Comment

This patient in severe Simmonds's disease crisis showed very little improvement when treated with eucortone, doca, and glucose saline, even after 48 hours, by which time the blood sugar had returned to normal. Within 24 hours of starting treatment with cortisone there was a marked improvement, which was thought to be associated with the cortisone. The cause of the patient's pyrexia is uncertain. There were no definite physical signs, apart from a few adventitious sounds in the lungs, and it seems unlikely that the toxæmia was due to infection and that the penicillin had anything to do with the dramatic recovery. It cannot, of course, be said with certainty that cortisone was responsible for the improvement. The other hormones had been given for some 48 hours previously, and it is possible that improvement was due to a delayed effect of the previous therapy, though the prompt response to cortisone following the very little change which had taken place during the previous therapeutic regime raised the strong possibility that the recovery was due to cortisone.

It is realized that this case is very far from proof that cortisone is a drug of choice in the treatment of acute Simmonds's disease crisis, but these observations have been recorded so that a wider trial can be given in future cases.

A CASE OF SIMMONDS'S DISEASE WITH MENTAL SYMPTOMS

BY

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The recent advances in endocrine therapeutics have revived interest in the disorder known as Simmonds's disease. In the past the missed diagnosis was often condoned, if not excused, by the fact that no effective treatment was available, but this no longer holds true. Furthermore, the diagnostic difficulties have been considerably lessened by the brilliant studies of Sheehan, whose portrayal of the typical case is unlikely to be surpassed. The earlier textbook descriptions were misleading in that undue stress was laid on such inconstant signs as progeria, cachexia, and hypotension, whereas insufficient notice was taken of the accompanying mental disturbance. Sheehan and Summers (1949), in a full review of the disease, write: "In the later stages a number of patients present mental symptoms and are removed to asylums, where attention is focused more on the psychological than the physical aspects of the condition."

The case described below is of especial interest in that it was the mental, not the physical, symptoms which brought the patient into hospital.

Case Report

A married woman aged 54 was admitted to hospital on February 3, 1950. She complained of depression, general weakness, and cramping pains in the calves. She was married in 1925 at the age of 29, and had had two uncomplicated pregnancies, in 1926 and 1929. In 1933 the birth of a still-born child was followed by a severe haemorrhage, for which she was given an infusion of saline but no blood transfusion. Permanent amenorrhoea followed the post-partum haemorrhage. Coitus ceased as a result of both a loss in sexual

appetite and a progressive shrinking of the vagina. Her axillary and pubic hair gradually disappeared, her head hair became dry and coarse, while her eyebrows grew steadily thinner. Her skin became dry and scaly. An insidious decline in her general health took place *pari passu* with the changes already described.

Since 1940 she had been subject to attacks of fainting and vague abdominal pain. From 1945 onwards her family noticed signs of increasing mental torpor and physical deterioration. She became slow in her speech and in the performance of simple routine tasks. She developed an inability to tolerate the vicissitudes of the climate, being prostrated by very hot or cold weather. Her cheeks, which were florid prior to the haemorrhage, assumed a remarkable pallor. Despite her failing health, she remained fairly cheerful until a few months before admission, when she suddenly became anxious and depressed. No marked loss of weight had taken place.

On admission she was noted to be in a fair state of nourishment. A striking degree of facial pallor gave rise to the suspicion that she had a severe degree of anaemia. Her eyebrows were scanty and the axillary and pubic hair absent (Fig. 1). Her skin was dry and wrinkled and showed a fine scalliness. Her fingernails were thin, dry, and brittle; they were not spoon-shaped. No abnormality was noted in the chest, abdomen, or central nervous system. The blood pressure was 140/80. The vagina admitted only the index finger. Her weight was 6 st. 4 lb. 10 oz. (40.2 kg.). Progeria was not in evidence. Pigmentation of the skin was absent, but erythema ab igne was conspicuous on the legs. The mental picture was one of slight retardation with depression and anxiety.

FIG. 1.—Photograph taken on March 22 (before treatment), showing scanty eyebrows and complete absence of pubic and axillary hair. Erythema ab igne is well shown on legs.

Investigations

On February 4 a blood count gave: red cells, 4,010,000 per c.mm.; haemoglobin, 85%; colour index, 1; white cells, 5,250 per c.mm. (polymorphs 28%, lymphocytes 67%, monocytes 3%, eosinophils 1%, basophils 1%). The corrected B.S.R. was 12 (Wintrobe). The W.R. was negative. X-ray studies of the skull (including the sella turcica), heart, and lungs showed no abnormality.

The 24-hour urinary excretion of 17-ketosteroids was 2.3 mg. The fasting blood-sugar and sugar-tolerance curve gave a fasting value of 100 mg. per 100 ml.; half an hour after 50 g. of glucose it was 100 mg.; one hour later, 90 mg.; one and a half hours later, 80 mg.; two hours later, 80 mg.; two and a half hours later, 80 mg.

On March 27 the following results were obtained by a biochemical study of the blood: blood urea, 20 mg./100 ml.; blood cholesterol, 234 mg./100 ml. Serum sodium, 285 mg./100 ml.; serum potassium, 17.7 mg./100 ml.; serum

FIG. 2.—Electrocardiogram taken on March 27 (before treatment), showing low-voltage deflections and inverted T waves.

chlorides, 545 mg. (NaCl)/100 ml. An electrocardiogram taken on the same day showed a very low voltage with inverted T waves (Fig. 2).

Kepler's test (Robinson *et al.*, 1941) was performed on April 14 with the following results: "Whole night" urine, 14 oz. (400 ml.); "largest morning specimen," 3 oz.; blood urea, 30 mg./100 ml.; serum chloride (NaCl) 486 mg./100 ml.; urine urea, 1.3%; urine chloride (NaCl), 169 mg./100 ml. Factor "A" = 26.7. Kepler's test (I) was therefore positive; Kepler's test (II) was a doubtful positive.

The average pulse rate over a four-day period was 60 a minute. Free hydrochloric acid was present in the gastric juice. Psychometric testing (Wechsler-Bellvue) showed an intellectual deterioration of 11% after due allowance had been made for normal deterioration with age.

An attempt to estimate the B.M.R. failed owing to the inability of the patient to co-operate with the technicians. The insulin-sensitivity test of Fraser and Smith (1941) was not performed, as it was feared that a refractory hypoglycaemia might occur.

Little change was observed in the patient's physical condition during the three-months interval between her admission and the beginning of treatment on May 8. The mental picture remained that of an agitated melancholia with ideas of unworthiness.

Treatment and Progress

Hormone treatment was started on May 8, her weight then being 6 st. 3 lb. 4 oz. (39.6 kg.). Sublingual tablets of methyl testosterone, 25 mg. daily, and thyroid, *B.P.*, $\frac{1}{4}$ gr. (16 mg.) daily, formed the initial basis of the treatment.

By September 8 she was taking each day oral methyl testosterone, 35 mg., thyroid $1\frac{1}{4}$ gr. (81 mg.), and D.C.A. linguets, 1 mg. A blood analysis and an electrocardiogram

taken at this time showed that a great improvement had occurred. The blood analysis gave: blood cholesterol, 133 mg./100 ml.; serum sodium, 336 mg./100 ml.; serum potassium, 18 mg./100 ml.; serum chlorides (NaCl), 600 mg./100 ml. The electrocardiogram showed a satisfactory voltage with upright T waves (Fig. 3).

When discharged she was taking sublingual methyl testosterone 30 mg. (20 mg. mornings, 10 mg. afternoons), and thyroid 1 gr. (65 mg.). The D.C.A. linguets had been discontinued, as she had had an implant of 200 mg. on October 3.

Her response to treatment was immediate and dramatic. By the end of the first week she looked more animated and seemed much quicker in her reactions. On May 31 her husband wrote an enthusiastic letter describing the improvement in her mental state and spoke of "her new-found capacity for laughter."

When she left hospital on October 8 all signs of mental disorder had gone. The Wechsler-Bellvue psychometric tests had been repeated and had failed to detect intellectual deterioration above that normal for her age. The hair of her head had acquired the normal greasiness and lustre. The skin was now moist and no longer scaly. The nails had become normal. The hair in the axillae was still absent, but a remarkable regrowth of the pubic hair had taken place (Fig. 4). Her weight was now 6 st. 12 lb. 12 oz. (43.9 kg.), representing a gain of 9 lb. 8 oz. (4.3 kg.). She had experienced a marked increase in strength since starting treatment.

FIG. 3.—Electrocardiogram taken on September 8 (after treatment), showing satisfactory voltage deflections with upright T waves.

FIG. 4.—Photograph taken on October 6 (after treatment), showing a remarkable regrowth of pubic hair. The dressing on the abdomen covers the D.C.A. implant.

A point worthy of note was the superiority of sublingual to swallowed testosterone; the patient was emphatic in her assurance that 25 mg. of sublingual testosterone was superior to a swallowed dose of 35 mg.

Discussion

In this case the history and clinical appearances were quite typical of Simmonds's disease arising from a subtotal pituitary necrosis produced by a post-partum haemorrhage. It would appear that the pituitary gland is peculiarly sensitive to the effects of haemorrhage at the moment of parturition; at other times it tends to escape destruction. Hobson and Fraser (1949) have, however, reported a case of Sim-

monds's disease following haematemeses due to a gastric ulcer.

A feature worthy of comment was the presence of well-marked erythema ab igne, which according to Sheehan and Summers (1949) "is almost always present on the legs of the female patients," the excessive sensitivity to cold causing these patients to sit huddled over a fire. The figures obtained for the blood-sugar and sugar-tolerance curve are similar to a set quoted by Farquharson (1950).

A noteworthy factor in the present case was the striking improvement in the wave pattern of the electrocardiogram after endocrine treatment, which did not include the use of extra salt. The abnormal cardiogram is not necessarily produced by the hypothyroid element in the disorder, but may arise from the secondary adrenal insufficiency. It is reported that cortisone has beneficial effects on the cardiogram in this type of case (Somerville, 1950).

Finally, it is interesting to speculate on the incidence of Simmonds's disease in the light of modern knowledge. In the past, spontaneous cures must have occurred as a result of the beneficial effects of subsequent pregnancies (Sheehan and Murdoch, 1938). In the future, Simmonds's disease due to post-partum haemorrhage may disappear following improvement in the blood transfusion and obstetric services.

Summary

A case of Simmonds's disease due to post-partum haemorrhage is described. The fact that the dominating symptoms were mental is stressed. An account, supported by biochemical data, is given of the beneficial effects of treatment with methyl testosterone, thyroid, and deoxycortone acetate.

My thanks are due to Dr. I. Atkin, physician-superintendent, for his encouragement and permission to record the case; and to Dr. J. Harkness for the steroid estimations. I am indebted to Dr. H. S. le Marquand for his practical assistance and advice. I am also grateful to those nurses and technicians of Rookdown House and Park Prewett Hospital who helped with the work involved.

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PLASMA PENTOSE LEVELS IN PRE-ECLAMPSIA AND THEIR AETIOLOGICAL SIGNIFICANCE

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One fact on which all agree is that overstretching of the wall of the pregnant uterus, from whatever cause, plays a decisive initiating part in the pre-eclamptic state. Since we (Green, 1943; Green and Stoner, 1950a, 1950b) have studied extensively the local and general effects of muscle ischaemia it was natural to wonder whether this overstretching resulted in a functional ischaemia of the pregnant uterus. If this were so it would then seem highly likely that a metabolite(s) from ischaemic muscle or placenta was the exciting cause of the pre-eclamptic and eclamptic state. As we shall see, this proved to be no new hypothesis, but all the evidence in its favour was circumstantial.

We were able to tackle the problem somewhat more directly when we had shown that after large-scale ischaemia of voluntary muscle adenine nucleotides and their breakdown products were increased in the blood (see Green and Stoner, 1950a). As these are pentose compounds, the most useful method of estimation when haemolysis can be avoided is the chemical determination of the total pentose and phosphorylated pentose contents of the plasma. The figures thus obtained give no precise information about the nature of these pentose compounds, but when significantly increased they appear to indicate that a mass of tissue with an inadequate blood supply exists, or recently existed, in the body (see Green *et al.*, 1949a). For these reasons the methods were applied to the study of pre-eclamptic patients solely for the purpose of providing practical evidence for or against the hypothesis that utero-placental ischaemia is the basic pathological state underlying all the features of the syndrome. Seven years ago, with Dr. M. Bielschowsky's help, a few observations were made and the results were such that further work seemed desirable. We are now able to report on more recent findings in a series of normal and pre-eclamptic pregnant women, together with a few cases of frank eclampsia.

Chemical Methods

The blood, after collection in waxed 15-ml. centrifuge tubes containing 1 mg. of heparin, is centrifuged. The plasma, after precipitation with an equal volume of 10% trichloroacetic acid, is shaken, stood for one hour, and then centrifuged. The supernatant fluid is removed.