ADDISON'S DISEASE OCCURRING IN TWO BROTHERS

BY

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There are two aspects of Addison's disease on which relatively little information is available: one is its occurrence in childhood (in all about 60 cases have been reported), and the other concerns the role of hereditary factors.

It has periodically been suggested, especially when this disease has occurred in several members of the same family, that the condition may be inherited. This hypothesis is perhaps plausible, since there is evidence that hereditary factors operate in other endocrine disorders—for example, diabetes mellitus and the Laurence–Moon–Biedl syndrome. In studying any such relationships the two important features necessary are reliable criteria of diagnosis and an adequate supply of clinical cases.

Addison's disease is a relatively rare condition; nevertheless several possible familial cases have been recorded. Fleming and Miller (1900) described a mother who was quite well until her first pregnancy, when she became pigmented and asthenic. Her condition showed an exacerbation after each succeeding pregnancy. One child died at birth and the four remaining children, whose ages ranged from 2½ to 7 years, were all pigmented and suffered from unexplained attacks of diarrhoea and vomiting. Unfortunately, there was no follow-up or necropsy. Croom (1909) described three sisters who were pigmented and asthenic, but there is insufficient biochemical evidence, and there was no follow-up or necropsy in any of his three cases. Wakefield and Smith (1927) presented the case of a man aged 28 in whom necropsy revealed absence of the right suprarenal. Two of the man's brothers, his father, grandfather, and a paternal uncle were all pigmented, while seven other brothers were fair-skinned, but there was no clinical examination or follow-up in any of these relatives.

In discussing Addison's disease in relation to heredity, Morabito (1927) has drawn attention to a case in which a brother and sister, aged 7 and 10 years respectively, became gradually pigmented and in whom the Von Pirquet test was strongly positive. In both parents and children the Wassermann reaction was positive. He attributed the pathology to congenital syphilis with superadded tuberculosis. Borghini (1937) reported the case of a 13-year-old Italian boy who was undernourished and subject to attacks of weakness on slight exertion. The boy's mother apparently had died from typical Addison's disease, but after a five-year follow-up the child's general condition was unaltered and there was no change in the pigmentation.

Not only is the number of reported cases small but in most of them the evidence does not satisfy the modern criteria for the diagnosis of Addison's disease. In his extensive review of 566 reported cases Guttman (1930), although doubtful whether heredity plays an important part in the genesis of the disease, states that it "cannot be denied that in rare instances there is a hereditary tendency."

In view of the relative paucity of information on this aspect of the subject it is important, now that reliable diagnostic methods are available, to investigate thoroughly all cases in which the disease occurs in more than one member of a family. We have recently observed two young brothers with Addison's disease whose case reports follow.

Case 1

A schoolboy aged 12 was admitted to the Sheffield Children's Hospital on July 30, 1946, complaining of listlessness, anorexia, loss of weight, vomiting, and diarrhoea, which had gradually increased during the previous three weeks. The symptoms were at first ascribed by his doctor to an attack of gastro-enteritis, but as there was no response to treatment the child was referred to hospital. His mother stated that since infancy the boy had been very fond of salt and would often eat this alone. He had had measles, chicken-pox, whooping-cough, and mumps. There was no family history of tuberculosis, abnormal pigmentation, or Addison's disease. Apart from his brother, there were no siblings.

On admission the patient was very drowsy, had intermittent attacks of retching and diarrhoea, and responded to questioning with difficulty. He was markedly dehydrated. There was diffuse dark-brown pigmentation of the face, back of the neck, dorsum of the hands, the forearms, and the extensor surfaces of the legs, extending from the knees to the ankles. The buccal mucous membrane was not pigmented.

The apex beat was not palpable, and by percussion the heart was 1½ in. (3.75 cm.) internal to the mid-clavicular line. The heart sounds were faint and regular; no murmurs were heard. The pulse rate was 120 a minute, weak but regular, and the blood pressure was 80/40. There were no abnormal features in the abdomen, lungs, or nervous system, and no costo-lumbar tenderness. He was of normal stature, but both testicles were undescended and the penis was underdeveloped. Apart from three carious teeth there was no other evidence of any local infection.

The urine showed: no albumin or sugar; ketones were present; there was no deposit. Examination of the blood showed: E.S.R., 16 mm. in one hour; fasting blood sugar, 50 mg. per 100 ml.; plasma potassium, 25 mg. per 100 ml.; serum sodium, 280 mg. per 100 ml.; Robinson, Power, and Kepler (1941) excretion test ratio A=4.5; haemoglobin, 100%; red cells, 5,010,000; white cells, 9,400 (neutrophil polymorphs 68%, monocytes 4%, basophils 1%, lymphocytes 27%). Radiographs of the chest showed a small heart shadow and normal lung fields (Fig. 1). The electrocardiogram revealed sinus tachycardia, and low-voltage curves with S–T depression and flat T waves in all leads. Radiographs of the abdomen showed two calcified glands in the region of the right iliac fossa. The Mantoux test with 1/1,000 old tuberculin was positive.

Immediately on completion of the investigations adrenal cortex extract ("eucortone") was given in 10-ml. doses intramuscularly every six hours and D.C.A. 5 mg. every 12 hours. The following day supplementary salt (4 g. six times a day) was given, and he drank fluids eagerly. By August 5 there was a striking clinical improvement. He was alert and answered questions quickly and accurately. He ate his food eagerly and took an active interest in his surroundings. The apex beat was now palpable, and the percussion note indicated an increase in cardiac dullness

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to the left. The blood pressure was 100/74, and radiographs of the chest revealed a marked increase in the heart shadow (Fig. 2). The electrocardiogram was normal.

On August 8 pigmentation was less diffuse and dark areas were still apparent on the flexor surfaces of the forearms and hands, along the vertebral column and anterior-superior iliac spines, and on the abdomen at the level of the trouser belt. There was no evidence of buccal pigmentation. Blood pressure was 100/75. On August 10 adrenal cortical extract was discontinued and D.C.A. reduced to 2.5 mg. every 48 hours. Supplementary salt therapy was continued. The next day he was able to walk unaided in the ward and his general clinical improvement was maintained. On August 19 the second Robinson–Power–Kepler test showed a value of 19. His blood pressure remained stationary at 102/72, and he gradually increased in weight. On August 30 a 25-mg. pellet of D.C.A. was implanted by Mr. Clifford Jones on the right rectus sheath under local analgesia. Two days later intramuscular injections of D.C.A. were discontinued. At this time the serum sodium was 315 mg. per 100 ml., plasma potassium 21 mg. per 100 ml., and the Robinson–Power–Kepler excretion test ratio A=25.

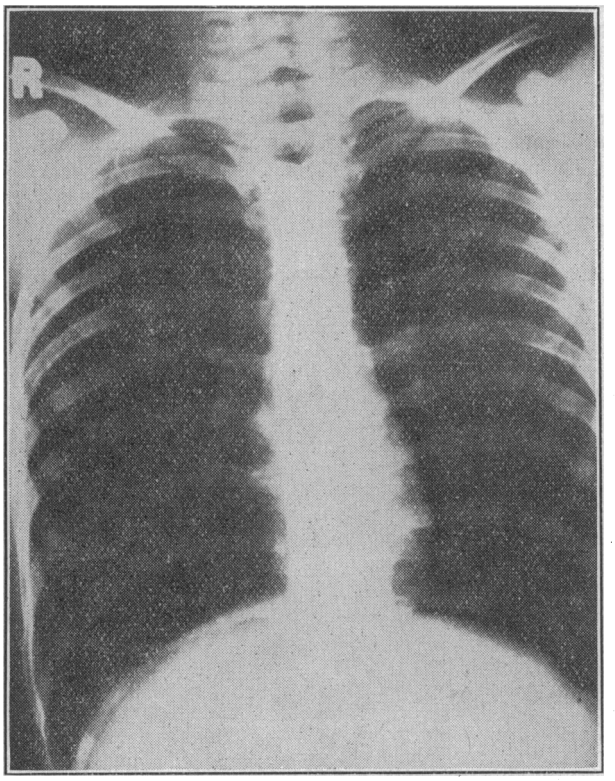

FIG. 1.—Case 1. Chest radiograph before treatment, showing a very small heart.

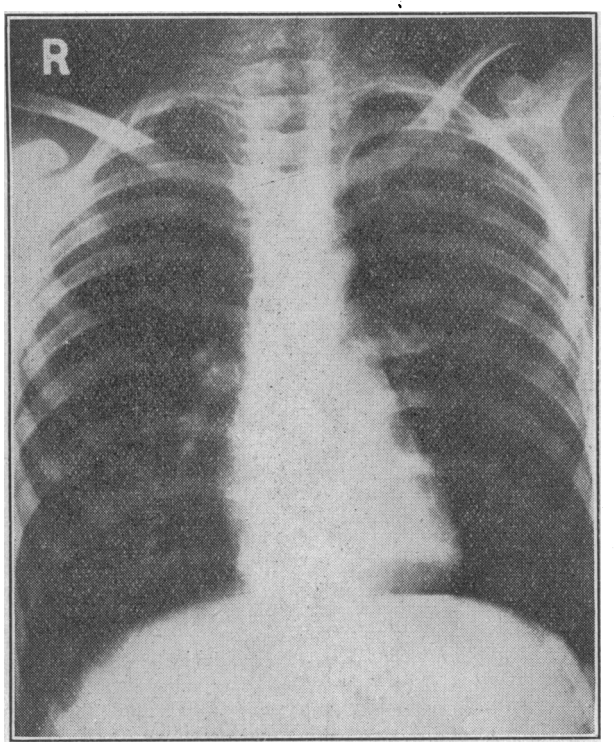

FIG. 2.—Case 1. Chest radiograph after treatment. The heart is now normal in size.

He was discharged and referred for follow-up as an outpatient. He required a second implantation after three months, and was then given 150 mg. of D.C.A. He has had two further pellets of 150 mg. of D.C.A.; the effects of each lasted approximately seven months. With this treatment he has for two years been adequately controlled and is able to attend school regularly and to walk distances up to two miles without excessive fatigue. His pigmentation has increased in intensity, and small areas are now present on the soft palate. His blood pressure remains at about 100/55 mm. Hg.

The 24-hourly urinary output of 17-ketosteroids was 5 mg., and, in view of his cryptorchidism, chorionic gonadotropin ("gonan") was given intramuscularly, 500 I.U. twice weekly for six weeks. His penis increased in size, and six months later both testicles were descended.

Case 2

The elder brother of Case 1, aged 17, was admitted to the Royal Infirmary, Sheffield, on July 31, 1947. He had been in good health until five weeks before admission, when he complained of epigastric pain and vomiting, which lasted 24 hours. One week later he had a recurrence of the pain while suffering from a septic great toe-nail. This was removed by his own practitioner, but he had two further attacks of abdominal pain and vomiting, the second attack leading to his admission to hospital. Pigmentation of skin and loss of weight had been noticed recently. There was no relevant past history.

He was a well-developed youth with very faint generalized pigmentation, and a small area of pigmentation on the buccal mucosa. There was slight dehydration. The cardiovascular system was normal: B.P. 120/70, pulse 104 regular. Respiratory, abdominal, and central nervous systems were normal. His temperature was 97° F. (36.1° C.). A trace of albumin was found in the urine. Examination of the blood showed: E.S.R., 12 mm. in one hour; serum sodium, 345 mg. per 100 ml.; serum potassium, 17 mg. per 100 ml.; N.P.N., 60 mg. per 100 ml.; Hb, 103%; red cells, 5,250,000; white cells, 5,400 (polymorphs 53%, lymphocytes 44%, monocytes 3%).

A tentative diagnosis of Addison's disease was made, and the patient was given liberal fluids and extra salt by mouth. This did not stop the vomiting, so an intravenous infusion of sodium chloride and 5% dextrose was set up. Three hours later he suddenly became extremely restless and the pulse rose to 140 a minute. There were no signs of pulmonary oedema and no abnormal signs in the central nervous system. The restlessness continued, and the next morning his condition had deteriorated; well-marked neck rigidity and pyrexia had developed. A lumbar puncture showed a normal pressure and no block. The fluid was clear and normal. His blood pressure was 125/65.

In spite of continuous therapy with adrenal cortical extract, penicillin, and intravenous glucose-saline, the patient died 72 hours after admission. His pigmentation had increased markedly during the last three days of his life, but the blood pressure remained normal until three hours before death, when the systolic pressure fell to 70.

A post-mortem examination was made by Dr. L. C. D. Hermitte. Both suprarenal glands were atrophic, and histological examination showed simple atrophy, involving mainly the cortex (Fig. 3). The thymus was considerably larger than normal and the thyroid gland was also enlarged; the gonads and pituitary body were normal. The heart was small, and the lungs were slightly oedematous, the right lung having six lobes and the left lung four. There were no other important findings.

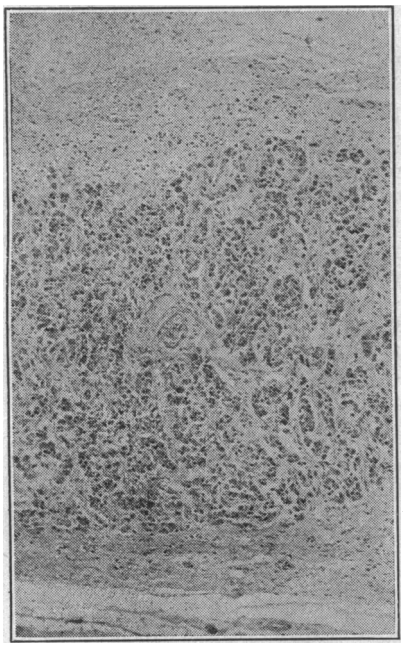

FIG. 3.—Case 2.—Section of suprarenal gland showing atrophy of the cortex with relative integrity of the medulla. Haematoxylin and eosin. (× 40.)

It is difficult to account for the sudden deterioration in this patient's condition and his failure to respond to treatment. It is possible that the maintenance of a normal blood pressure till the terminal stages of his illness was due to the relative integrity of the medullae of the suprarenal glands. The enlarged thymus gland directs attention to the possibility of myasthenia gravis, but there was not at any time clinical evidence of this disease. The congenital abnormality in the lungs is noteworthy.

Discussion

Because these two cases of Addison's disease occurred in brothers, their family history was carefully and exhaustively investigated. Both parents were healthy, They came from a large city and their families were not in any way related. They had only the two children. The maternal grandparents died in old age and their children were not pigmented, though one son had a wasting disease in childhood but recovered and was lost at sea in the second world war. No relevant information was available regarding the paternal grandparents other than that the grandmother died at the age of 82 and that the grandfather is still alive and well, aged 79. There are several paternal cousins who have not been traced but who, at least until adult life, are known to have been healthy.

We are of the opinion that in each patient the disease was due primarily to atrophy of the suprarenal glands. It is not surprising that the younger brother had calcified abdominal glands, since he had been taking farm milk which was neither pasteurized nor boiled.

The occurrence of such a rare disease in two brothers and at an early age suggests the possibility that a genetic factor may be involved.

Summary

The literature relating to the possibility of a familial factor in Addison's disease has been reviewed. The occurrence of Addison's disease in two brothers is described. In the patient who died, atrophic suprarenal glands and congenital abnormalities of the lungs were found at necropsy. The cause of the disease in the two cases presented is considered to be primary suprarenal atrophy. In view of the suggestive but inconclusive evidence afforded by this and other cases reported, we consider that the familial and genetic aspects of Addison's disease merit further study.

We wish to thank Professor E. J. Wayne for permission to publish these cases, and we are grateful to Dr. L. C. D. Hermitte for his report on the necropsy findings in Case 2.

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THE FLUORESCENCE PHENOMENON OF THE TONGUE

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When the mouth is viewed under ultra-violet light screened with Wood's glass a reddish-orange fluorescence is often visible on the dorsum of the tongue and sometimes on the teeth. This fluorescence has been recognized for some time, and has been proved to be due to the production of porphyrins by oral micro-organisms. So far, however, this fluorescence has not been adequately studied in relation to the various changes in the tongue that are known to result from nutritional deficiencies.

Several authors have described this phenomenon. Derrien (1924) noticed fluorescent points in dental cavities, which he attributed to decomposition of haemoglobin by bacteria. The fluorescence of the carious teeth or of tartar must be distinguished from that of healthy teeth in cases of congenital porphyria as first described by Mackey and Garrod (1925–6). Hymans van den Bergh (1928a, 1928b) described this fluorescence of the tongue in greater detail and endeavoured to explain its aetiology, but he did not study its clinical significance. More recently, Costello and Luttenberger (1944) attributed the absence of the normal fluorescence to vitamin-B deficiency. According to them it is intense in children but less marked in well-nourished adults.

Hagerman and Hirschfeld (1947) examined over 500 patients in a dermatological clinic. In about 60% of their patients the fluorescence extended over the whole tongue or covered about half of the dorsum, which was considered to be normal. About every fourth patient showed fluorescence over the whole surface. Tongues showing absent or very limited fluorescence were regarded as abnormal. These authors found that patients showing absent or greatly diminished fluorescence often suffered from the skin lesions usually associated with vitamin-B deficiency. They noticed also that vitamin-B preparations, especially those containing pantothenic acid, usually produced a change to the normal fluorescence (*British Medical Journal*, 1949).