof of the mouth there are two patches of pigmentation; on the velum there is slight pigmentation; no spots on the lips, cheeks, or gums. The skin of the hands and wrists is of a very deep bronze color. The pigmentation is more marked in the axillæ and at the bends of the elbow. The areolæ of the nipples and the genitals are dark brownish-black in color. The general surface of the body shows a marked bronzing. There are areas of very deep pigmentation on

the shins, and there is accentuation of the bronzing on either side of the great toes. The superficial glands are not enlarged. The epididymes and testes are normal. The pulse is regular, of medium volume, tension normal, the vessel wall slightly thickened.

The thorax is symmetrical, expansion slight, both clavicles prominent. The percussion-note is slightly impaired in the right front, and here from the second space there is a well-marked friction rub, heard throughout the mammary and axillary regions and around to the back, throughout the infrascapular area. At both apices behind there are a few fine moist râles. On the left side auscultation is negative. The sputum the day after admission was very abundant and frothy, containing a considerable quantity of greenish muco-pus, but tubercle bacilli were not found.

The apex-beat of the heart is in fifth interspace, just outside the nipple line. The sounds are everywhere clear.

The abdomen is somewhat retracted, nowhere tender; the border of the liver is not easily palpable; no increase in the area of liver flatness. The spleen is not palpable; neither kidney can be felt.

There is no enlargement of the thyroid or of the lymphatic glands; no nodes or lesions of the bones.

From the date of admission to May 16, the patient's temperature ranged from normal to about 101° F. The pulse-range was from 120 to 130; respirations from 25 to 35. He expectorated about two hundred and fifty cubic centimetres of sputum, which was examined every other day for tubercle bacilli, but without result; and no elastic tissue was found. The patient has been in bed, and the general prostration and the rapidity of the heart-action have been out of all proportion to the amount of local disease of the lung.

On May 16 the treatment with suprarenal extract was begun. Thirty-six pigs' suprarenals were obtained at the time of slaughtering, cut up finely, thoroughly powdered with pestle and mortar, and to this mass about six ounces of pure glycerin were added, and the whole allowed to macerate for thirty-six hours in a refrigerator. The mixture was then filtered several times through fine-meshed gauze. The filtrate consisted of a reddish-brown syrupy fluid of a rather disagreeable odor. After filtering there were thirty-eight drachms of the extract, so that one drachm corresponded to a capsule. The patient began with half a drachm of the extract three times a day.

The patient's blood-count when he began the treatment was: red corpuscles, 4,564,000; leucocytes, 6600; hæmoglobin, eighty-five per cent.

On May 20 tubercle bacilli were found in the expectoration for the first time. The cough and shortness of breath had been very much better. Prior to the treatment with the suprarenal extract the patient had gained one pound. The note by Dr. Thayer on May 24, eight days after beginning the use of the extract, was: The patient looks brighter and says he feels better. The pulse, which had ranged from 120 to 140, is now 100. He has gained three pounds in weight.

On June 6 the amount of the extract was increased so that he took the equivalent of three glands daily. Numerous careful blood-counts were made, and a differential count of the leucocytes. There was moderate leucocytosis; there were no nucleated corpuscles. The number of reds on June 6 was about 4,000,000 per cubic millimetre; leucocytes, 8000.

After May 20 the patient's temperature remained normal.

During the week ending June 16 the patient gained five and a half pounds,—a gain of nine and a half pounds since the use of the extract was begun. The patient continued to take the equivalent of three glands daily. A note by Dr. Thayer on June 19 is as follows: Temperature has been quite normal for more than a month. The pulse, which had ranged between 120 and 140 to the date of beginning the extract, has gradually fallen until during the last week the range was between 84 and

104. The amount of sputa has diminished to less than forty cubic centimetres in the day. The patient says he feels much better; his appetite is good, and he looks a great deal brighter. The condition of the lung has improved, and the friction murmur is no longer heard.

On June 28 tubercle bacilli were found. The treatment was continued throughout July and August, and in spite of the hot weather he improved progressively. The gain in weight was remarkable. In July his weight increased from one hundred and ten and a half to one hundred and fifteen pounds. In August, during the very hot weather, he lost again slightly in weight.

He left the hospital on September 10. The change in his condition had been very remarkable. When admitted he could scarcely walk to the bed, and was profoundly asthenic and emaciated. The general appearance had improved wonderfully; he was bright and active, and said he felt vigorous. His weight on discharge was one hundred and eighteen pounds, a gain of nineteen pounds. The pigmentation was unaltered.

Since his discharge he has been at work, and has reported at the hospital occasionally. He felt so well that throughout the latter part of November and December he remained without any of the suprarenal extract, and he lost three pounds in weight in that time. His condition to-day—January 15, 1896—is as follows:

The color is good. To me his face looks a little less pigmented, but Dr. Thayer, who had the patient in charge during the summer, while he was in the ward, does not think that there is any material change in the face, but thinks the discoloration is less intense on the trunk. It is still of a very advanced grade, such as is seen only in the most typical cases of the disease. The small patches of pigmentation on the palate have disappeared. The local condition in the lung has cleared, and there are now only a few râles to be heard occasionally on coughing. The friction is still audible just outside the right nipple. The change in the patient's general vigor is remarkable. He walks briskly, is active, energetic, in very good spirits, and says that he is as well as he ever was in his life.