

## **A case of Addison's disease / by William Pepper.**

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## A CASE OF ADDISON'S DISEASE.

By

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[Read January 7, 1885.]

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H. P., 27 years of age, married, with a healthy family, was born and always lived in the mountains of Pennsylvania. He worked hard, and often, when in the woods hunting or lumbering with men stronger than himself, overtaxed his strength. On one occasion he hurt his back so badly as to lay him up for a week or so. He often wrenched his back in lifting heavy articles. He drank a little whiskey, smoked a little, chewed to excess, and ate his meals rapidly, but for a man in his position his habits were good. He never had syphilis, and was never exposed to such depressing influences as worry and anxiety. There was no inherited family predisposition. He had the ordinary diseases of childhood, but was usually well until the age of twelve years. At that time his stomach began to trouble him, and he noted that indiscretions in diet would cause dyspepsia, with its usual symptoms, which would disappear when the diet was regulated. As he grew older, these symptoms of dyspepsia became more frequent and troublesome, and were often associated with spells of diarrhœa and colicky pains in the abdomen. Between the attacks the bowels were regular.

During the past six years his strength gradually failed, and for a year he had been unable to follow his accustomed avocation. His flesh was well preserved until six months before coming under observation, within which time he had lost ten pounds. For three or four years, he had had a pain between the shoulders, which, however, was not very troublesome. During the past few months, the dys-

pepsia had been almost constant, and more troublesome, and in addition there was a continual distress, and pain across the stomach running through to the back. There never were spells of vomiting with the dyspeptic symptoms, and during all this time the appetite was uniformly good.

Two and a half years ago, he noticed that his color was darker than usual. This he attributed to exposure to the sun, and during the following winter the discoloration grew less distinct, but it returned with the return of spring, and last winter, instead of growing less, the color became more intense.

Upon entering the wards of the Philadelphia Hospital, October 1, 1884, he thought that the color of the cheeks was lighter than it had been six months before. The general condition had failed no more rapidly since the appearance of the discoloration than it did before. His hair had begun to turn gray at the age of twenty.

The notes upon admission state that he was apparently a well-nourished man, with dark brown hair sprinkled with gray; the pupil of the right eye a trifle larger than that of the left (probably physiological). "He takes very little interest in anything but his family, and when away from home he suffers acutely with homesickness. Last spring he came to the hospital to stay, but ran off in twelve hours, stating that he could not stand the place. His mental condition is good, and he sleeps well. The tongue is moist, with only a little yellow coat. After eating he has a feeling of fulness in the stomach, and has a dull pain across the pit of the stomach and through into the back. This is aggravated by the presence of food, and is sometimes sufficiently severe to keep him awake. There is no tenderness, no nausea or vomiting. The bowels are costive, and since being more careful in his habits he does not have spells of diarrhoea as frequently as formerly. He has great weakness and a feeling of excessive muscular debility, and any exertion produces breathlessness, palpitation of the heart, and complete prostration. There are occasionally attacks of palpitation and short breathing even without exertion.

"The whole surface of the body is darker than natural, the discoloration being most marked on the face, where it extends from a little under the roots of the hair down over the neck to the line of

the collar, and on the backs of the hands, extending to above the wrists, where the color is, at least, as dark as the complexion of a mulatto. It, however, has not the yellow tinge of the mulatto, but is more of a mahogany tint, as though stained with walnut-juice. It is not uniform, but is distributed in patches with little intervals of lighter-colored skin. It is not at all affected by pressure, and is not bounded by a sharp line of demarcation, but fades gradually into the surrounding skin. The lighter-colored skin is somewhat darker than the average. There is no swelling. The whole surface of the body is darker than usual, and, as he states that it is darker than it used to be, we may say that it is darker than normal. He states that the color deepens as the surface becomes cold. The finger-nails are of the ordinary tint, and contrast strongly with the dark fingers. The mucous membrane of the inside of the lips is darker than natural, and scattered over it are irregular, sharply defined purplish patches."

An examination of the blood was made by Dr. William E. Hughes, to whom I owe this admirable history. The number of red globules was 5,130,000 to the cubic millimetre. There were 9000 white corpuscles to the centimetre, or 1 to 560 red. The red globules were a trifle smaller and a little paler than normal, and some of them deeply pigmented. The white were normal in size, some containing pigment-granules, and some deeply pigmented. There were also some free pigment-granules. I must add that his temperature was normal, or even below normal, as a rule, though on one or two occasions there was a rise to  $99\frac{1}{2}^{\circ}$  or even  $101^{\circ}$  or  $101\frac{1}{2}^{\circ}$  for a few hours, apparently due to gastric irritation.

He was confined to bed. His diet was carefully regulated, and was varied from time to time to suit the failing powers of the stomach. For the most part it consisted of milk. Several applications of the actual cautery (Paquelin's) were made over the renal region posteriorly. Internally, he took aromatic spirits of ammonia, which proved an acceptable and useful stimulant to him. He lost strength steadily and quite rapidly, and from the date of admission, October 1st, to the date of death, November 18th, he lost twenty pounds—from one hundred and twenty-four down to one hundred and four pounds. The pulse grew feeble and rapid. There were from time to time unaccountable sudden failures of appetite and digestive power.

He was very low-spirited, and complaining constantly of distress and of inability to sleep quietly. Vomiting occurred occasionally during the last three weeks of his life. The pulse was barely perceptible at the wrist for two weeks before death. The discoloration grew somewhat darker towards the close. For the last forty-eight hours he was profoundly unconscious.

The post-mortem examination was made five hours after death by Prof. William Osler, assisted by Drs. Formad, Hughes, and Sykes.

Body of medium size, fairly well-built man; moderate wasting, particularly of the face. The skin dark in color, most marked on face, neck, hands, penis, and scrotum. In those regions the color is that of a light mulatto. Rigor mortis not present. Panniculus on abdomen about one-half inch in thickness. Rectus and other abdominal muscles are of a dark-red color. The omentum is fatty, adherent to the parietal peritoneum in right hypochondrium and to front of cæcum. There is extensive perihepatitis and adhesion of the liver to the diaphragm by fibrous bands, which can with slight difficulty be torn through. The surface of rest of parietal peritoneum is a little opaque. Membrane over small intestines is smooth; over mesentery presents numerous superficial fibroid opacities (these are specially seen towards the root of the mesentery). The mesenteric and general subperitoneal fat *considerably increased* in amount. The coils of small intestines are somewhat shrunken. The stomach is also small and atrophic. In the preliminary dissection, the right supra-renal capsule was found firmly attached to the under surface of liver and to the side of inferior cava. No special thickening about its outer surface, but there is a fine capsule of fat. On attempting to separate the kidney and supra-renal capsule from the liver, firm fibrous union is found. The cardiac end of stomach is attached to the enlarged left supra-renal capsule, and the spleen and tail of pancreas are closely united to it. Kidneys, supra-renal capsules, spleen, and retro-peritoneal tissue taken out together for dissection.

*Lungs.*—Pale; crepitant throughout; a little congested at bases; no pleuritic adhesions; no caseous masses; one or two small pigmented nodules; bronchial glands not enlarged.

*Heart.*—Loose dark clots in right auricle, projecting into veins;

same in right ventricle; left ventricle in rigor mortis; left auricle contains a dark clot; valves healthy; no atheroma of intima of aorta; muscular substance a little rusty-brown in color; does not look fatty.

On removal of heart, a very considerable amount of blood exuded from the veins.

*Liver.*—Perfectly normal-looking, good color, and plenty of blood; the bile-vessels are normal.

*Stomach* is very small; contains only bile-stained fluid; the cardia a little thin; mucous membrane normal.

*Kidneys.*—Of average size; color good, except immediately beneath enlarged capsules, where the tissue is soft, pale, and many of the tubes are fatty

*Intestines.*—Cæcum and colon full of firm, hard scybala; ileum normal; Peyer's glands distinct; two inches from cæcum one long patch begins, which measures six inches in length, and presents in a typical manner the shaven-beard appearance; the solitary glands are a little swollen and prominent. Bladder is full of urine; the mesenteric glands not swollen; the mesentery is very fat.

*Spleen.*—Slightly enlarged; closely united to diaphragm and left supra-renal by old adhesions; pulp of medium consistency.

*Lymph-glands.*—Some of the lymph-glands of the abdomen, particularly those of the mesentery and retro-peritoneal, are swollen, grayish-red in color, and several of them contain grayish, translucent nodules, with opaque centres, looking like small tubercles; some as large as peas, and the centre distinctly caseous.

*Supra-renal Capsules.*—The *right* is closely adherent to the kidney, diaphragm, and inferior cava, and to the liver above. It is two and a half inches in length, one and three-quarter inches in vertical diameter, and rests upon the top of kidney, not descending into the hilus. It is exceedingly hard and firm, and on section shows a peripheral, dense, grayish-white, partially translucent tissue, and centrally three or four yellow, caseous masses, separated from each other by strands of fibrous tissue of almost cartilaginous hardness.

*Left Capsule* is much larger; covers the top of kidney, and descends on its inner surface well into the hilus, measuring three and a quarter inches in length, two inches vertical, and two and a half inches in thickness. The lower end of the spleen is firmly united to

it, and tail of pancreas is also attached to it. The splenic artery and vein run along its anterior surface in the thick fibroid fatty tissue, and at one point the calibre of these vessels is very materially reduced.

The mass is extraordinarily firm, cuts with the greatest resistance, and presents identical characters with the right, except that at the most anterior region there is a pocket of creamy-looking pus, and at a central spot the caseous matter has undergone softening. At the most anterior part, close to the cœliac axis, the left semilunar ganglion is directly embedded in the fibrous tissue, and can be seen as a rounded grayish mass about one-quarter inch in diameter, and three small nerve-fibres can be seen passing from the ganglia in the dense tissue about it.

*Semilunar Ganglia.*—The splanchnic nerves look normal, and can be traced directly into the semilunar ganglia; as the right passes on the crus there is a small ganglion developed upon it; it is free from all adhesions; the branches are readily dissected and look normal. The left semilunar ganglion is directly involved in the fibrous tissue of the supra-renal capsule, as stated above; the nerves of the left ganglion, as they pass out, are involved in the cicatricial tissue of the left suprarenal capsule, and cannot be dissected, but can be seen on section; several filaments can be traced to the branches of the cœliac axis.

At the concave margin between the two lunar ganglia there is a small dark-yellow body, probably a supernumerary adrenal. A bunch of normal-looking nerves passes from the right directly to the left semilunar ganglion. The branches passing to the right suprarenal can be traced in the fat and along the artery; they are neither numerous nor large.

#### MICROSCOPIC EXAMINATION.

*Left Semilunar Ganglion.*—Teased portions from the centre of it show innumerable ganglion-cells, most of which are very darkly granular, but the nuclei and, in places, the nerve-processes can be distinctly traced; nerve-fibres, medullated and non-medullated, are

numerous, and in many places show remarkably slight change; in some cords the fibres are less distinct, fat-granules numerous, nuclei elongated, and the process of disintegration appears to be going on. In sections the ganglion-cells can be seen separated from each other by a considerable amount of nucleated tissue. In places they are still closely set together, but in others they are in a great part atrophied, and only one or two can be seen in the fibrous connective tissue, being recognized by the dark granular pigment. The section showed the nerve-fibres through the hard sclerotic tissue, and the chief change noticeable is a marked elongation of the nuclei, and, indeed, a multiplication of them.

*Right Semilunar Ganglion.*—The cells are very readily isolated; the nuclei distinct, and in each instance surrounded by tolerably dense, dark pigment-granules; the nerve-fibres appear normal.

Several portions of nerve-fibres passing out from the right semilunar ganglion were examined, none of which showed any special change; the cord of the thoracic sympathetic and the ganglia normal; the cells of the latter moderately pigmented.

*Marrow from Rib.*—It is dark red in color, does not look fatty, and presents the character of ordinary red marrow; many of the colorless cells are very granular and of average size; no great number of small ones; nucleated red blood-corpuscles tolerably abundant; no cells containing red blood-corpuscles.

*Marrow of Vertebra.*—Rather more fatty, of a deep, rich color, and differs further from the fact that it contains a number of cells containing red blood-corpuscles; in places these are extraordinarily numerous and large.

*Heart-muscle* of left ventricle in a state of brown atrophy; a few of the fibres present fat-granules throughout them.

*Spleen-pulp.*—In addition to the ordinary elements, there are also very numerous corpuscles containing red blood-corpuscles in all stages of degeneration.

It will be seen that this case was a very typical one of Addison's disease, both as to its clinical symptoms and as to the lesions present. The absence of anæmia is shown by careful examination of the blood, indicating



that the main cause of the symptoms was to be sought in connection with the sympathetic nervous system; and the extensive and positive lesions carefully made out by Prof. Osler in this case fully confirm this view. Undoubtedly in many cases of Addison's disease the chief cause of the symptoms is to be found in such nervous implications and lesions; but in other instances it is clear that there is a progressive anæmia associated which must play a part in causing the symptoms. In cases where the exudation in the capsules undergoes cheesy degeneration with absorption of the disintegrating organic materials, it is not improbable that there may also be an element of sepsis which would aid in inducing cachexia, even if it did not lead to tuberculosis, which, as is well known, not rarely appears in the late stages of Addison's disease.

The frequent allusion to severe strains or injury of the back in the history of this case suggests the possible origin of the disease of the capsule from repeated irritations caused by violent muscular strain or by sudden shocks to the frame. It will be noted that in a considerable proportion of cases this disease has arisen in subjects liable to such causes as the above.

[After the reading of the preceding paper:—]

Dr. FREDERICK P. HENRY remarked that this was undoubtedly a genuine case of Addison's disease, and remarkably free from the frequent complications of that affection. The rarity of Addison's disease in this country may be judged of by the fact that in the eleven volumes of the *Transactions of the Pathological Society of Philadelphia*, there are reports of only two cases, and these were made by Dr. Henry, in whose practice they occurred. They are to be found in vols. v. and x. The specimens from one of the cases are now in the museum of the Episcopal Hospital. Dr. Hughes's report upon the condition of the blood in this case is very interesting. Most writers upon Addison's disease are accustomed to attribute the profound adynamia, so characteristic of the affection, to a high degree of general anæmia, in spite of the absence of any facts to support such a theory. This adynamia is due to an insufficient supply of blood, although of good quality, to the supra-diaphragmatic portion of the body, the result of an accumulation of blood in the abdominal bloodvessels caused by vaso-motor paralysis. Free pigment in the blood has only been once before observed, so far as the speaker is aware, by Van den Corput (*Gaz. Hebdomadaire*, 24 Juillet, 1863). The changes observed in the sympathetic ganglia are of undoubted interest, but it must not be forgotten that typical cases of Addison's disease have been observed without perceptible lesion of these ganglia. Eulenberg and Guttman (*Journal of Mental Science*, January, 1879) have collected twenty cases in which changes were found in the nerves of the supra-renal plexus and the ganglia of the solar plexus, opposed to which they place twelve cases in which careful examination demonstrated no change whatever. The positive observations included fatty degeneration (found by Queckett in one of Addison's original cases), swelling and redness of the nerves of the lesser splanchnic and ganglia of the solar plexus, atrophy, pigmentation of the ganglionic cells, increase of connective tissue in the ganglia and in the neurilemma of the nerve-fibres, and caseation of the semilunar ganglia.

Primary affection of the abdominal sympathetic has been appealed to as a cause of numerous other affections, notably of Bright's disease, by Drs. Da Costa and Longstreth, on the basis of careful microscopic examination of the ganglia in nine cases (*Am. Journ. Med. Sci.*, July,

1880). The accuracy of their description of the condition of the ganglia has been confirmed by Dr. Robert Saundby (*Brit. Med. Journ.*, January 13, 1883), whose observation has been still more extensive (fifteen cases), but he entirely dissents from their conclusion as to the primary nature of the sympathetic affection, and points out that similar changes have been found in the ganglia in diffuse eczema, pseudo-hypertrophic muscular paralysis, pernicious anæmia, glio-sarcoma of the brain, general paralysis of the insane, cholera, and diabetes. He points out, in conclusion, that Giovanni (*Patologia di Simpatia*, Milan, 1876) "found cellular infiltration of the sympathetic ganglia in an immense variety of visceral and general diseases, showing that structural changes in the organs are very generally accompanied by signs of irritation in the ganglia."

It is not necessary, however, that there should be a destructive lesion of the solar plexus and semilunar ganglia in order to produce vaso-motor paralysis of the abdominal vessels. Irritation of a sensory nerve produces vaso-motor paralysis in the irritated region, and the well-known experiments of Goltz (*Klopfversuch*) have shown that irritation of the intestines produces complete vaso-motor paralysis of their bloodvessels, causing thereby so great an accumulation of blood that the animal shows symptoms of syncope, the same as if it had been bled copiously. In Addison's disease, from the beginning of the morbid deposit in the medullary substance of the supra-renal capsule, an irritation is transmitted to the semilunar ganglia and solar plexus, by which means a vaso-motor paralysis of the abdominal vessels is produced, as in the experiments of Goltz. This constant hyperæmia leads to enlargement of the glands of Brunner, the solitary glands, and Peyer's patches, so constantly met with, and, when more intense, to catarrh and ulceration of the intestinal mucous membrane. It also accounts for the dark color of the liver, spleen, kidneys, and pancreas so often observed, as well as for the brown color of the peritoneum sometimes noted, notably in a case of Severini. Indirectly it explains the anæmic and dry condition of other parts of the body, and fully accounts for the symptoms of muscular weakness, syncope, and gastrointestinal disturbance.

In the case under discussion no mention is made of the size of the heart, which is noted as being small in numerous autopsies, and the seat of fatty degeneration in several. On account of the abdominal hyperæmia, the quantity of blood reaching the heart at each diastole

is less than under normal circumstances, and thus the invariable weakness, smallness, and softness of the pulse are explained. The heart is never normally distended, and thus its cavity becomes permanently diminished. On account of these heart-changes the abnormal distribution of the blood due to the abdominal hyperæmia is still further facilitated. Anæmia of the central nervous organs explains the dizziness, tendency to somnolence, lassitude, and lowness of spirits so often observed; also attacks of prolonged prostration and loss of consciousness, with convulsions; sometimes a condition of collapse that has been compared by Wilks to that of cholera. All the nervous symptoms of Addison's disease are not, however, to be explained by the theory of cerebral anæmia: such, for example, as restlessness, sleeplessness, psychical disturbances, clonic spasms in various muscle-groups, and sensory and motor paralyzes. In such cases there is probably irritation of a cerebro-spinal vaso-motor centre, causing local hyperæmias of the central nervous organs. There are two paths by which such a reflex action may travel: 1, through the cœliac axis and its connection with the medulla spinalis; 2, through the branches of the phrenic and pneumogastric distributed to the supra-renal capsules; and the degree of this irritability probably varies in each individual.

In connection with the abnormal deposit in the skin in Addison's disease, certain observations of Thudichum are of great interest. For sixty-five consecutive days, he examined the urine of a patient of Dr. Burdon Sanderson. Without complicating fever or diarrhœa, there was a great diminution in the daily amount of urine excreted; the sp. gr. was 1020 and upwards, and the reaction acid. The observations were chiefly directed towards the determination of the percentage of uromelanin, omicholin, and uropittin, three products of decomposition of urine-pigment, of which the first is the most important. It has almost the same chemical composition as the melanin of the choroid and of the melanotic tumors, and, like the pigment in the skin, is iron-free. Thudichum found these pigments greatly reduced in amount, the uromelanin never rising above one-twelfth the normal. The speaker has been unable to find any record of a spectroscopic examination of the pigment deposited in the skin in Addison's disease, and would suggest the importance of such examination being made. There is an iron-free product of decomposition of hæmoglobin, namely, hæmatoporphyrin, which is iron-free hæmatin, the absorption-bands of

which are figured in Hermann's *Handbuch der Physiologie*, Bd. iv., Theil I. It would be interesting to compare the absorption-bands of these two iron-free pigments, both of which have their origin in the coloring-matter of the blood. It is evident that the diminution in the amount of urine-pigment may be in relation to the excess of pigment in the skin. The observations of Thudichum await further confirmation.