TABLE I—*Percentage of women reporting side effects and changes in menstrual bleeding in first three cycles of oral contraceptive use, by weight categories*

	Cycle 1			Cycle 2			Cycle 3		
	Underweight (n = 77)	Normal weight (n = 244)	Overweight (n = 119)	Underweight (n = 77)	Normal weight (n = 233)	Overweight (n = 113)	Underweight (n = 72)	Normal weight (n = 217)	Overweight (n = 104)
Side effects									
Breakthrough spotting	22·1	22·2	21·0	15·6	13·7	19·5	9·7	12·4	9·6
Breakthrough bleeding	23·4	25·4	28·6	24·7	30·5	27·4	29·2	28·1	26·0
Cramps	54·2	52·9	52·9	48·1	39·1	37·2	41·7	32·7	33·7
Nausea	44·2	45·5	42·0	32·5	29·6	11·5	16·7	22·1	16·3
Vomiting	10·4	9·8	3·4	7·8	9·4	2·7	5·6	9·2	7·7
Headache	32·5	27·5	41·1	24·7	16·7	23·0	18·1	17·1	18·3
Depression	33·8	29·1	28·6	19·5	17·6	25·7	19·4	17·1	19·2
Breast discomfort	50·6	52·9	45·4	45·5	47·2	34·5	29·2	35·0	31·7
Increase in acne	45·5	43·4	41·2	35·1	33·0	31·0	23·6	24·0	26·9
Decrease in acne	19·5	17·2	17·6	20·8	14·6	18·6	15·3	11·1	12·5
Change in sexual desire	22·1	18·4	22·7	19·5	16·3	20·4	16·7	13·4	11·5
*Menstrual bleeding**									
No change	16·9	22·1	19·3	23·4	19·7	19·5	19·4	18·4	21·2
Increased flow	14·3	11·9	14·3	6·3	9·0	10·6	6·9	8·3	9·6
Decreased flow	66·2	59·4	58·8	71·4	67·0	67·3	69·4	71·0	67·3
No flow	6·5	6·1	7·6	3·9	4·3	3·5	4·2	2·3	4·8

*Columns may total over 100% because some women reported more than one type of change in menstrual bleeding per cycle.

cycles more underweight women reported either decreased or absent menstrual bleeding than normal or overweight women, but this difference was not statistically significant.

Changes in weight and blood pressure—Heavier women had significantly lower ($P < 0.05$) weight gains at the end of the first three cycles on oral contraceptives (table II). Although there was no significant association ($P > 0.10$) between weight and changes in blood pressure, the relatively larger decline in diastolic blood pressure among the overweight women after three cycles suggested a possible relationship between these two variables.

TABLE II—*Weight and blood pressure measurements at enrolment and changes after three cycles of oral contraceptive use according to weight categories*

	Weight (kg)		Blood pressure (mm Hg)			
			Systolic		Diastolic	
	Enrolment	Change*	Enrolment	Change	Enrolment	Change
Underweight	50·8	+1·94	112·5	−3·83	68·6	−1·61
Normal weight	61·1	+1·32	114·8	−3·37	70·2	−1·63
Overweight	76·6	+0·16	120·7	−3·86	75·7	−3·73

*Change is defined as difference in patient's measurements after three cycles of oral contraceptive use.

Comment

Overweight women reported the lowest incidence of side effects while taking oral contraceptives. Conversely, underweight women experienced the highest incidence. These findings are consistent with the hypothesis that response is based on the drug dose related to body weight. Only the higher incidence of headache among underweight and overweight women deviated from the general pattern, and this suggests that factors other than contraceptive use contribute to side effects. Underweight women should be made aware that they are more likely to experience certain side effects (nausea, vomiting, breast discomfort, cramps, and weight gain) on starting oral contraception. (For this group of patients a gain in weight is not necessarily undesirable.)

Most of the associations noted were stronger during the first two cycles, and the differences between the groups tended to disappear during the third cycle. There is some evidence that this trend would continue over more prolonged use.[5] Therefore all women who experience side effects should bear in mind, when deciding whether or not to continue using oral contraceptives, that the incidence of side effects diminishes by the third cycle of use.

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Megaloblastic anaemia associated with sulphasalazine treatment

Sulphasalazine was introduced in 1942 by Svartz[1] for treating ulcerative colitis and has been used extensively ever since. More recently, it has found a limited place in the management of Crohn's disease. Various toxic effects of this drug on the haemopoietic system have been described,[2 3] mainly agranulocytosis, thrombocytopenia, and haemolytic anaemia, but megaloblastic anaemia has not been mentioned. We describe here a patient who developed megaloblastic anaemia five months after starting the drug and who promptly recovered after its withdrawal and treatment with folic acid.

Case report

A 68-year-old man (weight 66 kg) who had lived in a hospital for the mentally subnormal for 22 years had been suffering from attacks of loose stools since March 1974; these occasionally contained bright red blood but no mucus. No pathogens were found. The results of barium studies were unsatisfactory, but no evidence of ulceration or a neoplasm could be found in the distal colon. He was treated with kaolin mixture *BPC* and Lomotil but continued to have intermittent diarrhoea.

At the beginning of June 1976 he was given sulphasalazine 4·0 g daily. At this time he also had distinct signs of Parkinsonism and was therefore given Sinemet (levodopa and carbidopa) in increasing amounts and eventually stabilised on levodopa 1000 mg and carbidopa 100 mg daily. He improved rapidly. Towards the middle of November 1976 he deteriorated once more. He had become pale. His haemoglobin had dropped from 14·5 g/dl (March 1976) to 7·9 g/dl and the mean cell volume was 117 fl. A marrow biopsy showed increased activity with megaloblastic erythropoiesis. The serum lactate dehydrogenase level was considerably raised (799 mU/ml). Liver function values were normal. Serum folate was 1·0 μg/l and serum B_{12} 200 ng/l. Thereon sulphasalazine was completely withdrawn and treatment with oral folic acid (10 mg daily) started on 4 December 1976. He once

again improved rapidly. A daily reticulocyte count showed a peak of 20% on days 4 and 5 and his haemoglobin gradually rose to 13 g/dl by 7 January 1977.

Comment

The very low serum folate value may have been exaggerated by sulphasalazine interfering with the microbiological assay, but the rapid clinical and haematological improvement, including the prompt reticulocyte response to treatment with folic acid, leaves little doubt that folate deficiency was the cause of the megaloblastic anaemia in this patient.

There are several causes of folate deficiency in the elderly. Dietary deficiency was unlikely in this patient because he had been on the same mixed hospital diet without any major changes for 22 years without ill effect. His primary intestinal disease, probably some form of colitis, was not sufficiently severe to have caused gross folic acid deficiency, and, moreover, he had been suffering from it for over two years with no effect on his haematological status until drug treatment was started. Coeliac disease may cause folate deficiency but there was no evidence of this disease in this patient. His stools never showed the typical frothy appearance of the coeliac stool, and the values for faecal fat and xylose absorption were within normal limits. A small-intestinal biopsy, therefore, did not seem justified.

Levodopa and carbidopa are not known to affect the haemopoietic system, nor is diazepam, the only other drug he was given. In 1973, however, Franklin and Rosenberg[4] reported a significant reduction in serum folate levels in 10 patients with inflammatory bowel disease who were being treated with Azulfidine (sulphasalazine) compared with values in a control group of 16 similar patients not on this drug, and in 1976 Juhl *et al*[5] showed that sulphasalazine interferes with the absorption of digoxin. Therefore treatment with sulphasalazine seems the most likely cause of this patient's megaloblastic anaemia.

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Chondrodysplasia punctata and maternal warfarin treatment

In March 1975 Becker *et al*[1] reported from the United States two cases of children with chondrodysplasia punctata whose mothers had taken warfarin during the first trimester of pregnancy. Since then there have been reports from the United States and South Africa of five further cases[2-5] of this syndrome, the main features of which are nasal hypoplasia and epiphyseal stippling. We report here a similar case to alert obstetricians, physicians, and paediatricians in the United Kingdom to the likely teratogenic effect of warfarin.

Case report

A 1200-g boy was born to a 28-year-old woman in December 1976. The mother had been started on continuous oral anticoagulation with warfarin (6-7 mg daily) six months before becoming pregnant, when she was diagnosed as having thromboembolic pulmonary hypertension possibly related to the oral contraceptives that she had taken for the preceding year. The oral contraceptives were discontinued after this episode. She had had three previous pregnancies, the first two resulting uneventfully in full-term, normal deliveries and the third resulting in the spontaneous delivery of a 1000-g stillborn infant at home. There was no consanguinity, no family history of short stature, and skeletal survey radiographs of both parents were normal.

In her fourth pregnancy she was first seen at nine weeks' gestation, when she expressed a wish to continue with the pregnancy. Her only drug treatment at that time was warfarin. She received no other medication, apart from an iron and folic acid preparation, until she was admitted to hospital at 24 weeks' gestation with a history of vaginal bleeding. The warfarin was discontinued and she was given heparin. She had further vaginal bleeding

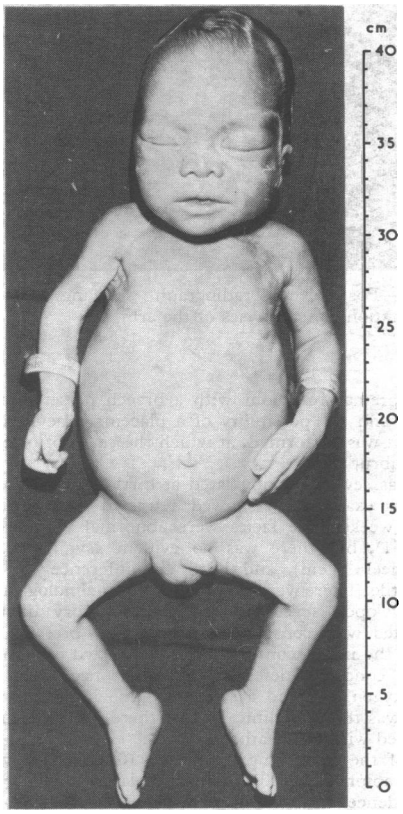

FIG 1—Wasted infant with abnormal facies and nasal hypoplasia.

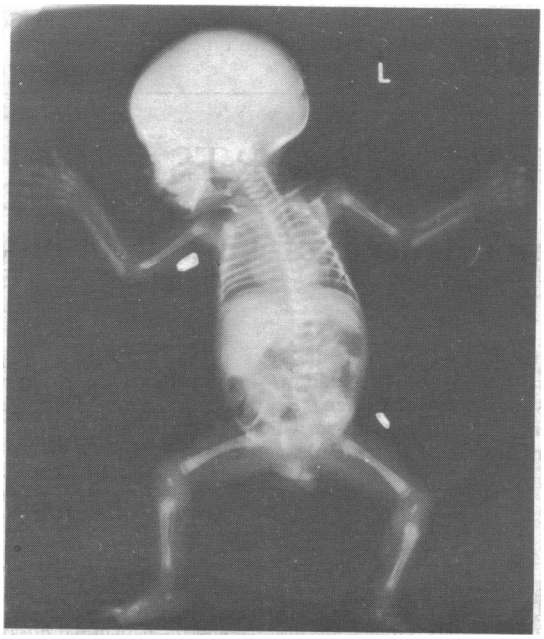

FIG 2—Radiograph on 10th day showing stippling of all epiphyses.