therapy for six weeks, and, as in the patient carefully studied by Walshe and Warin (1963), were unable to demonstrate any significant alteration of porphyrin excretion. Some variables, such as exposure to sunlight and the taking of alcohol and drugs, were controlled by admitting the patients to hospital. We made daily porphyrin estimations, often over several consecutive days, because isolated readings may be misleading owing to day-to-day fluctuations. In symptomatic cutaneous hepatic porphyrria alcohol is a well-known precipitant (Brunsting, 1954); barbiturates and sulphonamides are probably less important (Dean, 1963), but often reports fail to distinguish between hereditary and symptomatic types of cutaneous hepatic porphyrria (Eales, 1963).

The difficulties to be considered before allocating the blame for the porphyric state can be seen in the examples of acquired cutaneous hepatic porphyrria due to hexachlorbenzene and other chemical poisons, in which the toxins not only appeared to initiate it but caused a prolonged or permanent disorder of porphyrin metabolism (Schmid, 1960; Özen, 1963; Bleiberg *et al.*, 1964). Our two patients, and that of Walshe and Warin (1963), had had barbiturates, including thiopentone, and sulphonamides at the time of prostatectomy, and oestrogens were started shortly afterwards, but the disease did not become manifest until 1, 8, and 18 months later, so the possible effect of barbiturates and sulphonamides is difficult to assess.

As a control group we studied six patients with cancer of the prostate without metastases who were not porphyrics or alcoholics and who had had feminizing doses of oestrogens for up to five years. The porphyrin levels in the blood, urine, and faeces were normal. The only similar study is that of Theologides *et al.* (1964), who found no alteration in porphyrin levels in two similar non-porphyric men investigated prospectively during the first few months of oestrogen therapy.

Summary

Two chronic alcoholics developed cutaneous hepatic porphyrria within a year of prostatectomy and subsequent

oestrogen therapy. Oestrogens have been reported to exacerbate some varieties of porphyrria. Neither of our patients had a decrease in porphyrin excretion when oestrogens were stopped.

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Medical Memoranda

Syndrome Resembling Addison's Disease Following Prolonged Treatment with Busulphan

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Busulphan is the most effective treatment in myeloid leukaemia. Toxic effects of this drug are infrequent; the most common, and one which may occur with only small doses, is excessive depression of bone-marrow. Others include hyperpigmentation of the skin (Galton, 1953; Haut *et al.*, 1961), pulmonary interstitial fibrosis (Oliner *et al.*, 1961; Leake *et al.*, 1963), and a syndrome resembling adrenocortical insufficiency. This syndrome has been reported in six patients (Marinho and Martins, 1956; Kyle *et al.*, 1961; Leake *et al.*, 1963), in two of whom it was associated with pulmonary interstitial fibrosis and in one with chronic hyperpigmentation of the skin. This is a report of a patient in whom the syndrome resembling adrenocortical insufficiency was found with chronic skin pigmentation, pul-

monary interstitial fibrosis, and heart block, an association not hitherto described.

CASE REPORT

A married woman was first seen in hospital in 1955 aged 63 years. She had been ill for 18 months. She was very anaemic and had a large spleen, her peripheral white blood cell count and sternal marrow examination confirmed a diagnosis of chronic myeloid leukaemia.

She was treated with busulphan and had an excellent clinical and haematological remission. She remained on maintenance doses of busulphan, and from May 1958 until her last illness in June 1963 she had been given 2 mg. every third day. During these five years her white blood count varied between 8,000 and 16,000 per c.mm. and the haemoglobin between 87% and 110%. There were never more than 3% myelocytes in the peripheral blood film.

In June 1963 she was admitted to hospital weak and ill. Skin pigmentation had been present for five years. She had had increasing anorexia and had lost 46 lb. (20.9 kg.) in weight over two years. For six months more and more of her life had been spent in bed, and when she got up she frequently fainted. She had no nausea

or vomiting. For two months she had had a troublesome cough with some white sputum.

On examination she was apathetic, wasted, weak, confused, and pigmented. Her skin was dry, wrinkled, and a dusky brown colour, being more deeply pigmented around the eyes, neck, upper chest, and abdomen than elsewhere. The palmar creases were pigmented, but the buccal mucosa was normal. There was some stippled pigmentation of the face, but the general facial appearance was of pallor. Her blood-pressure was 110/70 mm. Hg and the pulse 100 and the rhythm regular. There was no evidence of cardiac or pulmonary disease. The liver and spleen were not palpable and there was no lymphadenopathy. Her peripheral reflexes were normal.

Carcinoma of the stomach was suspected, but no gastric abnormality was found on barium-meal examination. Her leukaemia was in remission with a haemoglobin of 94%, total white cell count 11,400, 7,600 polymorphs, and 4% myelocytes. The serum alkaline phosphatase was 41 King-Armstrong units/100 ml. Her urinary excretion of 17-hydroxycorticosteroids was 6.5 mg. per 24 hours (Norymberski) and gave no support to a suspicion of Addison's disease. There was no evidence of steatorrhoea, faecal fat forming 1% of the weight of dried faeces. The chest radiograph showed a fine generalized mottling of both lung fields. The electrocardiogram (Fig. 1) showed a prolongation of the P-R interval to 0.4 sec., left axis deviation, low voltage QRS complex in the limb leads, and flattened T waves in lead I. After busulphan treatment was stopped the patient slowly improved. In three weeks she was lucid, cheerful, and walking in the ward. Her blood-pressure was 120/80 mm. Hg and she had no episodes of fainting.

Three months after withdrawal of busulphan she developed herpes zoster and was readmitted to hospital. At this time, except for left axis deviation, her electrocardiogram (Fig. 2) had returned to normal, the P-R interval being 0.16 sec. Her skin pigmentation was unchanged. The total white cell count had risen to 40,000 per c.mm. with 11% myelocytes. The serum alkaline phosphatase was 90 King-Armstrong units/100 ml. She recovered from her herpes zoster; but she was admitted to hospital again four months later with bronchopneumonia. Her white cell count was 106,000 per c.mm. and the haemoglobin 33%. Her anaemia and infection were treated but no anti-leukaemic agents were given. She died at home a month later. At necropsy there was widespread bronchopneumonia and generalized pulmonary fibrosis. No myocardial infarction was seen and though the coronary arteries were calcified no occlusions were found. The adrenal and pituitary glands were grossly and microscopically normal, there being nothing to support a diagnosis of adrenocortical failure.

FIG. 1.—Electrocardiogram taken in June 1963 showing prolongation of the P-R interval to 0.4 sec. FIG. 2.—Electrocardiogram taken in September 1963 showing normal P-R interval.

COMMENT

The syndrome of hyperpigmentation of the skin, severe weakness, fatigue, anorexia, nausea, and loss of weight following prolonged treatment with busulphan has resembled Addison's disease in many of its features. However this diagnosis could not be substantiated by electrolyte measurements, levels of corticosteroid excretion, or their response to adrenocorticotrophin stimulation. The syndrome appeared from one to five years after starting continuous treatment with busulphan, the

total dose prescribed varying from 820 to 5,710 mg. That the syndrome is related to busulphan administration was well shown by one patient, a man (Kyle *et al.*, 1961) who having recovered from the syndrome after withdrawal of the drug had a relapse five months after restarting treatment. In three other cases from the same report death occurred within four months of withdrawing busulphan. In two cases the syndrome was found in association with pulmonary interstitial fibrosis (Kyle *et al.*, 1961; Leake *et al.*, 1963). Both were febrile early in their illness, one died of pulmonary oedema three months after the syndrome presented, the other was still alive at three months and had improved since stopping busulphan.

The present case again illustrates how very ill a patient may become while receiving prolonged treatment with busulphan for myeloid leukaemia which is in remission. Though she had no nausea the other features of her illness closely resembled those described by Kyle *et al.* (1961) and Leake *et al.* (1963). She had had a total dose of 1,945 mg. of busulphan over a period of eight years. At the onset of her final illness she was in haematological remission. She had been pigmented for five years and had been losing weight for two years, a much slower onset of symptoms than in the other cases. As in the previous cases no evidence was found to support a diagnosis of suprarenal failure. An interesting feature of her illness, and one not described before in association with busulphan treatment, was a considerable slowing in atrio-ventricular conduction time. This returned to normal after stopping busulphan. She had not taken digitalis and had no abnormality of the serum electrolytes at the time the electrocardiogram was taken. No mention is made of the electrocardiographic findings in the cases previously described. Several other patients on continuous busulphan treatment without complications were found to have normal electrocardiograms. Nevertheless, in view of the widespread effects of busulphan on cellular metabolism it seems likely that this was an unusual but specific action of the drug.

The mechanism of busulphan toxicity is not understood. Kyle *et al.* (1961) suggest that skin pigmentation is caused by removal of an inhibitor of tyrosinase, thus accelerating the formation of melanin from tyrosine. The other features of weakness, loss of weight, and anorexia they suggest are due to the generalized effect of busulphan on cellular metabolism of protein. Interstitial pulmonary fibrosis first described by Oliner *et al.* (1961) and later by Leake *et al.* (1963) was thought to be due to an immunological response. One of the cases (Oliner *et al.*, 1961) was found on lung biopsy to have a vasculitis; he improved after treatment with cortisone.

Recovery from the toxic effects of busulphan has depended upon withdrawal of the drug. Afterwards other myelo-suppressive agents or splenic irradiation have been used to treat the leukaemia.

Though this patient survived only eight months, and three others less than four months after withdrawal of busulphan, one has survived longer and demonstrates that it is not always a terminal state, and that it is reversible. On this rests the importance of recognizing this uncommon syndrome.

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