SOME OBSERVATIONS ON THE BLOOD-PRESSURE-RAISING SUBSTANCE OF THE ADRENALS IN ACUTE ADRENAL INSUFFICIENCY *

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By acute adrenal insufficiency is usually meant that group of cases in which, after a short fatal illness accompanied sometimes by severe gastrointestinal symptoms, sometimes by acute symptoms referable to the central nervous system, and sometimes merely by profound asthenia, or some combination of these, there is found at autopsy no adequate cause for death except some destructive process in the adrenal glands. The cases are distinguished from Addison's disease by their short course and by the absence of pigmentation. At autopsy the lesion is usually a thrombosis of the adrenal veins with hemorrhage into the medulla, but cases have also been noted of an acute inflammatory process, carcinoma, sarcoma or tuberculosis, involving the adrenal glands. Those cases of adrenal hemorrhage occurring in infants and, as is thought by many observers, resulting in some way from an acute infection, may also belong to this group. As to whether symptoms referable to an insufficiency of the adrenals can be recognized in the course of acute infectious fevers — a view championed especially by Sergent and other French clinicians — it is not the province of this paper to discuss, nor shall I detail the clinical symptoms that have been described in connection with the cases of acute adrenal insufficiency which have been reported. It is sufficient to remark that the cases may present any of the symptoms that accompany Addison's disease except the pigmentation, and that the symptoms are usually severe. A collection of cases was made by Lavenson¹ in 1908, and Sergent² has critically discussed the subject.

REPORT OF CASE

The patient whose case I wish to report was admitted to the Pennsylvania Hospital, Feb. 4, 1911, in the service of Dr. A. V. Meigs, to whom I am indebted for the notes on the clinical history.

History.—The patient was an Austrian, 40 years of age, with delirium and muscular twitchings. The history obtained was very meager on account of his

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1. Lavenson, R. S.: *THE ARCHIVES INT. MED.*, 1908, ii, 62.

2. Sergent: *Rev. mens. de méd. int. et de therap.*, 1909, i, 801.

mental condition and the fact that he spoke no English. He had always been well until two days before admission, when, following excessive indulgence in oysters and whisky, he became ill.

Examination.—On admission, examination revealed a muscular, well-nourished man with expressionless face and staring eyes. The muscles of his face, arms and hands were continually twitching and he continually muttered sentences that an interpreter said referred to obscene things. Both pupils were moderately dilated and equal. The breathing was jerky and spasmodic. Physical examination was otherwise negative.

Course.—During the three days following, the patient was noisy and apparently irrational. He passed urine and feces involuntarily. The blood-pressure was unfortunately not taken. The temperature ranged from 99 to 101.8, averaging about 100, and the pulse varied between 86 and 136. The urine showed a moderate cloud of albumin, but no casts. Three days after admission the pulse became very weak and rapid, the face cyanotic and the patient died.

Autopsy was performed one-half hour post mortem, and the following is an abstract of the autopsy protocol (A. 1416).

Fig. 1.—Injection of 1 minim of epinephrin solution (1-1000). In this and all following tracings, the upper line is the blood-pressure, the middle line is the signal and the lower line is the time in seconds. All injections of tissue extracts were 2 c.c. of an extraction with ten volumes of normal salt solution.

Fig. 2.—Injection of extract of normal-appearing portion of right adrenal.

MACROSCOPICAL POST-MORTEM EXAMINATION

The body is that of a large, well-nourished man, 171 cm. in length. There is no rigor mortis. There is slight post-mortem discoloration of the back, neck and head, but no abnormal pigmentation of the skin and mucous membranes. There is no edema of the extremities.

Abdominal Cavity.—There is a well-marked panniculus adiposus, and the serous surfaces are everywhere smooth and glistening. The appendix is converted into a fibrous cord.

Thorax.—Both lungs are firmly bound to the chest-wall by fibrous adhesions. The left lung is everywhere crepitant, and on section the cut surfaces are pale and appear normal. At the apex is a firm scar. The bronchial lymph-nodes are small and pigmented black. The right lung shows some irregular patches of bronchopneumonia in the lower lobe, otherwise it is crepitant and pale and dry on section. The bronchial lymph-nodes are small.

Pericardium.—The pericardium is smooth and contains no excess of fluid.

Heart.—The heart weighs 300 gm. The cavities and valves and coronary arteries appear normal. The myocardium is firm and pale brown in color.

Spleen.—The spleen weighs 190 gm. and shows no gross lesions.

Liver.—The liver weighs 1,250 gm. and measures 24 by 16 by 6.5 cm. The capsule is smooth and rather dark brown in color. Scattered beneath the capsule there are rather numerous small, light gray, rather opaque areas, about 1 mm. in diameter. On section the liver is rather pale reddish-brown in color, and scattered through the parenchyma there are numerous small gray, semi-translucent areas, about 1 mm. in size.

Kidneys.—The kidneys weigh 300 gm. and show nothing abnormal.

Adrenals.—The right adrenal is much enlarged and weighs 17.5 gm. It has approximately the same shape as the normal adrenal, but is quite firm and rubbery. The surface is rather opaque and light yellow in color. At the superior portion it has a normal appearance and the normal-appearing portion weighs approximately 2.5 gm. The remainder of the gland is firm and section is made easily. The cut surface presents a smooth, uniform, rather firm, very pale yellowish appearance and is sharply marked off from the normal-looking adrenal, which occupies the superior extremity of the gland. The left capsule, when dissected

Fig. 3.—Injection of extract of left adrenal.

Fig. 4.—Injection of extract of tuberculous portion of right adrenal.

free from the surrounding fat, weighs 0.8 gm. About one-half of this gland consists of what appears to be a fibrous tissue, which on section is quite firm and in one place is seen to be a somewhat softened, caseous-appearing area about 2 mm. in diameter. The remainder of the gland is about 4 mm. in thickness and on section shows a light yellowish-brown tissue which has only a slight resemblance to the adrenal tissue.

Urinary bladder, prostate, stomach, intestines, pancreas, larynx, pharynx and trachea appear normal.

Thyroid Gland.—This is of moderate size and on section is reddish-brown. One large normal-appearing parathyroid is found on either side.

Aorta.—The aorta is smooth, elastic and shows a slight yellowish flecking of the intima.

Brain.—There is a congestion of the pial vessels and the pia is distended with clear fluid. The cortex is in no place opaque and the meninges at the base and over the cortex appear normal. The lateral ventricles are slightly dilated and filled with clear fluid. No gross lesions are found on section of the brain substance.

MICROSCOPICAL EXAMINATION

Sections of the heart, spleen, kidney, pancreas, thyroid, parathyroids and pituitary body show nothing unusual. The lung shows some small areas of broncho-pneumonia. In the liver the small opaque areas are epithelioid tubercles, some of which show a slight central caseation.

Adrenals.—The right adrenal shows an extensive caseous tuberculosis. There is in the large yellowish portion of the right adrenal an extensive destruction of the gland, only a few cells of the zona glomerulosa being left. Around the pink-staining caseous tissue there are seen epithelioid and lymphoid cells and an occasional giant cell. Toward the superior pole the destruction is less extensive, and here are seen normal-appearing medullary and cortical tissue.

Left adrenal: That portion of the gland which grossly appeared fibrous shows a caseous area in the center, encapsulated by connective tissue infiltrated with lymphocytes. In one portion there is a nodule of cells resembling adrenal cortex. Sections of the glandular portion of this gland show several areas of tuberculosis with caseation and epithelioid and giant cells. There are a few cells in places which resemble adrenal cortex but most of the cells resemble adrenal medulla.

Bacteriology.—Cultures from the heart's blood remain sterile.

Fig. 5.—Injection of second extraction of normal appearing portion of right adrenal.

Fig. 6.—Injection of second extraction of tuberculous portion of right adrenal. Dog 2.

ANATOMICAL AND MICROSCOPICAL DIAGNOSIS

Tuberculosis of adrenals and liver. Edema of brain. Bronchopneumonia. Scar at apex of right lung. Chronic adhesive pleuritis. Chronic obliterative appendicitis.

It was thought of interest to determine if possible, whether the adrenals from this case contained the usual blood-pressure-raising substance, and if so, whether the amount was the same as that from normal human adrenals. Accordingly, the adrenal tissue present was divided into three portions: The first consisted of 1.5 gm. of the normal-appearing portion of the right adrenal, the second of 8 gm. of the tuberculous portion of the same gland, and the third consisted of about 0.5 gm. of the left adrenal. Each of these was ground up in a mortar with sea-sand, glass and ten volumes of normal salt solution. Each was then centrifugalized in a high-power centrifuge and the supernatant fluid used for the experiments. A second extraction of the residue was made in a similar manner and kept separately. These extractions were done immediately and kept on ice. The following day, a small dog was anesthetized and blood-pressure was taken from

the femoral artery. Injections of 2 c.c. of each of the extracts were made into the femoral vein. Tracings were also made from similarly prepared extracts of adrenals from three cases which showed no gross or microscopic adrenal lesion. One of these individuals died from chronic valvular disease of the heart, one from acute encephalitis and one from acute lobar pneumonia. For comparison, in each case one minim of a solution of epinephrin (adrenalin, 1:1000, Parke, Davis & Co.) was injected, the same solution being used each time.

The extract from the much atrophied left adrenal, which microscopically showed principally medullary cells, caused a slight but definite rise in blood-pressure (Fig. 3), while the extract of the tuberculous part of the right adrenal caused none (Fig. 4).

The tracings from the normal-appearing portion of the right adrenal (Fig. 2) showed that it contained blood-pressure-raising substance, and that the rise in pressure obtained with 2 c.c. of the extract from this portion of the gland was quite similar to that caused by the injection of one minim of epinephrin solution (1:1000) (Fig. 1). Each of the three tracings made from the normal adrenal extracts, however, gave a much more marked rise in pressure than that obtained from one minim of epinephrin solution (1:1000) (Figs. 7 and 8). No rise in pressure followed injections of the second extraction of the tissue (Figs. 5 and 6). It was assumed that all the principle had been obtained in the first extract.

Fig. 7.—Injection of 1 minim of epinephrin solution (1:1000).

Fig. 8.—Injection of extract of normal adrenal gland.

It seems probable that in this case, although a portion of adrenal tissue having a relatively normal appearance remained uninvolved in the tuberculous process, yet demands were made for adrenal secretion which this small amount of remaining tissue could not supply and that there ensued an acute adrenal insufficiency. That there was a diminution in the blood-pressure-raising substance contained in the glands, as compared with normal glands, indicates that the deficiency may have also involved the other functions or other internal secretion of the adrenal, but of this one can only conjecture. It is interesting that there were no histological evidences of any abnormality in the other organs of internal secretion.

In some respects the above case is analogous to a case of experimental acute insufficiency of the parathyroid glands that I observed during the past year.³ In the experimental case, two operations were performed on a dog at an interval of about three weeks. At the first operation, two

3. Cooke: Jour. Exper. Med., 1911, xiii, 439.

parathyroids were removed from each side. As the animal developed no symptoms, a second operation was performed and one lobe of the thyroid was removed. The animal recovered rapidly from the operations and showed no symptoms of parathyroid insufficiency, except a slight increase in reflexes and in muscle irritability. Ten months afterward, however, the dog suddenly developed violent tetany with vomiting, dyspnea and convulsive attacks, and died after three days. At autopsy no lesions were found. Serial sections of the remaining thyroid lobe showed a small imbedded parathyroid about 1 mm. in diameter.

It was assumed that in this case, the small amount of parathyroid tissue remaining had been sufficient for the ordinary needs of the animal, and when, from some unknown cause, the demand for parathyroid secretion by the organism exceeded the capabilities of this small nodule, an acute fatal parathyroid insufficiency developed.

In 1895 Oliver and Schäfer⁴ found that injections of the extracts of the fibrocaseous adrenals from a case of Addison's disease had no effect on blood-pressure, and Crowell⁵ made a like observation in two similar cases. I have been able to find no other physiological study of diseased adrenals.

If one can compare the tracings obtained by injections of extracts of adrenal glands made post mortem, the marked difference observed in the extracts of normal adrenals and that of the tuberculous adrenals from the case here reported indicate that there was a rather marked functional deficiency in the latter and that this decreased function involved even adrenal tissue which showed no gross or microscopic lesion.

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4. Oliver and Schäfer: *Jour. Physiol.*, 1895, xviii, 230.

5. Crowell: *Proc. New York Path. Soc.*, 1909, new series, ix, 75.