TABLE IV—*Fifteen-minute Fetal Movement Counts with Inactivated and Activated Ultrasonic Heads with Intervening Air Cell and Activated Ultrasonic Head without Air Cell*

Case No.	Maturity (Weeks)	No. of Fetal Movements			Parity	Obstetric Disorder
		Non-activated Ultrasonic Head with Air Cell (15 Min)	Activated Ultrasonic Head with Air Cell (15 Min)	Activated Ultrasonic Head Without Air Cell (15 Min)		
22	33	1	4	11	M.	Placenta praevia
23	36	0	0	5	P.	Placenta praevia
24	36	0	4	5	M.	Raised B.P.
25	38	4	3	3	M.	Rhesus isoimmunization
26	40	2	1	5	P.	Anaemia
27	38	0	0	2	M.	Placenta praevia
28	38	7	9	11	P.	False labour
29	36	4	6	16	M.	Antepartum haemorrhage
30	38	10	5	7	P.	Raised B.P.
31	35	0	6	7	P.	Raised B.P.
32	38	8	4	23	M.	Diabetes
33	32	5	6	18	P.	Antepartum haemorrhage
34	33	8	2	13	P.	Raised B.P.
35	33	19	13	20	P.	Urinary tract infection
36	36	1	5	6	P.	Raised B.P.
Mean		4·6	4·5	10·1		

During the past 12 months in our unit four infants have died antenatally. Each mother had reported absent fetal movements for at least 12 hours before the fetal heart became inaudible. During this time each patient underwent external cardiotocography using Doppler ultrasound without fetal response. Other patients who recorded low daily fetal movement counts (below 11/24 h) and in whom the fetal outcome was satisfactory showed an increase in fetal activity during the 24 hours after a one-hour exposure to Doppler ultrasound; however, the reverse was not always true. Though we do not know why the fetus responds to Doppler ultrasound, it is a procedure without known risk,[5] and we think that with further development the study of this response might provide further information about the fetus.

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Accumulation of Storage Iron in Patients Treated for Iron-deficiency Anaemia

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Summary

The repletion of iron stores after treatment was studied in 38 patients with uncomplicated iron-deficiency anaemia. The serum ferritin concentration rose significantly when oral treatment was continued for two months after the attainment of a normal haemoglobin concentration. Patients treated with a total-dose infusion of iron dextran had the highest final serum levels, which were significantly greater than in patients given Ferro-Gradumet. Oral ferrous sulphate was almost as effective as parenteral iron in producing iron stores.

Introduction

In the management of patients with iron-deficiency anaemia it is generally recommended that oral treatment should be continued for several weeks after the peripheral blood has returned to normal so that iron stores are adequately replenished.[1 2] The validity of this concept remains unproved as the repeated measurement of body iron stores during treatment has not previously been feasible. Measurement of the serum ferritin concentration, however, provides a simple and accurate means for assessing iron stores,[3] and we have used this in patients being treated for simple iron-deficiency anaemia as a guide to the rate at which storage iron accumulates.

Patients and Methods

All the patients studied had iron-deficiency anaemia with a haemoglobin concentration of less than 10 g/dl, a mean corpuscualr volume (M.C.V.) of less than 75 fl, and a mean corpuscular haemoglobin concentration of less than 25 pg. The peripheral blood films all showed hypochromic, microcytic red cells. In all cases the serum iron concentration was less than 7 μmol/l (39 μg/100 ml), the total iron binding capacity greater than 70 μmol/l (390 μg/100 ml), and the transferrin saturation less than 10%. The patients were allocated at random to four treatment groups. Group 1 received a total-dose infusion of iron dextran (Imferon) according to the manufacturer's instructions; group 2 ferrous sulphate tablets (200 mg three times daily); group 3 Ferro-Gradumet one tablet daily; and group 4 Ferrograd C one tablet daily. Ferro-Gradumet is a controlled-release preparation containing 525 mg ferrous sulphate in each tablet, while Ferrograd C also contains 500 mg ascorbic acid in each tablet. All patients except those in group 1 were treated until two months after

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TABLE I—*Mean Blood Values (±S.E.) of all Patients before Treatment and during Treatment, (a) when Haemoglobin Concentration had Reached Normal Level (See Text) and (b) Two Months after Achieving Normal Haemoglobin Concentration*

Group	No. of Patients	Treatment	Before Treatment				During Last Two Months of Treatment							Total Duration of Therapy (Months)
							(a)				(b)			
			Hb. (g/dl)	M.C.V. (fl)	Serum Iron (μmol/l)	Transferrin saturation (%)	Hb. (g/dl)	M.C.V. (fl)	Serum Iron (μmol/l)	Transferrin saturation (%)	Hb. (g/dl)	M.C.V. (fl)	Transferrin saturation (%)	
1	12	Total-dose infusion	8·8±0·8	64·8±4·5	4·15±1·34	4·3±0·6	13·5±0·2	91·3±1·8	20·40±1·25	33·5±1·6	(7 months after treatment)			
2	7	Ferrous sulphate 200 mg thrice daily	9·2±0·3	68·2±1·6	3·93±0·53	3·8±0·6	14·0±0·3	86·8±3·3	19·33±2·68	29·0±4·1	14·7±0·5	93·7±3·2	30·2±2·9	4·8±0·5
3	8	Ferro-Gradumet 1 tablet daily	8·5±0·4	63·9±2·2	3·40±0·34	3·7±0·5	13·1±0·1	84·4±1·8	22·55±5·72	32·0±8·1	13·1±1·7	87·5±1·3	38·7±5·9	4·6±0·7
4	11	Ferrograd C 1 tablet only	8·4±0·3	64·6±1·5	3·77±0·50	4·1±0·6	13·5±0·2	83·2±1·1	20·76±1·96	40·6±5·1	13·9±0·3	87·6±0·8	36·7±0·5	4·7±0·2
Mean (oral therapy)			8·6±0·2	64·2±1·1	3·70±0·03	4·1±0·5	13·5±0·1	84·5±1·1	21·48±2·15	35·8±3·4	13·8±0·2	89·1±1·1	35·5±2·5	4·7±0·2

Conversion: SI to Traditional Units: Iron: 1 μmol/l ≈ 5·6 μg/100 ml.

they had first attained a normal haemoglobin concentration (over 12·5 g/dl in women and 13·5 g/dl in men).

All the men and postmenopausal women were investigated for gastrointestinal blood loss by faecal examination for occult blood, sigmoidoscopy, proctoscopy, and barium meal and enema examinations. Menstruating women were not extensively investigated unless their iron deficiency had arisen possibly from other than excessive menstrual loss. Patients with a gastrointestinal lesion or systemic disorder likely to affect the therapeutic response were excluded. All who completed the study showed a satisfactory response to treatment and only one relapsed within the next 12 months.

Haemoglobin concentration and red cell indices were measured at monthly intervals on a Coulter S automatic cell counter. Serum iron concentration and total iron binding capacity were measured by the method of Young and Hicks,[4] and serum ferritin concentrations by that of Addison *et al.*[5]

Results

Out of 38 patients completing the study 12 (1 man and 11 women) were in group 1, 7 (4 men and 3 women) in group 2, 8 (1 man and 7 women) in group 3, and 11 (2 men and 9 women) in group 4 (table I). There was no significant difference among the groups: all patients showed a satisfactory therapeutic response with no difference in its rate.

Patients with iron-deficiency anaemia and depleted iron stores have serum ferritin concentrations under 12 μg/l,[3 6] and this was found in the present study (table II). In 18 of the 26 patients on oral treatment the serum ferritin concentration was over 20 μg/l when the haemoglobin concentration had reached normal levels. These patients were equally distributed throughout all the groups. The mean serum ferritin concentration at that stage was higher in patients taking ferrous sulphate tablets than in those taking the other oral preparations but this was not statistically significant.

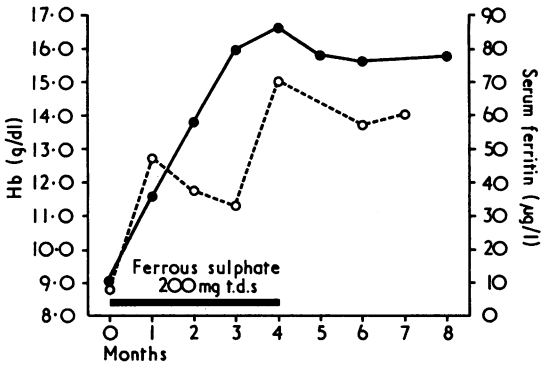
TABLE II—*Mean Serum Ferritin Concentration (±S.E.) after Treatment in All Groups of Patients; (a) and (b) as in Table I*

Group	No. of Patients	Treatment	Serum Ferritin Concentration μg/l		
			Initial	(a)	(b)
1	12	Total dose infusion	5·7±1·0	144·5±35·6 (7 months after treatment)	
2	7	Ferrous sulphate 200 mg thrice daily	6·3±1·2	47·0±11·8	84·4±15·2
3	8	Ferro-Gradumet 1 tablet daily	3·6±1·6	22·8±2·0	46·5±13·2
4	11	Ferrograd C 1 tablet daily	9·12±1·2	26·3±4·5	53·4±12·3
Mean (oral-therapy)	26		6·5±0·96	30·5±4·14	60·1±7·8

In the last two months of treatment, during which iron was given after correction of the anaemia the serum ferritin concentrations rose significantly in patients taking ferrous sulphate ($t=4·27$; $P<0.01$) and Ferrograd C ($t=2·6$; $P<0·05$). This was not observed in those on Ferro-Gradumet. The mean serum ferritin concentrations for all patients on oral treatment were 30·5 μg/l after correction of the anaemia and 60·1 μg/l ($t=4·44$; $P<0·001$) after two months of further treatment. At the end of the full course only two patients had serum ferritin concentrations under 20 μg/l.

In the patients taking oral preparations there was no significant difference between the mean serum ferritin concentrations at the end of treatment. Those treated by total-dose infusion of iron dextran, however, had a significantly higher serum ferritin concentration seven months after treatment than that found at the end of treatment in those who had received Ferro-Gradumet ($t=2·5$; $P<0·01$) or Ferrograd C ($t=2·4$; $P<0·02$) but not in those who had received ferrous sulphate ($t=1·55$; $P>0·05$).

In some patients the serum ferritin concentration was measured on several occasions during treatment, and in these an initial slight rise was followed by a greater rise when the haemoglobin depletion had been corrected (fig.). The final serum ferritin concentration was maintained after treatment.



Man aged 50. Effect of ferrous sulphate 200 mg thrice daily on haemoglobin (●——●) and serum ferritin concentrations (o..... o).

Discussion

Patients with iron-deficiency anaemia respond to oral treatment as rapidly and completely as they do to parenteral treatment.[7] Little is known, however, of the efficacy of oral treatment in restoring iron stores. Beutler *et al.*[8] showed the absence of stainable marrow iron in patients treated for up to four weeks with oral iron, whereas patients treated for longer periods developed visible iron deposits, and thus continued treatment after restoration of the haemoglobin concentration to normal has been recommended. The lack of sensitivity of this method in assessing iron stores compared with the measurement of serum ferritin concentration has been shown.[9] Our results show that a large proportion of patients acculumate iron stores during the period of increasing haemoglobin concentration. Iron, however, stimulates ferritin synthesis in vivo.[10] Siimes *et al.*[11] found a rapid rise in the serum ferritin concentration in the first week of treatment with oral ferrous sulphate in patients with iron-deficiency anaemia, suggesting that an inappropriately high serum ferritin concentration may be found in those taking iron. We found an initial slight rise in the serum ferritin con-

centration at the beginning of treatment and a further rise once the haemoglobin depletion had been corrected. The serum ferritin concentration was maintained after treatment had been discontinued and the values found in all groups corresponded to those in normal people.

Our data support the view that oral treatment should be continued for two months after the haemoglobin concentration has reached normal levels to replete iron stores. More-prolonged administration of iron is not indicated. Though high serum ferritin concentrations were found in some patients treated by total-dose infusion of iron dextran the results with oral ferrous sulphate were similar, suggesting that parenteral therapy has no special advantage.

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Peripheral Neuropathy and Indomethacin

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Summary

A patient with seronegative inflammatory polyarthritis developed a predominantly motor peripheral neuropathy associated with the use of indomethacin. Three other cases of peripheral neuropathy associated with indomethacin treatment have been reported to the Committee on Safety of Medicines. In all cases the neuropathy regressed when indomethacin was stopped. Peripheral neuropathy should be recognized as a rare complication of indomethacin therapy and considered in the differential diagnosis of a neuropathy accompanying rheumatoid arthritis.

Introduction

Peripheral neuropathy is a well-recognized complication of rheumatoid arthritis,[1-3] and the following types of neuropathy have been described: (*a*) entrapment neuropathies; (*b*) distal sensory neuropathy, with a generally good prognosis; (*c*) mononeuritis multiplex with a variable prognosis, often forming part of a generalized vasculitis with a picture resembling polyarteritis nodosa; and (*d*) a severe distal sensorimotor neuropathy which may follow a mononeuritis multiplex and is characterized by symmetrical distal weakness, muscle wasting, and sensory impairment in all limbs. This last type carries a poor prognosis and may be due to vasculitis of the vasa nervorum[4-6] or segmental demyelination.[7] Some cases of severe neuropathy seem to be associated with the use of corticosteroids, but we have found no report of indomethacin being suspected as a causative factor.

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Case 1

In June 1972 a 70-year-old man developed arthritis in the right knee, which later spread to most joints with accompanying morning stiffness. He was treated with salicylates, ibuprofen, and Panadeine Co without improvement. In December the ibuprofen was discontinued and he was started on indomethacin 75 mg/day, which was increased to 150 mg/day. He was receiving frusemide for ankle oedema, and benorylate was added to the regimen on 30 December. His joint symptoms improved, but towards the end of May he noticed increasing weakness and unsteadiness of his legs with paraesthesiae in the hands and feet. The weakness progressed slowly until he was unable to climb stairs and needed support in walking. On admission to hospital on 5 July 1973 there was ulnar deviation and spindling of the fingers with restricted movement of both wrists. Other joints were inactive and there were no rheumatoid nodules. There was no abnormality of the cranial nerves. Power and tone were normal in the arms, but in the legs there was definite impairment of power, which was prominent in distal muscle groups. The right triceps jerk was just elicitable but all other tendon jerks were absent. There was no detectable sensory loss. Plantar responses were flexor and his gait was high-stepping. Nerve conduction studies confirmed slowing of motor conduction with normal sensory latencies (see table).

Results of Nerve Conduction Studies on Admission to Hospital and After Recovery of Patient in Case 1

		July 1973		June 1974	
		Wrist/Ankle Latency (ms)	Forearm/Leg Velocity (m/s)	Wrist/Ankle Latency (ms)	Forearm/Leg Velocity (m/s)
Left common peroneal		5·5	27	5·9	39
Right median	motor	3·2	32	3·8	48
	sensory	2·5	—	2·6	—
Right ulnar	motor	2·6	33	3·1	51
	sensory	2·5		2·6	

Investigations did not show any underlying cause for his neuropathy; in particular, we found no evidence of a neoplasm. The progress of the illness was unlike a Guillain-Barré syndrome, and the fact that he was negative for rheumatoid factor was unusual for a rheumatoid neuropathy of this severity. The possibility of a drug-induced peripheral neuropathy was considered. Three cases of neuropathy in association with the use of indomethacin had previously been reported to the Committee on Safety of Medicines, so indomethacin was discontinued on 17 July 1973 and replaced by phenylbutazone suppositories. Benorylate had been discontinued on admission and he continued on frusemide for his ankle oedema. Before stopping indomethacin he had continued to deteriorate, but by 21 July he began to show some improvement in his walking. The paraesthesiae