studied 11 anaemic pregnant women in Gambia and treated eight with a high-protein diet for one to three months. He noted no improvement in haemoglobin concentration and also concluded that dietary deficiency of protein is not a cause of anaemia in pregnancy in Gambia.

With the exception of the seroflocculation tests, no significant differences exist between the results of the liver-function tests in normal pregnancy and in pregnancy with anaemia. Of the anaemic patients, 10% had abnormal seroflocculation reactions, but this finding is considered to be secondary to the anaemia. It is clear from the analysis of our results that the majority of the anaemic patients must be free from severe liver disease.

On the other hand, our data show dietary deficiencies of haemopoietic factors—and in particular deficiency of folic acid—to be important in producing the anaemias of pregnancy in Nigerian women.

Summary

The serum proteins and liver function of non-pregnant Nigerian women and of pregnant women, with and without anaemia, have been investigated.

Dietary deficiency of protein and hepatic damage are not important aetiological factors in the anaemias of pregnancy in Nigerian women.

The majority of the anaemic pregnant women had megaloblastic erythropoiesis. The response of the patients to treatment with antimalarials, iron, and folic acid was satisfactory.

We are indebted to Drs. J. B. Lawson, U. G. Lister, and W. T. Fullerton, all of the department of obstetrics and gynaecology, University College, Ibadan, for their co-operation over the patients and for clinical facilities to carry out this investigation.

REFERENCES

Anderson, C. G., and Altmann, A. (1951). *Lancet*, **1**, 203.
Berry, C. G. (1955). *Brit. med. J.*, **2**, 819.
Bodansky, M., Campbell, K., and Ball, E. (1939). *Amer. J. clin. Path.*, **9**, 36.
Bothwell, T. H., and Mallett, B. (1955). *Biochem. J.*, **59**, 599.
Cayla, J., and Fabre, F. (1935). *C.R. Soc. Biol. (Paris)*, **120**, 748.
Christhilf, S. M., and Bonsnes, R. W. (1950). *Amer. J. Obstet. Gynec.*, **59**, 1100.
Dacie, J. V. (1956). *Practical Haematology*, 2nd ed. Churchill, London.
Denz, F. A. (1947). *Quart. J. Med.*, **16**, 1.
Edozien, J. C. (1958a). *J. clin. Path.*, **11**, 437.
—— (1958b). *W. Afr. med. J.*, **7**, 121.
—— (1960). *J. Pediat.* In press.
Foy, H., and Kondi, A. (1958). *Trans. roy. Soc. trop. Med. Hyg.*, **52**, 46.
Hoch, H., Marrack, J. R., Ruse, R. H., and Hoch, R. (1948). *J. Obstet. Gynaec. Brit. Emp.*, **55**, 1.
Lawson, J. B., and Lister, U. G. (1955). *Clinical Report of the Department of Obstetrics and Gynaecology, University College, Ibadan.* Vail, London.
Mack, H. C. (1955). *The Plasma Proteins in Pregnancy.* Thomas, Springfield, Illinois, U.S.A.
Meranze, T., Meranze, D. R., and Rothman, M. M. (1937). *Amer. J. Obstet. Gynec.*, **33**, 444.
Peters, J. P., Wakeman, A. M., and Eisenman, A. J. (1927). *J. clin. Invest.*, **3**, 491.
Schofield, F. D. (1957). *Trans. roy. Soc. trop. Med. Hyg.*, **51**, 221.
Speert, H., Graff, S., and Graff, A. M. (1950). *Amer. J. Obstet. Gynec.*, **59**, 148.
Trowell, H. C., Davies, J. N. P., and Dean, R. F. A. (1954). *Kwashiorkor.* Arnold, London.
Walters, J. H., Rossiter, R. J., and Lehmann, H. (1947). *Lancet*, **1**, 205.
Watson-Williams, E. J. (1959). In *Annual Report, West African Council for Medical Research, 1958–9.*
—— (1960). Unpublished personal observations.
Woodruff, A. W. (1951). *Brit. med. J.*, **2**, 1415.
—— (1956). Ibid., **1**, 682.
Young, J., King, E. J., Wood, E., and Wootton, I. D. P. (1946). *J. Obstet. Gynaec. Brit. Emp.*, **53**, 251.

CYCLICAL CUSHING'S SYNDROME

BY

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Though Cushing's syndrome is not uncommon, the following case is most unusual, demonstrating a picture of gross cyclical endocrine activity of an abnormal pattern.

Remissions in Cushing's syndrome are well known. These may be spontaneous, as was seen in one of Cushing's original cases (Cushing, 1932, Case 16), and reference to this type of remission has been made by other workers (Thompson and Eisenhardt, 1943; Anderson and Haymaker, 1944; Plotz *et al.*, 1952; Knowlton, 1953; Crooke, 1958), though the relationship of these remissions to therapeutic measures is uncertain in some of these cases. Remissions induced by removal of the pituitary gland or by bilateral adrenalectomy are quite common, while radiotherapy directed at these sites has been used with varying success (Cushing, 1932; Thompson and Eisenhardt, 1943; Anderson and Haymaker, 1944; Heinbecker, 1944; Sosman, 1949; Cochran *et al.*, 1950; Knowlton, 1953).

Cases with spontaneous cyclical recurrence of symptoms in Cushing's syndrome, while they are stated to occur quite commonly, are rare in the literature. Several cases of this type are recorded (Thompson and Eisenhardt, 1953; Anderson and Haymaker, 1944; Sosman, 1949; Crooke, 1958; Luft, 1958), but only that reported by Anderson and Haymaker (1944) closely resembles the present case. Their patient was a 34-year-old woman who had experienced cyclical recurrence of symptoms of Cushing's syndrome during the 12 years prior to her death. Exacerbations were seen in the spring and summer, with remissions in the autumn and winter. The remissions became progressively shorter, none occurring in the last year of life. Radiotherapy to the pituitary and adrenal glands and treatment with methyltestosterone proved ineffective. Exploration revealed no evidence of either adenomatous or carcinomatous lesions of the adrenal glands, but promoted a remission lasting four months. A right adrenalectomy was then performed, with subsequent improvement, but she died two years later in left ventricular failure. Necropsy revealed hyperplasia of the zona reticularis of the remaining adrenal gland (similar to the changes found in the right adrenal gland after its removal two years previously), and a benign thymic neoplasm. The pituitary showed that in a moderate number of basophils there was cytoplasmic degranulation, vacuolization, and hyalinization. Sections of the hypothalamus showed some changes in the proportion of cell types.

Case Report

The patient was a 59-year-old woman who was 10 years post-menopausal. Her past illnesses included an attack of encephalitis in 1921.

In August, 1953, after a domestic crisis she developed transient ankle and leg oedema of four days' duration. She

was then well until July, 1954, when, after four attacks of left renal colic, a small ureteric calculus was passed. Subsequently she developed vague limb pains for which she received 80 g. of calcium aspirin per day for 10 days, by which time she was nauseated and vomiting, necessitating discontinuation of treatment. Within four days she noticed for the first time facial erythema and oedema, which lasted 10 days. Hospital studies at this time revealed no definite abnormality. Two weeks later her facial oedema and erythema had advanced considerably, facial hirsutism had developed, and she had become frankly hallucinated. Further investigations revealed a mild hypertension—B.P. 170/110 (previously 130/50)—and an elevated 17-ketogenic steroid excretion (26 mg./day). At this time her facial appearance was that shown in Fig. 1.

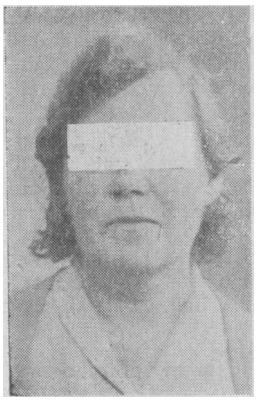

FIG. 1.—Facial appearance, autumn, 1954.

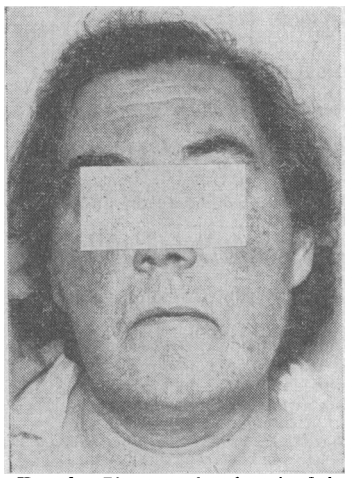

FIG. 2.—Photograph taken in July, 1958, showing marked hirsuties.

By December, 1954, she had resumed her normal appearance without receiving any active treatment. She remained well up to July, 1956, when, two weeks after further domestic upheavals, the above picture again recurred, being accompanied by marked nocturia and some gruffness of her voice. Within three months the clinical picture had again completely resolved. In July, 1957, after more domestic troubles, a further relapse occurred, lasting again two to three months. During the winter of 1957–8 she remained well. Her most recent relapse began in July, 1958, after an upset at home and at work, and her appearance at this time is shown in Fig. 2. There was marked facial hirsutism and plethora, with proptosis and chemosis. Her voice was gruff, and she was extremely agitated. There was spontaneous bruising of both legs, and an acneiform eruption was present on her shoulders. No striae or generalized obesity were evident, but definite supraclavicular fatty pads and a small buffalo hump were present.

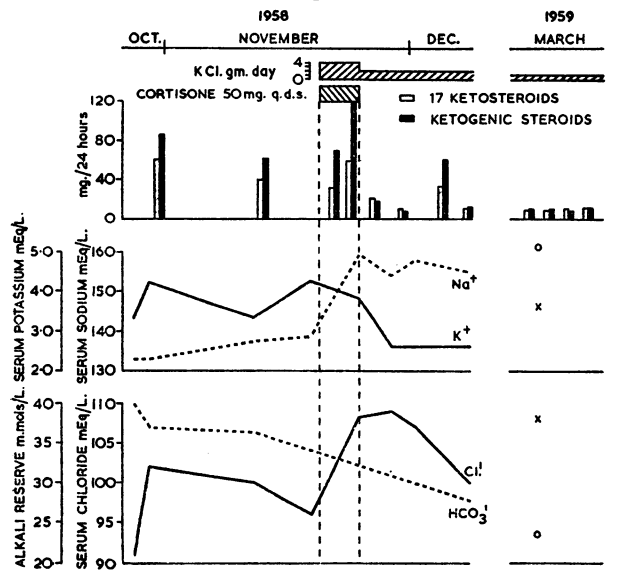

FIG. 3.—Chart showing biochemical results after treatment with cortisone and potassium chloride.

Investigations.—17-Ketosteroid excretion, 61 and 40 mg./24 hours. 17-Ketogenic steroid excretion, 84 and 60 mg./24 hours. Urinary aldosterone excretion, 38 μg./24 hours (normal 3–15 μg.). Urinary cortisol excretion, 210 μg./24 hours (normal 15–80 μg.). Serum potassium, 2.3 mEq/l. Serum sodium, 152 mEq/1. Serum chloride, 91 mEq/l. Serum CO_2-combining power 40 m.mols/l. Glucose-tolerance test, using 50 g. of glucose orally; fasting blood sugar, 107 mg./100 ml.; 45 minutes, 130 mg./100 ml.; 75 minutes, 172 mg./100 ml.; 120 minutes, 172 mg./100 ml.; 135 minutes, 200 mg./100 ml.; 195 minutes, 196 mg./100 ml. Routine urine, albumin ++. Water concentration-dilution test, maximum S.G. 1010, minimum S.G. 1001. Blood urea, 28 mg./100 ml. Plasma creatinine, 1.4 mg./100 ml. Creatinine clearance, 44 ml./minute. Plasma proteins, 5.8 g./100 ml. (albumin 3.6 g., globulin 2.2 g.). Serum calcium, 8.6 mg./100 ml. Serum inorganic phosphorus, 1.7 mg./100 ml. Serum alkaline phosphatase, 4.5 King–Armstrong units/100 ml. Serum cholesterol, 198 mg./100 ml. Urine calcium, 358 mg./24 hours. *X*-ray films of chest, long bones, pituitary fossa, and skull, I.V.P., and perirenal air insufflation were all normal. E.C.G. showed changes of hypokalaemia. E.E.G. revealed non-specific generalized abnormalities.

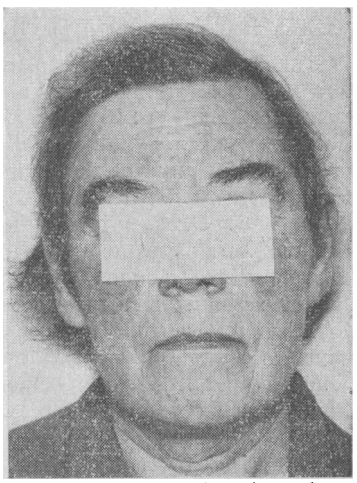

FIG. 4.—Photograph taken three months after starting treatment with cortisone.

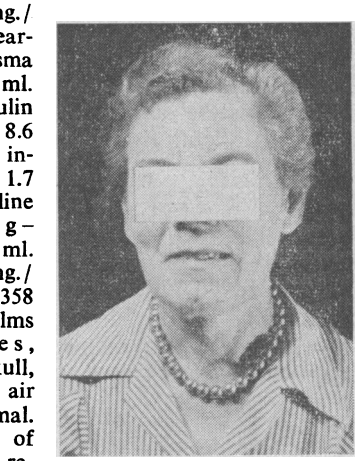

FIG. 5.—July, 1959, appearance normal.

Progress.—The above findings supported the diagnosis of Cushing's syndrome, and in November, 1958, cortisone (200 mg. daily) and potassium chloride (4 g. daily) were given for five days in the hope that a remission might be induced. The biochemical results obtained are shown in Fig. 3. Within two weeks the patient began to feel better, and this improvement was clearly established three months later. During this improvement, as on previous occasions, her facial hair disappeared and at the same time there was considerable loss of scalp hair (Fig. 4). This remission was confirmed by later changes in steroid excretion and blood electrolyte levels, and her appearance in July, 1959, was completely normal (Fig. 5).

Discussion

The unusual features of this case stimulate speculation into the aetiology of the condition and its relation to the more common types of Cushing's syndrome.

The sites of primary disturbance to be considered in Cushing's syndrome are the adrenals, the pituitary, and the hypothalamus (Jailer and Longson, 1957). In this patient, though there is no direct evidence of primary lesions in the adrenals or pituitary, there is some indication that a hypothalamic disorder may be present, as disturbances at this site occur not uncommonly as sequelae of encephalitis.

In addition, variations in endocrine function, particularly adrenal over-activity, including Cushing's syndrome, have been attributed to hypothalamic disorders (Heinbecker, 1944; Wilkins, 1950; Rey *et al.*, 1957). Cyclical variations in hypothalamic activity are well known in animals (Zuckerman, 1954) and may be seen in patients with post-encephalitic Parkinsonism. Furthermore, in hypothalamic disorders psychological factors often influence the course of the disease, and it would seem that this type of stress may have occurred in the present case prior to the onset of each relapse, although in this patient and in the only similar case (Anderson and Haymaker, 1944) the relapses had a definite seasonal incidence. There seems to be little doubt, however, that in the present case a definite remission had been induced by giving cortisone, even though spontaneous improvement had been noticed at this time of the year during previous relapses.

Two further features of this case deserve comment. Firstly, it has been reported that Cushing's syndrome may occur during salicylate therapy (Cochran *et al.*, 1950), and, as moderate doses of aspirin were given to this patient during her initial symptoms in 1954, it was then suggested that salicylates may have been responsible. However, the subsequent course of her disease makes this unlikely. Secondly, a less well known clinical feature of Cushing's syndrome which this case illustrates is the occurrence in the early stages of renal calculi (Albright, 1943; Soffer *et al.*, 1955).

Summary

An unusual example of Cushing's syndrome demonstrating several spontaneous remissions is reported, along with a brief review of the literature on such cases.

We thank Dr. E. Wyn Jones for permission to publish a report on the above patient.

ADDENDUM

After the completion of the above report the patient remained well until July, 1960, when she experienced a further attack of Cushing's syndrome. About this time she also fell and injured her right leg.

In October she was readmitted to hospital as an acute abdominal emergency. At laparotomy, generalized peritonitis due to diverticulitis of the pelvic colon was found, and a transverse colostomy was performed. At this time she still showed all the clinical features of Cushing's syndrome, and a 24-hour specimen of urine contained 64 mg. of 17-ketosteroids and 94 mg. of 17-ketogenic steroids, and her serum electrolytes revealed a hypokalaemic alkalosis.

Her immediate post-operative progress was satisfactory, but on the tenth post-operative day she became hypotensive and died.

At necropsy there was a generalized peritonitis with fibrinous adhesions and a loculated pelvic abscess containing about 500 ml. of pus. The pelvic colon contained diverticula with some diverticulitis. The lungs showed bronchopneumonia, with abscess formation in the left lower lobe. The kidneys were somewhat fibrotic and small abscesses were present at the bases of some of the pyramids. The adrenals were uniformly enlarged to about twice the normal dimensions, the left weighing 12.2 g. and the right 14.7 g. The cortex was thickened and showed bright yellow radial streaks. The pituitary was macroscopically normal and weighed 0.72 g. The thyroid, parathyroids, ovaries, and pancreas also appeared normal. No thymic tissue was recognized. The brain was macroscopically normal and the substantia nigra well pigmented. The head of the right femur was destroyed and the hip-joint contained 20–30 ml. of turbid yellowish fluid.

Microscopical Examination.—The adrenals were of normal architecture, but the cortical cells contained only small amounts of lipoid. The pituitary basophils showed well-marked hyaline changes. No adenomata of the pituitary or adrenals were found. The thyroid, parathyroids, pancreas, and ovaries were histologically normal. Sections of the hypothalamus and mid-brain revealed no obvious abnormality. The lungs showed bronchopneumonia and early abscess formation.

We thank Professor H. L. Sheehan for the post-mortem report and histological studies.

REFERENCES

Albright, F. (1943). *Harvey Lectures, 1942–43*, **38**, 123.
Anderson, E., and Haymaker, W. (1944). *J. ment. nerv. Dis.*, **99**, 511.
Cochran, J. B., Watson, R. D., and Reid, J. (1950). *Brit. med. J.*, **2**, 1411.
Crooke, P. C. (1958). *Ciba Foundation Colloquia on Endocrinology*, **12**, 149.
Cushing, H. (1932). *Bull. Johns Hopk. Hosp.*, **50**, 137.
Heinbecker, P. (1944). *Medicine (Baltimore)*, **23**, 225.
Jailer, J. W., and Longson, D. (1957). *Biochemical Disorders in Human Disease*, edited by R. H. S. Thompson and E. J. King, Chapter 7. Churchill, London.
Knowlton, A. I. (1953). *Bull. N.Y. Acad. Med.*, **29**, 441.
Luft, R. (1958). *Ciba Foundation Colloquia on Endocrinology*, **12**, 116.
Plotz, C. M., Knowlton, A. I., and Ragan, C. (1952). *Amer. J. Med.*, **13**, 597.
Rey, J. H., Nicholson-Bailey, U., and Trappl, A. (1957). *Brit. med. J.*, **2**, 843.
Rowntree, D. W., and Kay, W. W. (1952). *J. ment. Sci.*, **98**, 100.
Soffer, L. J., Eisenberg, J., Iannaccone, A., and Gabrilove, J. L. (1955). *Ciba Foundation Colloquia on Endocrinology*, **8**, 487.
Sosman, M. C. (1949) *Amer. J. Roentgenol.*, **62**, 1.
Thompson, K. W., and Eisenhardt, L. (1943). *J. clin. Endocr.*, **3**, 445.
Wilkins, L. (1950). *Diagnosis and Treatment of Endocrine Disorders in Childhood*. Thomas, Illinois, U.S.A.
Zuckerman, S. (1954). *Lancet*, **1**, 739.

Medical Memoranda

Imipramine Overdosage—Report of a Fatal Case

Imipramine ("tofranil") is being increasingly used in psychiatric practice. It was introduced into this country in 1959 and has been found to be most useful in depression, particularly when this is endogenous. In a recent trial in this country (Ball and Kiloh, 1959), 74% of cases of endogenous depression showed a good result on imipramine compared with 54% on iproniazid; in addition, 59% of cases of reactive depression did well. The authors concluded that it is worth trying either iproniazid or imipramine in most cases of endogenous depression before trying electric convulsion therapy. Other reports show comparable results, and a large number of patients must now be taking the drug. Side-effects include dryness of the mouth, sweating, dizzy feelings, drowsiness, and nausea. In addition, English (1959) first drew attention to a coarse, often violent, tremor occurring in patients on imipramine. Foster and