A SYNDROME RESEMBLING ADDISON'S DISEASE, WITH SEVERE ANAEMIA, STEATORRHOEA, AND MELANURIA

BY

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A case resembling Addison's disease with a severe normocytic normochromic anaemia, which was at first treated as a macrocytic anaemia of unknown aetiology, is here described. Addison (1855) in his original description of the disease mentioned anaemia, but it is not accepted nowadays as a common or characteristic feature of the syndrome (Goldzieher, 1939).

Case Record

Miss A., aged 22, had a sudden attack of stomatitis in Feb., 1943. At times it was so severe that for several days she was unable to eat or drink. It continued until her admission to a military hospital on July 5, 1943. She had post-prandial upper abdominal pain and loose motions. Amenorrhoea had been present for three months. She was extremely ill, had a lemon-yellow tint, and was wasted. Shallow ulcers were present inside the mouth. The spleen was not palpable and there were no changes in the nails. Blood picture on admission: haemoglobin, 36%; R.B.C., 1,600,000; colour index, 1.1; W.B.C., 2,000, with a normal differential white count; reticulocytes 0.1%; polychromasia; occasional Howell-Jolly bodies; marked anisocytosis; one primitive megaloblast, and one normoblast. Red-cell fragility was normal.

She was treated with liver extract intramuscularly, iron, marmite, vitamin C, vitamins A and D, nicotinic acid, and a high-calorie diet. The stomatitis recurred several times. She apparently improved, and on discharge the blood picture was: haemoglobin, 92%; R.B.C., 4½ millions; W.B.C., 9,000. A test meal showed that free acid was present. She was still feeling subnormal, however, and the amenorrhoea persisted. She was discharged from the Forces in 1943, all treatment being discontinued.

Two weeks before admission to the County Hospital, Pembury, on March 8, 1944, she had an attack of "influenza." A blood count showed R.B.C. 2,000,000. Liver injections were given without response. The temperature persisted.

On admission she complained of lack of energy, dizziness, especially on standing, cold hands and feet, and sore mouth. There were no previous illnesses. Her mother, two stepbrothers, and two stepsisters were alive and well. Her father died from an unknown cause.

Examination.—The temperature was 99.5°. She was a thin short girl, and lay in bed, making few spontaneous movements. She had a pale waxy appearance and there were numerous dark-brown pigmented spots on the limbs, trunk, and face, none exceeding 3 mm. in diameter. She stated that these spots first appeared when she became sick in Feb., 1943. They began to disappear when her condition improved in the military hospital, but have recently been increasing. The apex of the heart was 3½ in. from the midline in the fourth left intercostal space; there was an apical systolic murmur. The blood pressure was 86/34 mm. Hg. Lungs, normal. The tongue was clean and not abnormally smooth. There were a few shallow ulcers on the inner side of the lip, 3-4 mm. in diameter. They had a greyish base and red periphery, and in appearance were identical with those of aphthous stomatitis. Numerous pigmented spots were present on the hard palate. The liver and spleen were not palpable. C.N.S., normal. Urine: Albumin, nil; sugar (Benedict), nil; reaction, acid; specific gravity range, 1010-1030; volume, maximal 25 oz. daily, minimum 6 oz. daily; average daily volume of urine, 20 oz., dark orange-yellow with a tinge of brown; no blood and no casts. Blood examination showed: haemoglobin, 34%; R.B.C., 1.55 millions; colour index, 1.1; reticulocytes, 1%; mean cell diameter, 7.7 µ; W.B.C., 9,400—polymorphs 70%, lymphocytes 18%, large hyalines 4%, eosinophils 8%; anisocytosis and polychromasia present.

In view of the original diagnosis the patient was given 2 c.cm. of neohepatex daily for six days, and two pints of blood were transfused. No improvement followed. The blood pressure did not rise, there was marked asthenia, and the reticulocyte count remained at 1%. From the seventh day (March 15) 5 c.cm. of extract of suprarenal cortex (B.P.C.) was given intramuscularly daily for six days, and then desoxycortone acetate 10 mg. daily for eight days—i.e., until March 29. The blood pressure rose rapidly (March 23). The reticulocyte count began to rise between March 18 and 28. It was found that 15 mg. of desoxycortone acetate every other day maintained the blood pressure at 120/80 mm. Hg. The haemoglobin

increased, and on discharge it was 80-85% (Haldane scale); R.B.C., 4 millions, and colour index 1.0 (Fig. 1).

The evening pyrexia fell to normal 11 days after there was clinical response to desoxycortone acetate, suggesting that the pyrexia was also due to the cortical insufficiency. This is at variance with the

FIG. 1.—Showing haemoglobin and erythrocyte response to treatment.

usually described "subnormal temperature" (Leyton, 1939), though Loeb (1940) describes pyrexia occurring pre-terminally in this disease.

On admission the sodium ion content of the blood was at a normal minimum, while the blood potassium ionic content was at a normal maximum. It is interesting to note in Fig. 2 the rise in

FIG. 2.—Showing blood ionic changes during treatment.

the potassium ion as the sodium ion falls, and vice versa. Radiographs of the chest were normal. A test meal showed that free acid was present, and a barium meal and follow-through revealed nothing abnormal.

The patient rapidly became ambulatory; her appetite was ravenous and, except for occasional headaches, she appeared to be a normal active girl. Towards the end of April the blood pressure fell steadily from 120/75 to 105/60 (Fig. 3) and general asthenia

FIG. 3.—Record of blood pressure during treatment.

returned; desoxycortone acetate and sodium chloride were pushed (NaCl 15 g. and desoxycortone acetate 30 mg. daily). She became drowsy in the second week in May, when the blood pressure rose to 140/90 mm. Hg and some oedema of the legs appeared (Loeb, 1940). Cutting down the salt intake to 4 g. daily and the desoxycortone acetate to 15 mg. every other day resulted in a marked improvement, with a fall in blood pressure. Although she would not drink much and the urinary output was not high (20 oz. daily) before treatment, the blood urea was never above 35 mg. per 100 c.cm.

Subsequent Progress

On Oct. 26, 1944, 500 mg. of desoxycortone acetate was implanted subcutaneously under local analgesia at the West Glamorgan County Hospital, Neath. On Nov. 10 the blood pressure rose to 152/100 and there was some puffiness of the face. Her blood pressure thereafter remained at a satisfactory level until Jan. 8, 1945. A further subcutaneous implantation of 600 mg. of desoxycortone acetate was made on Jan. 17. The blood picture on Dec. 11, 1944, was: haemoglobin, 86%; red cell count, $4\frac{1}{2}$ millions; reticulocytes, 0.11%.

She was readmitted to this hospital on Feb. 8, 1945. The blood picture was then: haemoglobin, 77% (Haldane scale); red cells, 3.53 millions; colour index, 1.1; white blood count, 7,400—polymorphs 67%; mean cell diameter, 7.4μ ; reticulocytes 3%. A test meal showed low free acid. Blood pressure range, 110–115/60–70. Blood ions: Na, 335 mg.; K, 22.5 mg.; chloride, 635 mg. (as NaCl); blood urea, 30 mg. per 100 c.cm. The urine contained melanin. Faeces: Neutral unsplit fat, 7.5%; free fatty acids, 13.1%; soaps, 39.3% (total fat, 59.9%). Of the faecal fat 12.5% was unsplit and 87.5% was split.

It was noticed during this admission that the incision where the crystals had been implanted was discharging a little pus. On various days during the follow-up period she discharged crystals of desoxycortone acetate equal to 300 mg. Investigations were carried out during this stage of her illness, without any further injections of desoxycortone acetate. On May 3 her blood pressure had fallen to 90/60. On May 14 asthenia was marked; B.P. 100/60. Two days later she complained of nausea, and then vomiting and diarrhoea began (May 19), and became quite persistent. Vertigo was marked. Injections of desoxycortone, 15 mg. every other day, were restarted on May 23, with rapid cessation of the gastro-intestinal symptoms. On May 25 300 mg. of desoxycortone acetate was implanted subcutaneously. On June 4 her blood pressure had risen to 120/90 and she was able to walk about the ward, feeling much improved.

Differential Diagnosis

That this patient is not suffering from *pernicious anaemia* is indicated by the presence of free acid in the test meal, the colour index range of 1.0 to 1.1, the mean cell diameter (halo method) in neighbourhood of 7.5μ , the absence of response to liver, and the dramatic response to desoxycortone acetate. Against a diagnosis of *Simmonds's disease* is the absence of a history of past pregnancy and post-partum haemorrhage, no bradycardia, no loss of secondary sexual characteristics, and the presence of pigmentation. *Pellagra* would presumably respond to liver injections, owing to the high nicotinic acid content of the usual liver extracts. The absence of reducing substance in the urine and the normal colour of the cartilages of the nose and ears are against diagnoses of *ochronosis* and *alkaptonuria*. No evidence of a primary *melanotic carcinoma* was found. The choroid appeared normal; no glandular or hepatic enlargement was present; and there was a dramatic response to desoxycortone.

Mesenteric chyladenectasis and *steatorrhoea*, with features of Addison's disease, have been described (Glynn and Rosenheim, 1938). The patient improved for a while on extract of suprarenal cortex (B.P.C.), but ultimately relapsed and died. At necropsy no lesion of the suprarenals was found, and a functional deficiency of these glands was postulated. Suprarenal insufficiency was diagnosed in a case of non-tropical sprue by Holmes and Starr (1929), but the rapid improvement in their patient with daily parathyroid extract Collip made this diagnosis, in their opinion, untenable. Functional suprarenal insufficiency has also been suggested by Gloor (1929–30) in non-tropical sprue.

Tuberculosis of the Suprarenals and the Mesenteric Lymph Glands.—The rapid response to desoxycortone acetate indicates that the steatorrhoea is due to a functional failure of absorption and not to an organic obstruction.

Idiopathic Steatorrhoea.—Many cases of idiopathic steatorrhoea have been seen in this hospital in the last few years, and a further paper on these cases is in preparation. They differ from the present case in many features. They give histories of much longer duration, the weight loss is more pronounced, and anaemia varies from hypochromic microcytic to hyperchromic macrocytic. Stools are pale and greasy, and have a persistently high total fat and split-fat content. The tongue is smooth and may show aphthous ulceration. The blood pressure is variable, depending upon the age of the patient, but the systolic was not below 100 mm. Hg except terminally or when the patient was collapsed, and then there was no response to desoxycortone

acetate. A high-potassium low-sodium diet with added potassium chloride did not produce an exacerbation of the condition or a fall in blood pressure. The blood calcium is usually low in idiopathic steatorrhoea and tetany is frequent, but there may be a hypercalcaemia in Addison's disease (Loeb, 1940). In the case under discussion the blood calcium was 10.6 mg. per 100 c.cm. Pigmentation of skin was variable, but was not present on mucosae. Test meals usually showed an achlorhydria. Oedema of the limbs, in many cases massive, was often present on admission before the onset of any treatment.

Discussion

Addison's disease is suggested by the history, pigmentation of skin and mucosae, ionic changes in the blood, low blood pressure, melanuria, and response to desoxycortone acetate—and also the fall in blood pressure and onset of vomiting, diarrhoea, and vertigo, on deliberately withholding the desoxycortone acetate (see progress notes). The marked improvement with desoxycortone acetate suggests that the entire clinical picture is a single entity.

In Addison's disease the sodium loss leads to dehydration, haemoconcentration, diminished glomerular filtration, and an increase in the blood urea. Increased protein destruction occurs in dehydration (Black, 1942), and this contributes to the raised blood urea. The normal blood urea figures in this patient suggest adequate glomerular filtration and a normal blood volume.

It was noticed that the urine was dark in colour, particularly after it had been standing for 24 hours. When at the end of April the blood pressure fell the urine became black with pigment identified as melanin. The urine eventually became paler, though its colour fluctuated considerably. The increased alkalinity of the urine on standing had resulted in the rapid oxidation of melanogen to melanin. At this time, too, it was noticed that the stools had a very foul odour, were of enormous volume, and looked like the stools of idiopathic steatorrhoea, being unformed and very greasy. In the cold they set like cooling fat; they were, however, dark and not clay-coloured. When the blood pressure rose the stools diminished in size and became almost normal in appearance, though now and again, with a bout of "general malaise" but no obvious fall in the blood pressure, blood sodium, or blood chloride ions, they would revert to a "steatorrhoic" state. In three fat estimations of these stools—the third during a remission—the total fat was 48%, 73%, and 21% respectively, and in every instance over 75% was split fat.

Fat Analysis: % of Dried Faeces

			During Remission produced by Desoxycortone Acetate
Neutral unsplit fat	6.4%	16.6%	1.6%
Free fatty acids	32.1%	24.4%	14.2%
Soaps	9.1%	32.2%	5.0%
Total fat	47.6%	73.2%	20.8%
% of faecal fat: (a) Unsplit ..	13.4%	22.7%	7.7%
" " (b) Split ..	86.6%	77.3%	92.3%

Steatorrhoea, with or without diarrhoea, has been demonstrated in Addison's disease (Zondek, 1944) and also in experimental adrenal insufficiency (Verzar and McDougall, 1936). It is suggested that the dark colour of the stools might in this patient be due to melanin.

Abnormality of cell permeability would account for the failure in fat absorption, the split fat indicating that the enzymes of the bowel were functioning normally. In adrenalectomized animals there is a marked delay in the rate of absorption of sodium, potassium, and chloride ions from the ileum (Hadfield and Garrod, 1942), and the production of a stool comparable to that in chronic jejuno-ileal insufficiency would be understandable. Actual atrophy of the alimentary canal comparable to that observed in idiopathic steatorrhoea appears to be uncommon in Addison's disease (Guttman, 1930).

A glucose-tolerance test showed a low curve but a normal fasting sugar. An intravenous glucose-tolerance test to find whether this apparent increased glucose tolerance was really due to poor intestinal absorption was not done. However, it is

known that in Addison's disease there is a greatly increased glucose tolerance due to unbalanced action of insulin, and that this state of hypoglycaemia is not corrected by injections of desoxycortone acetate.

It is stated by some authorities that "anaemia may occur in Addison's disease but is not specific" (Whitby and Britton, 1942). According to Goldzieher (1939), "anaemia, originally mentioned as a feature by Addison, is actually not a symptom of the disease. The red cell count is not infrequently increased, and the haemoglobin higher, as the result of the inspissation of the blood." Other sources (Leyton and Simpson, 1936-41) tentatively suggest that the adrenal cortical hormones might be needed for adequate haemopoiesis, but still favour failure of iron absorption, possibly due to achlorhydria, as the more likely cause.

Brown and Roth (1925) found definite anaemia in one of 17 cases of Addison's disease they observed. It showed haemoglobin 50% and 53% (Dare scale) and R.B.C. 2,960,000 and 3,280,000. The patient died three days after admission. They quote a case observed by Neumann with a red cell count of 1,120,000. The lowest figures given by Goldzieher (1939) are Hb 67%, R.B.C. 3,450,000; and by Rowntree and Snell (1931) Hb 30% and 39% (Dare scale), R.B.C. 1.5 and 1.9 millions.

The rapid response to desoxycortone acetate in the present case suggests that this substance is here essential for the normal formation of red cells. That intestinal insufficiency, as indicated by the high fat content of the stools, was not the cause of the anaemia is shown by the persistent colour index of 1.0 to 1.1 (excepting one reading of 1.3); this argues against the absence of the pernicious anaemia haemopoietic factor being the primary cause, as also does the absence of therapeutic response to liver. The normal colour index suggests that the absence of iron is not the primary cause. As there was no achlorhydria, this too could not have participated in the causation of the anaemia. Indirect evidence of the specific action of the cortical hormones in haemopoiesis is that polycythaemia occurs in suprarenal cortical excess, due to cortical hyperplasia, adenoma, or carcinoma.

It is probable, therefore, that in this case of Addison's disease the anaemia is due to the direct specific effect on the bone marrow of an absence of suprarenal cortical hormone. This may often occur in Addison's disease, but, being slight, may be hidden. In addition, diminished bowel absorption may add the features of iron- or "liver"-deficiency anaemia. To these factors must be added the effect of dehydration (probably absent in this case), acidosis, and ionic change on the individual and total red cell volume. A variable blood picture may thus result. A normocytic anaemia of this degree of severity will, in view of the failure of response to all the usual haematinics, resemble "idiopathic aplastic anaemia."

The presence of "one primitive megaloblast" in the earliest blood count does not make the diagnosis a macrocytic anaemia, as none have been seen since then. The 8% eosinophils on first admission to this hospital may have been due to the injections of liver before admission, though eosinophilia has been reported in Addison's disease by Zondek (1944).

Melanuria is rare in Addison's disease, and it is not more common or more pronounced in cases of the disease with deeper pigmentation. It is said to occur in severe cases (Karsner, 1938). This suggests that cell permeability is not dependent upon the same cortical hormone the absence of which results in pigmentation. A severe alteration in cellular permeability may therefore occur with slight or no pigmentation, and vice versa. Non-pigmented cases of Addison's disease have been described by Conybeare and Millis (1924) and White and James (1927). A severe alteration in cellular permeability might result in the liberation of melanin, and its immediate precursor melanogen, into the circulation; the melanin is then reduced to melanogen in the serum (Karsner, 1938), and excreted in the urine, where it is reoxidized to melanin.

In the present instance there was no direct relation between exacerbation of the syndrome and of the stomatitis, which, however, improved when the clinical condition responded to desoxycortone acetate.

Methods Used

Faecal Fats.—The Soxhlet extraction method, substantially the same as that of Holt, Courtney, and Fales, and referred to in

Harrison's *Chemical Methods in Clinical Medicine*, 2nd edition, pp. 469 and 470.

Blood Chlorides.—Whitehorn's method (*J. biol. Chem.*, 1920-1, 45, 449).

Serum Sodium.—Modification of method of McCance and Shipp described in Harrison's *Chemical Methods in Clinical Medicine*, pp. 379 and 380.

Serum Potassium.—Method described by Jacobs and Hoffman (*J. biol. Chem.*, 1931, 93, 685).

The serum sodium and serum potassium methods are colorimetric methods, and a "Spekker" absorptiometer has been used in these estimations.

Summary

A case simulating Addison's disease with severe normocytic normochromic anaemia, steatorrhoea, and melanuria, and its treatment, are described.

A tentative explanation of the underlying mechanism of the syndrome anaemia, steatorrhoea, and melanuria is put forward.

The differential diagnosis is discussed.

The relevant literature is reviewed.

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THREE CASES OF CLOSED INTRA-ABDOMINAL INJURY

BY

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Cases of visceral injury resulting from blunt injuries to the abdomen are interesting clinically. The exact mechanisms by which the lesions are produced have occasioned some discussion. The following are case notes of three such injuries produced by three different types of trauma. All three cases were seen within the latter six months of 1944.

Case I: Propeller Accident; Ruptured Jejunum

The patient—a young man of the Fleet Air Arm—gave a history of having been struck in the abdomen by the blades of a propeller, against which he was leaning when the engine of the aircraft was started. The only visible external injuries were abrasions in the right groin and over the lower half of the sternum. At first he appeared to have no serious internal injuries, and his general condition was good. He was admitted to R.A.F. sick quarters, where the medical officer wisely put him to bed and made half-hourly records of his pulse rate and blood-pressure readings. His pulse rate continued to be normal and constant, but he vomited twice. In view of his abdominal symptoms, the M.O. was not happy about him.

When I first saw the patient there were guarding and tenderness of the upper abdomen, but peristalsis was audible through the