suggest that in this patient who was not thrombocytopenic, the hypothalamic lesion was a deposit. In previously reported cases, diabetes insipidus has been described as a presenting symptom (Joseph and Levin, 1956) and also has occurred during the course of the disease (Laakso, 1964). Most cases have been adults who have all had acute leukaemia and there are a few reports of children having diabetes insipidus as a complication of acute lymphoblastic (Malter *et al.*, 1969) or acute myeloblastic leukaemia (Joseph and Levin, 1956).

No cases found in the literature had a markedly raised Hb F and it seems likely from our studies that this was a consequence of his leukaemia.

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Megaloblastic anaemia associated with the oral contraceptive pill

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Summary

A 27-year-old housewife suffered from severe headaches for a period of 2 years which developed after she started taking an oral contraceptive pill. During this time she gradually developed folic acid deficiency anaemia. This resulted from the inhibition by 'the pill' of the intestinal conjugase system required to deconjugate polyglutamic folate. The patient's headache did not recur after stopping the pill and her anaemia improved with folic acid supplement. The relation between folic acid metabolism and 'the pill' is discussed.

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Megaloblastic anaemia associated with oral contraception

A large number of metabolic side effects induced by the contraceptive pill have been described (Drill, 1965). Shojania, Hornady and Barnes (1968), Snyder and Necheles (1969) and Streiff (1970) have described lowered levels of serum folate in women on oral contraceptives, but overt megaloblastic anaemia appears to be uncommon. The following report describes this entirely remediable condition which presented in an insidious form.

Case report

Mrs M.K., aged 27 years, was seen in the casualty department. She had taken 16 tablets of codeine

FIG. 1. The course of haematological changes and their relation to medication. ○, reticulocytes; ●, haemoglobin; ● --- ●, in hospital; ↑, serum folate (ng/ml).

compound over the previous 6 hr for a severe headache. For the past 2 years she had recurrent severe diffuse headaches which had been attributed to tension caused by her domestic problems. Her past medical history was non-contributory. She had two children aged 5 and 2 years and following the birth of her second child she was prescribed a contraceptive pill containing 2.5 mg Lynoestrenol and 75 µg/Mestranol.

On admission she complained of dizziness and tinnitus. She was drowsy, tachypnoeic, lean and pale. There were no palpable lymph glands, and the remainder of the physical examination was normal. She was admitted for observation and her symptoms subsided over a 24-hr period.

Investigations confirmed anaemia. The haemoglobin was 7.9 g/100 ml, the PCV 27%, the MCHC 29.5%, the reticulocyte count was 4%. The blood film showed moderate anisocytosis with some hypochromia. The platelets appeared normal. The sedimentation rate was 5 mm/hr (Westergren). The direct Coombs test was negative. The serum iron was 143 µg/100 ml, total iron binding capacity 380 µg/ml. The serum Vitamin B₁₂ was 150 pg/ml, the serum folate was 15.5 ng/ml, but gradually fell to 1.7 ng/ml over the next 10 months.

She was discharged after 48 hr and outpatient follow-up was arranged. During the following 11 months the patient was readmitted three times for recurrent anaemia (Fig. 1). Repeated investigations which gave normal results included the following: urinalysis, blood urea and electrolytes, serum proteins and immuno-electrophoresis, direct Coombs test, blood LE cells, anti-nuclear factor, Wassermann reaction and gastric and thyroid antibodies.

Chest X-ray, barium meal and follow-through revealed no abnormalities. The red blood cell osmotic fragility and glucose-6-phosphate dehydrogenase were also normal, as were Ham's test for paroxysmal nocturnal haemoglobinuria, haemoglobin electrophoresis, serum calcium and phosphate, alkaline phosphatase, bilirubin and liver function tests, faecal fat and a pentagastrin gastric secretion test. Tests for occult blood and a Schilling test were negative.

During her first outpatient visit a bone marrow aspiration was done. Erythropoiesis was markedly increased and, although the red cell series was mainly normoblastic, a few megaloblasts were noted. Stainable iron was markedly increased. The differential diagnosis was thought to be either idiopathic or drug induced haemolytic anaemia. She was therefore instructed to stop all medication, but she continued taking the pill unknown to us. The anaemia persisted and a second bone marrow aspiration, 6 months later, showed that the marked erythroid hyperplasia was now predominantly megaloblastic. Serum folate at the time was lower but still within normal limits. Each hospital admission appeared to cause a remission in the anaemia, but these remissions were not sustained. On the last admission the serum folate level was abnormally low and a further bone marrow aspiration showed grossly megaloblastic erythropoiesis. It was now discovered that she had continued to take the contraceptive pill, and a careful dietary history established that her estimated intake of folate was also well below normal, at 9 µg/day. The pill was stopped and she was started on an oral folate supplement of 5 mg daily. Four days later the reticulocyte count was 14.4% and the haemoglobin

remained at normal levels thereafter. Her headaches did not recur after stopping the pill.

Discussion

The daily requirement of folate is said to be between 50 µg (Herbert, 1962) and over 100 µg (Perry and Chanarin, 1968). In normal mixed diets 75% of folate is in the polyglutamate form, having a chain of seven glutamic acid residues (Chanarin *et al.*, 1968). The polyglutamate compound is poorly absorbed by man (Perry and Chanarin, 1968). Much of this polyglutamic folate is deconjugated at the intestinal mucosa into 'free' monoglutamic folate (Streiff, 1969). The 'free' folate is readily absorbed, up to 80% in fasting subjects (Chanarin *et al.*, 1968).

Streiff (1969) gave a physiological dose of polyglutamic folate by mouth to two groups of women. Serum folate rose significantly less in the women who were taking the contraceptive pill than in the control group. When 'free' folate was given no significant difference in the rise of serum folate was noted between these two groups. Similar observations were made by Snyder and Necheles (1969). This effect on polyglutamic folate absorption was ascribed to inhibition of the intestinal conjugase system by the pill.

A similar mechanism appears to operate in the folate deficiency associated with phenytoin medication. Rosenberg *et al.* (1968) have shown that phenytoin caused inhibition of folate deconjugation *in vitro* and impaired the absorption of polyglutamic folate in some healthy volunteers, whereas the absorption of 'free' folate was not impaired.

Although our patient thought she ate an adequate diet, a detailed dietary history revealed a gross deficiency of folate intake. Chanarin *et al.* (1968) found that the average daily 'free' folate content in urban diets was 160 µg. Thus even if the pill could have completely blocked the deconjugation of polyglutamic folate, no folate deficiency should have resulted in a woman who ate a balanced diet.

In our patient the combined effects of dietary folate deficiency and enzymatic blockage of folate

deconjugation by the pill were sufficient to cause gradual folate depletion and anaemia. When she ate hospital food her increased folate intake induced a rise in haemoglobin despite the continuation of the contraceptive pill. A similar observation was made by Streiff (1969).

We felt that we could not rely on the patient to change her diet. Therefore, we did not feel justified in withholding folate supplement after she stopped taking the pill, merely to confirm the role of the contraceptive pill in inducing her folate deficiency.

Many young women now start a family after taking the pill for some years. An insidious depletion of folate may thus have taken place, especially if dietary intake has been inadequate. This mechanism may be an additional cause of anaemia in early pregnancy.

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