The pathogenesis is uncertain. It may be local oedema due to migration of an adult worm, or a vascular lesion, or even vascular block due to the presence of large number of microfilariae in cerebral vessels.

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³ Orihel, T C, *American Journal of Tropical Medicine and Hygiene*, 1973, **22**, 596.
⁴ Kivits, M, *Annales de la Société Belge de Médecine Tropicale*, 1952, **32**, 235.
⁵ Browne, S G, *Journal of Tropical Medicine and Hygiene*, 1954, **57**, 229.

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Treatment of palindromic rheumatism with D-penicillamine

Palindromic rheumatism is uncommon but important, firstly because it may lead to chronic rheumatoid arthritis, and, secondly, as a cause of disability if attacks are frequent. It is regarded as a variant of rheumatoid arthritis, and this is supported by the finding of positive tests for rheumatoid factor and other immunological abnormalities.¹ Mattingly² reported that gold treatment appeared to halt the attacks, often within a few weeks, though relapse was frequent when treatment was stopped or the dose reduced. The similarity of the effects of gold and D-penicillamine in chronic rheumatoid arthritis³ suggested the possibility of using D-penicillamine for palindromic rheumatism.

Patients, methods, and results

Details of the patients treated are shown in the table. All had a typical history of recurrent acute attacks of joint pain and swelling affecting various joints, each lasting for two or three days. They were kept under observation for a sufficient period of time to record the frequency of the attacks before treatment was started with D-penicillamine in a dose of 250 mg. daily. All have been followed up for at least a year while receiving the treatment. In four patients no further attacks occurred after starting D-penicillamine and dosage was not increased. One patient subsequently reduced the dose of D-penicillamine progressively and had a further attack while receiving 500 mg weekly; she has again been free of attacks on 250 mg daily. No side effects occurred in these four patients. One patient (case 3) continued to have attacks of arthritis and the dose was increased at fortnightly intervals up to 750 mg daily. Treatment was interrupted by a rash, which developed after four weeks; the drug was restarted when the rash disappeared and it did not recur. In this patient the frequency and severity of attacks were reduced.

Details of patients with palindromic rheumatism treated with D-penicillamine, including the number of attacks of arthritis during the period of observation before the start of treatment and for one year after

Case number	Age	Sex	Duration of disease (years)	Latex titre	Daily maintenance dose (mg)	Number of attacks	
						Before treatment	After treatment
1	45	F	8	neg	250	16 in four months	None for one year
2	33	F	7	neg	250	12 in 10 months	None for one year
3	65	F	5	1/80	750	25 in six months	Four in one year
4	19	F	3	1/20	250	8 in two years	None for one year
5	52	M	4	neg	250	17 in three years	None for one year

Discussion

Like gold, D-penicillamine appears to be a useful therapeutic agent in palindromic rheumatism. Though the course of palindromic rheumatism is unpredictable, it is most unlikely that such a sudden and spectacular change in the frequency of attacks would have occurred by chance or continued for so long. It is a considerable advantage that D-penicillamine can be used in a small dose which is unlikely to cause side effects. The rarity of the disease would make controlled trials difficult, but it would be desirable to confirm the effectiveness of D-penicillamine and to investigate the possibility that this drug might prevent the development of chronic rheumatoid arthritis. D-penicillamine treatment should certainly be considered in patients with frequent attacks of palindromic rheumatism.

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² Mattingly, S, *Annals of the Rheumatic Diseases*, 1966, **25**, 307.
³ Huskisson, E C, *et al*, *Annals of the Rheumatic Diseases*, 1974, **33**, 532.

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Megaloblastic anaemia due to pyridoxine deficiency associated with prolonged ingestion of an oestrogen-containing oral contraceptive

Pyridoxine deficiency is an uncommon cause of hypochromic and megaloblastic anaemias. I report here a case of macrocytic hypochromic megaloblastic anaemia responding to pyridoxine in a patient taking an oestrogen-containing oral contraceptive agent, in the absence of any other apparent cause for pyridoxine deficiency.

Case report

A 46-year-old Caucasian woman presented with tiredness and mild depression. There was nothing significant in her past medical history and the only drug she was taking was the oral contraceptive agent Gynovlar (ethinyl-oestradiol 50 µg and norethisterone acetate 3 mg), which she had used continuously for the previous seven years. The only abnormal finding on examination was clinical anaemia. Investigations showed haemoglobin 7.6 g/dl, a hypochromic macrocytic film, a reticulocyte count of less than 1 %, and a normal white cell count. The bone marrow showed "appearances typical of a frankly megaloblastic anaemia" and special stains failed to show any free iron. Serum folate was low at 1.0 µg/l, but red cell folate was normal at 200 µg/l. Urea, electrolytes, glucose, calcium, phosphate, alkaline phosphatase, and thyroid function tests were all normal. Stools were negative for occult blood. Tests for antinuclear factor, intrinsic factor antibody, and parietal cell antibody were all negative, and a chest x-ray was normal. Barium meal and follow-through showed "gastric rugae, probably flatter than the average, and compatible with pernicious anaemia. The small

intestine is normal with no evidence of malabsorption." Three-day faecal fat excretion and xylose absorption test were normal.

Although the serum B_{12} level was not available at the time, the evidence from blood, marrow, and barium meal examinations suggested vitamin B_{12} deficiency due to pernicious anaemia, and treatment was started with hydroxocobalamin 1 mg intramuscularly daily for four days, and then weekly. There was no haematological response, and the haemoglobin fell further to 34%. The patient was then admitted to the Luton and Dunstable Hospital (under Dr B P Harrold), where folic acid was added to her treatment, again with no response in the peripheral blood or marrow. A blood transfusion brought her haemoglobin up to 10.8 g/dl, but a subsequent marrow aspiration confirmed the previous findings of a megaloblastic picture, with a few ring sideroblasts, insufficient to justify a diagnosis of sideroblastic anaemia. At the suggestion of the haematologist (Dr J R B Williams) a therapeutic trial of pyridoxine was begun with a dose of 50 mg twice a day. Seven days later the marrow had reverted to normal and the patient was discharged on pyridoxine alone. In the following weeks her haemoglobin gradually returned to normal levels. After the diagnosis had been established the serum B_{12} level, in a sample of blood taken at the start of the investigation and before the administration of hydroxocobalamin, was reported as normal at 360 ng/l. A Schilling test was also normal.

Comment

Administration of combined oestrogen-progestogen oral contraceptive agents (OCA) can lead to a disturbance of tryptophan and vitamin B_6 metabolism owing to the oestrogen component causing induction of tryptophan oxygenase in the liver. This causes increased metabolism of tryptophan and hence an increased need for the necessary coenzyme pyridoxal phosphate.¹ Boots *et al*² report that a tenfold or greater increase in vitamin B_6 requirements is necessary to compensate for this effect. Rose *et al*³ reported that a subclinical vitamin B_6 deficiency may result, and Adams *et al*⁴ reported that a form of depression found in OCA users responds to pyridoxine administration. Brown *et al*⁵ concluded that a small subgroup of women may exist who are particularly vulnerable to vitamin B_6 deficiency when taking OCA, but I can find no previous reports of megaloblastic anaemia associated with OCA usage in a patient with no other apparent cause and responding to vitamin B_6 administration. I suggest that the above patient represents such a case.

¹ Leklam, J E, *et al*, *American Journal of Clinical Nutrition*, 1975, **28**, 146.

² Boots, L, *et al*, *American Journal of Clinical Nutrition*, 1975, **28**, 354.

³ Rose, D P, *et al*, *American Journal of Clinical Nutrition*, 1973, **26**, 48.

⁴ Adams, P W, *et al*, *Lancet*, 1973, **1**, 897.

⁵ Brown, R R, *et al*, *American Journal of Clinical Nutrition*, 1975, **28**, 10.

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Prolactin concentrations during anaesthesia

Because of the difficulty in detecting prolactin receptors in breast-tumour specimens obtained at operation, we postulated that the stress of the procedure might lead to raised serum prolactin levels with blocking of available receptor sites. We therefore studied the changes in serum prolactin concentrations during anaesthesia.

Patients, methods, and results

Nine men and ten women undergoing general surgery and nine women having a lump in the breast removed were studied. Patients receiving medication known to affect serum prolactin concentrations (such as chlorpromazine) were excluded. Venous samples were obtained before induction of anaesthesia and at about 15-minute intervals during the operation. The number of samples obtained depended on the length of the operation. Premedication was with atropine and papaveretum. Anaesthesia was induced in most cases with thiopentone and suxamethonium and maintained with N_2O/O_2 and halothane.

Radioimmunoassay of human prolactin used materials supplied by NIH and human standard supplied by Dr H Friesen (code 72/11/23). Radio-

immunoassay of human growth hormone used materials supplied by the MRC and as standard WHO First IRP 66/217.

Serum prolactin and GH concentrations are shown in the figure. The difference between resting levels in the three groups is not significant but the peroperative levels are statistically significantly different from each other and from the resting levels ($P < 0.025$ Mann-Whitney U Test). Prolactin concentrations rose within 15 minutes and remained high for up to one hour, by which time most operations in this series were completed. The readings shown in the figure are from samples taken between 15 and 30 minutes after induction. The removal of a lump in the breast was for a benign lesion in five cases and for a malignant tumour in four. The mean peroperative level for the benign group was $71 \pm 8.4 \mu\text{g/l}$ (standard error of the mean) and for the malignant group $124 \pm 13.5 \mu\text{g/l}$.

Effect of general anaesthesia on serum growth hormone and prolactin concentrations.

Discussion

There is little published data on prolactin concentrations during anaesthesia in man. One study shows a significant rise in both men and women, with a greater rise in women.¹ We have found a significant rise in all groups studied but of special interest is the finding of much higher concentrations in women undergoing surgery for a lump in the breast. The women with malignant lumps seem to have the highest concentrations, but the numbers are too small to draw definite conclusions. Abnormalities in basal prolactin concentrations have been reported in some women with benign and malignant breast lumps.²⁻⁴ A small difference in peak prolactin response to TRH has been claimed in advanced breast cancer compared with earlier stages and with normal people.⁵

Whether these differences are due to inherent differences in prolactin secretion or to greater stress in women with breast lumps is not clear. The failure of growth hormone concentrations to rise significantly is against the latter explanation.

We thank the Dame Barbara Hepworth Fund and the Wolfson and Westminster Medical School Research Trusts for financial support, and Professor J R Hobbs for his advice.

¹ Noel, G L, *et al*, *Journal of Clinical Endocrinology and Metabolism*, 1972, **35**, 840.

² Kwa, H G, *et al*, *Lancet*, 1974, **1**, 433.

³ Franks, S, *et al*, *British Medical Journal*, 1974, **4**, 320.

⁴ Cole, E N, *et al*, *Journal of Endocrinology*, 1976, **69**, 49P.

⁵ Mittra, I, Hayward, J L, and McNeilly, A S, *Lancet*, 1974, **1**, 889.

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