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ARRHENOBLASTOMA FOLLOWED BY CUSHING'S SYNDROME— A PROBLEM IN DIFFERENTIAL DIAGNOSIS

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CUSHING's syndrome has been described in association with malignant tumours of the lung, predominantly oat-cell carcinoma (Bagshawe, 1960) pancreas (Crooke, 1946) thymus (Hubble, 1949) prostate (Webster, Touchstone and Suzuki, 1959) breast (Lockwood, 1958) pheochromocytoma, undifferentiated mediastinal tumours (Liddle, Bland, Ney, Nicholson and Shimizu, 1962) and ovary (Deaton and Freedman, 1957; Parsons and Rigby, 1958). The adrenal overactivity has now been shown to be due to the production of an adrenocorticotrophin-like substance by the tumours (Liddle and others, 1962; Christy, 1961). These patients may show the clinical features of florid Cushing's syndrome or may appear clinically normal despite biochemical evidence of considerable adrenal overactivity. Each case is usually characterised at the time of investigation by gross elevation of the urinary 17-hydroxycorticosteroids and 17-ketosteroids and a characteristic hypokalaemic alkalosis which is unusual for Cushing's syndrome due to disorders of the pituitary-adrenal axis (Bagshawe, 1960). However, Hymes and Doe (1962) investigated 55 cases of bronchogenic carcinoma and found evidence of increased adrenocortical activity without any clinical evidence of hypercorticism. It may be that some examples of this syndrome do not have the gross biochemical changes associated with the established case and that the distinction between 'ectopic adrenocorticotrophin production' and cases of Cushing's syndrome due to other causes may not be clear. The case reported illustrates the difficulty in investigating a patient with clinical Cushing's syndrome in whom there was a possible recurrence of a tumour of known endocrine potentiality.

Case Report

Mrs. J.B., a 30 year old housewife previously in good health, first developed amenorrhoea in July 1962. When she was seen in the gynaecological department, Royal Victoria Infirmary, Newcastle, on November 1963 there was definite evidence of virilisation. She was hirsute with male-type distribution of hair over the abdomen and face, the breasts were under developed and the clitoris enlarged. Vaginal examination revealed a cystic left ovary. At laparotomy in November 1963 performed by Mr. F. Stabler a yellow cystic tumour of the ovary measuring 10 cm. by 7.5 cm. was found partly adherent to the posterior parietal peritoneum. A left salpingo-oophorectomy was performed. The uterus and right ovary were normal and palpation of the suprarenals was also noted to be normal. Histology of the tumour was reported: "There is loss of tubular differentiation. The bulk of the viable areas show an intermediate degree of differentiation in which solid alveoli or interlacing solid cords or trabeculae of tumour cells are seen, often flanked by vacuolated or granular eosinophilic cells. The appearances are those of an arrhenoblastoma."

Progress. The patient made an uncomplicated recovery. In January 1964, within two months of the operation, she restarted menstruation and when next seen in July 1964 she was found to be three months pregnant. The pregnancy proceeded normally until at six months she developed thirst, polyuria and glycosuria. GTT: fasting 100 mg./100 ml.; 302, 208, 194, 154 mg./100 ml. at 30-minute intervals. A diagnosis of diabetes mellitus was made and she was started on twice-daily soluble insulin. In November 1964, at seven months, she was delivered of a premature male child weighing 3 lb. 11 ozs. Lactation was suppressed. Menstruation restarted and continued normally. In April 1965, five months after delivery, at a routine diabetic clinic follow up it was noted that she showed slight facial mooning, persistent hirsutism, a definite buffalo hump, livid striae, thin skin and areas of bruising.

FIG. 1.—The graph illustrates the plasma and urinary steroid figures during a control period, metapyrone and dexamethasone tests. The shaded area in the plasma cortisol figure represents the normal range of diurnal rhythm.

Investigations. BP 140/90 mm. Hg. Hb. 13.9 g./100 ml., WBC 10,400/cu. mm.; platelets 550,000/cu. mm.; serum urea 28 mg./100 ml.; sodium 141; potassium 3.8; chloride 99; CO₂ content 30 mEq./l. X-rays of skull, chest, spine and hands were all normal. Tomography of the pituitary fossa did not show any evidence of a space-occupying lesion. The visual fields were intact. Investigations of adrenal function are shown in Fig. 1. Adrenocortical overactivity was confirmed by the presence of elevated 17-hydroxycorticosteroids (Appleby and Norymberski, 1955), elevated 24-hour urinary free fluorescent 11-hydroxylated corticosteroids (Mattingly, Dennin, Pearson and Cope, 1964) and persistently elevated plasma cortisols (Mattingly, 1962) which failed to show the normal diurnal rhythm (Eckman, Hakansson, McCarthy, Lehmann and Sjögren, 1961). The dexamethasone suppression test at 8 mg./day for three days showed only a slight fall in the 24-hour 17-hydroxycorticosteroids by the third day. There was however no suppression of the plasma cortisol level at 9.00 a.m. on the second day of the test. The metapyrone test employing dosages of 3 g./day and 4.5 g./day on two separate occasions failed to give any rise in urinary steroids and on the second occasion the hydroxycorticosteroids actually fell. The

plasma cortisol at 9.00 a.m. after 24 hours on metapyrone had also fallen to 7.3 μg./100 ml. The slight response to the dexamethasone test could have indicated pituitary-dependent Cushing's syndrome but the complete failure to respond to metapyrone was more suggestive of loss of pituitary reserve. Similar biochemical responses could, however, have occurred in a patient with an adrenal adenoma or an ectopic source of corticotrophin. It was thought at this point that the original ovarian tumour could have recurred and be acting as such a source. Perirenal air insufflation performed by Dr. C. K. Warrick showed that both adrenals were within normal limits for size but the gland on the right showed convex margins which was thought to be compatible with an adenoma.

Operation. In July 1965, under steroid cover, the late Professor A. G. R. Lowdon explored the right suprarenal and removed a small adenoma weighing 9 g. Histology confirmed an adrenocortical adenoma with a rim of atrophic cortex surrounding it. Exogenous steroid therapy was gradually withdrawn and the contralateral adrenal was stimulated with daily ACTH. The 9.00 a.m. plasma cortisol before ACTH was 2.8 μg./100 ml. but the 9.00 a.m. figure by the third day had risen to 14.8, indicating increasing

adrenal responsiveness. Three weeks post-operatively the steroids and ACTH were withdrawn without any complications. The insulin requirements fell progressively post-operatively and by discharge the patient was controlled by diet alone.

Discussion

In most cases of Cushing's syndrome the basic cause of the adrenal overactivity can be determined by a combination of the dexamethasone and metapyrone tests (Hartog, Doyle, Fotherby, Frazer and Joplin, 1965; Liddle, Estep, Kendall, William and Townes, 1959; Liddle, 1960). In the cases of pituitary-dependent Cushing's syndrome, whether these be due to hyperplasia or adenoma of the pituitary, partial suppression of the excess corticotrophin output can be achieved by large doses of steroids, usually dexamethasone (Liddle, 1960). Metapyrone on the other hand by diminishing the rate of production of cortisol in the adrenals stimulates the pituitary by the negative feedback of a falling cortisol level to produce even more corticotrophins. This is reflected by an increased output of 11-desoxycortisol (compound S) and its breakdown products in the urine which are measured as 17-hydroxycorticosteroids. The adrenal adenoma with its autonomous production of cortisol suppresses the normal pituitary which is then unable to sustain the contralateral adrenal and is unable to respond to stimulating or suppressing tests. This is shown, as in this case, by a failure of the urinary steroids to fall on dexamethasone and a lack of response to metapyrone.

However in cases of Cushing's syndrome associated with malignant tumours outside the pituitary-adrenal axis (the group termed 'ectopic corticotrophin from non-endocrine tumours' by Liddle and others (1962)) the tumours, by producing excessive ACTH-like substance, cause bilateral adrenal hyperplasia (Christy, 1961). The excessive cortisol production in turn suppresses the normal pituitary. Liddle and others (1962) have shown that the pituitaries in four such cases that have been investigated were not only atrophic but contained no detectable ACTH by bioassay methods. Hence this latter group will behave in response to the dexamethasone and metapyrone tests in a similar fashion to an adrenal adenoma. In most cases of Cushing's syndrome associated with malignant tumours the diagnosis is made easier by finding unusually high levels of 17-hydroxycorticosteroids and 17-ketosteroids and a hypokalaemic alkalosis (Bagshawe, 1960). Out of 23 such cases collected by Bagshawe, 21 had a serum potassium of less than 3 mEq./l. and a plasma bicarbonate greater than 30 mEq./l., whereas in 88 cases of Cushing's syndrome due to other causes the mean serum potassium was between 4.1 and 4.3 and in 25 cases analysed the plasma bicarbonate was less than 30. Wilson, Power and Kepler (1940) have also reported similar findings. Only three of 30 Cushing's

syndromes collected at that time had evidence of a low serum potassium and in two of these cases a tumour was present. In this case the association of the previous hormonally active malignant ovarian tumour and the biochemical tests that could have supported a diagnosis of an ectopic source of ACTH made the differential diagnosis difficult. The serum potassium of 3.8 and the plasma bicarbonate of 30 mEq./l. were just borderline and therefore unhelpful. The relatively low 17-hydroxycorticosteroids and the persistently low normal 17-ketosteroids favoured an adrenal adenoma which was fortunately demonstrated despite its smallness by perirenal air insufflation.

Ovarian tumours have been described in association with Cushing's syndrome but these are very rare (Deaton and Freedman, 1955; Parsons and Rigby, 1958). The histology of these tumours has been that of an adenocarcinoma and masculinoblastoma. Presumably these too are examples of an ectopic source of ACTH. These are not to be confused with a very rare group of ovarian tumours that contain active adrenal rests (Kepler, Dockerty and Prestley, 1944).

The association in this case of two hormonally active tumours is probably therefore fortuitous but it does serve to illustrate the difficulties in finding the basic cause of a Cushing's syndrome and emphasizes that the development of Cushing's syndrome in association with a previous or present tumour may not necessarily have a direct causal relationship.

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MELIOIDOSIS IN A DIABETIC

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IN REPORTING a case which had reached hospital in England, Maegraith and Leithhead (1964) mentioned the value to others of writing up this little-known disease when it is met. Burma and Malaya have been the main source of recently recorded cases (Peck and Zwanenberg, 1947; Paton, Peck and Van de Schaef, 1947; Harries, Lewis, Waring and Dowling, 1948; Green and Mankikar, 1949; Khaira, Young and Hart, 1959). The association of lung abscesses with the pyaemia in ours as well as other cases favours the suggestion of Khaira and others (1959) that the portal of entry may be respiratory; and, in the case of the officer serving in North Borneo described by Baird and Meers (1965), Whitmore's bacillus (*Pseudomonas pseudomallei*) was recovered from the sputum.

Case Report

Patient 036030 was a 52-year-old native of Goa, employed as a ship's pantryman, with a history of typhoid fever five years before, cystotomy for stone in the urinary bladder one year before, and diabetes for five years, for which he had ceased taking tablets one year before. He complained that his urine was red and that for two weeks he had had pain in the left loin, which had become swollen, hot and tender in the last three days. Temperature 102°F, pulse 120, BP 115/60 mm. Hg.; spleen just palpable; there were signs of subcutaneous abscess formation along the left tenth and eleventh ribs to the angle of the scapula. Pus was drained by incision two days after admission and chloramphenicol treatment begun. Another subcutaneous abscess appeared in the right groin, and was also incised. The temperature oscillated for the next few days

in a near-normal range, then began to rise and remained above 101°F till the patient's death on the sixteenth day after admission.

Investigations. Urinary glucose on admission was 1% but no ketosis was found. Soluble insulin, 20 units b.d., was given when the fasting blood sugar was reported as 248 mg./100 ml. on the tenth day after admission. Blood findings were: ESR 46 mm./hr., an absence of anaemia (PCV 44%) and an initially low white cell level of 3,500/cu. mm., which rose to 6,800 one week later and fell to 4,200 on the day of death. Complement fixation tests for syphilis and amoebiasis were negative. The urine contained pus and bile and grew *Aerobacter*. Serum bilirubin 3.5 mg./ml., thymol turbidity 10 units, serum colloidal gold flocculation 221000 and serum alkaline phosphatase 27 K.A. units. Serum sodium 117 mEq/l, total protein 6.4, γ-globulin 2.6 g./100 ml. The sputum yielded a heavy growth of *Candida*. The faeces contained a few ova of *Trichuris*. Agglutination tests with *Salmonella*, *Proteus* OX and *Brucella* were negative.

Bacteriology. The pus obtained on incising the subcutaneous abscess in the left loin, the blood culture taken two days before death and the pus obtained post-mortem from the left subdiaphragmatic abscess all gave a growth of Whitmore's bacillus. It was a motile, irregularly staining, gram-negative bacillus, with a tendency to form parallel bundles. It fermented glucose without gas, liquefied gelatin after three days, gave a soft clot in milk, reduced nitrate, formed a pellicle, grew on MacConkey's medium, showed very slight yellow pigmentation on nutrient agar, was not haemolytic on horse-blood agar and gave negative Voges-Proskauer, methyl red, indol, urea-splitting and citrate-utilization tests. The organism was agglutinated by the patient's serum diluted 1 in 60 but not by a control normal serum diluted 1 in 30. A guinea-pig, intraperitoneally