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Splenic siderosis and parenteral iron dextran in maintenance haemodialysis patients

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SUMMARY The histological features of 40 spleens surgically removed from maintenance haemodialysis patients are reported. Twenty-four of the 40 (60%) showed massive iron loading and a significant direct correlation was found between iron loading and the amount of intravenous iron dextran administered. Since parenteral iron dextran appears to be a major factor in causing iron overload in haemodialysis patients its use as a method of iron replacement in these patients would appear inappropriate.

The spleens of patients maintained by regular haemodialysis are usually enlarged[1] and may show variable degrees of siderosis.[2] Previous histological studies have also demonstrated lymphoid hyperplasia[3] and foreign inclusions[4] thought to be fragments of silastic from the pump insert of the haemodialysis circuit. There has been no consensus as to the cause of the splenic enlargement and which, if any, of the above histological features contribute to it. Maintenance haemodialysis is an iron-depleting process[5,6] for which oral or intravenous iron replacement is required. The appropriateness of intravenous iron dextran for this purpose has recently been questioned because many haemodialysis patients have been found to have siderosis of the liver and spleen accompanied by very high serum ferritin concentrations.[7] However, there is still controversy about the relative roles of intravenous iron dextran, oral iron supplements and blood transfusions in the causation of this iron overload.[8] We have studied the histology of 40 spleens removed from regular haemodialysis patients in conjunction with their clinical histories to try to answer some of these questions.

Patients and methods

The patients had been maintained on regular haemodialysis (ranging from three months to 11 yr) performed three times per week for 5 to 7h each session. Patients used either a one square metre Kiil or similar disposable dialyser. Between 1975 and the end of 1978 all patients received approximately 250 mg of iron dextran intravenously each month. Oral iron supplements were not used at this time. In 1978 when serum ferritin estimations showed that almost all patients were overloaded with iron, administration of intravenous iron was stopped and these patients have subsequently rarely received oral iron. Patients commencing haemodialysis from 1979 onwards received no intravenous iron but most took oral ferrous sulphate. Only two patients received regular ascorbic acid supplements but all patients were maintained on folic acid.

None of the patients had had clinical hepatitis during their haemodialysis career and none was hepatitis B surface antigen or antibody positive.

In our unit splenectomy is not routine prior to transplantation but spleens are removed prior to, at the time of or shortly after the operation if the patient has a leucopenia which may interfere with the administration of adequate doses of azathioprine. Spleens were removed from 40 such patients.

Clinical information including the quantity of intravenous iron dextran given and the number of blood transfusions was obtained from the patients' records. Absolute reticulocyte counts, serum bilirubin concentrations, serum haptoglobin, haemopexin and methaemalbumin were measured in 22 patients. Serum ferritin concentrations measured by radioimmunoassay prior to splenectomy were available in 17 patients. Bone marrow examination was not performed.

The spleens were weighed fresh and fixed in buf-

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fered formalin. One 1·5 cm × 1·5 cm × 0·2 cm block of tissue per 100 g was processed to paraffin wax and sections examined by haematoxylin and eosin, Perls' and reticulin stains. Splenic iron deposition in the sections was retrospectively assessed qualitatively on a 0 to 3+ scale (where 0 denotes absence of stainable iron, 1+ denotes detectable or normal iron deposits, 2+ indicates moderately increased, and 3+ indicates grossly increased stores). The slides were examined by DNS and MAP with no knowledge of the clinical data. Unfortunately when the retrospective analysis was performed splenic tissue was not available to quantify the amount of iron present chemically.

Results

Details of the 40 splenectomised patients are summarised in Table 1. Ten patients had normal splenic iron deposits and only one had absent splenic iron. The remaining patients had either moderately increased (five patients) or greatly increased (24 patients) stores.

The 10 with normal stores had received a mean total iron dextran dose of 2·69 g (Table 2) whereas the 24 patients with greatly increased iron deposition had received a mean of 8·88 g ($p < 0·01$). Six of the eight patients who had never received intravenous iron had normal iron stores when on proportional representation only two would have been expected ($p < 0·001$)—Fig. 1.

The amount of blood transfused to each group was small (< 3 units) and insufficient to cause siderosis in its own right. Furthermore, many patients with massive iron deposition had never received any blood products (Fig. 2).

Spleen weights ranged from 50 to 625 g with a mean of 268·8 g (Fig. 3).

Normal deposition of iron was seen in the sinusoidal lining cells (1+). With heavier deposition (grades 2+ and 3+) iron was also observed within the cells of the splenic pulp. The iron-containing

Table 1 *Clinical and histological details of 40 haemodialysis patients who had splenectomy performed*

Patient	*Sex*	*Spleen iron grading*	*Spleen weight (g)*	*Imferon dose (g)*	*Hb (g/dl)*	*MCH (27–32 pg)*	*Ferritin (15–200 µg/l)*
PB	M	0	190	0	6·7	27·6	36
RB	F	1+	135	0	7·0	—	377
PC	M	1+	255	5·0	7·7	27·1	135
DG	F	1+	50	0	9·8	29·8	90
CH	M	1+	625	8·5	8·7	28·2	228
DH	F	1+	230	0	6·5	19·8	—
BK	M	1+	380	7·7	14·4	—	—
BO	F	1+	103	0	5·7	—	284
HR	F	1+	191	0	6·8	25·9	—
KS	F	1+	180	5·7	6·9	—	—
NW	F	1+	118	0	6·8	27·7	79
GB	M	2+	168	4·75	9·4	28·3	229
VB	F	2+	287	13·3	7·3	24·5	—
DK	M	2+	275	10·2	9·9	29·9	—
AT	M	2+	285	0	7·4	31·2	—
KT	M	2+	210	5·3	6·8	32·0	558
DA	M	3+	327	7·1	9·8	31·0	—
RB	M	3+	560	21·0	11·6	30·1	—
DB	F	3+	290	9·2	6·3	—	—
JB	M	3+	250	6·0	6·6	29·3	—
SC	F	3+	330	6·0	6·3	—	1938
SC	M	3+	335	8·2	8·4	31·9	—
WC	F	3+	260	4·5	9·2	—	—
MD	M	3+	354	6·0	10·2	26·6	—
PF	M	3+	235	9·5	6·9	26·3	2203
JG	F	3+	250	11·7	6·1	—	—
JJ	F	3+	322	15·1	5·9	—	—
RL	M	3+	275	7·5	6·4	29·5	2077
GN	F	3+	350	6·3	5·3	30·1	1900
JO	F	3+	360	4·5	6·0	—	—
OP	F	3+	312	7·0	7·8	30·0	1460
BR	F	3+	315	23·1	10·8	28·3	—
MR	F	3+	150	13·0	5·9	32·9	1330
JS	M	3+	395	14·1	7·4	28·1	—
WS	F	3+	240	8·0	5·9	—	—
AS	M	3+	200	3·0	6·1	29·2	709
CT	F	3+	180	5·25	8·3	34·3	1100
JT	F	3+	170	5·2	9·3	35·1	—
LW	F	3+	110	4·5	6·1	31·7	—
MW	M	3+	500	7·5	6·6	—	—

Table 2 *Parenteral iron sources in 39* haemodialysis patients with splenic iron deposits*

Mean values	*Patients with normal (1+) iron content of spleen (n = 10)*	*Patients with moderately increased (2+) iron content of spleen (n = 5)*	*Patients with greatly increased (3+) iron content of spleen (n = 24)*
Quantity of iron dextran (g)	2·69	6·71	8·88
Units of blood transfused	2·70	1·20	2·79

*One patient had no detectable splenic iron.

cells in this location were frequently clustered into groups (Fig. 4). The red pulp appeared prominent together with congestion of the splenic sinusoids. In most respects the white pulp appeared normal but germinal centre formation was not observed. No foreign-body giant cells or macrophages with inclusion bodies were seen. No other histopathological abnormality was found including the spleen of 625 g.

Absolute reticulocyte counts were not raised in 22 patients who were studied and the serum bilirubin, haemopexin and haptoglobin concentrations were within normal limits. No methaemalbumin could be detected in patients' sera.

Serum ferritin concentrations measured in 17 patients showed a good correlation with the qualitative grading of splenic iron stores. Six patients with normal (1+) splenic iron had a mean serum ferritin of 198·8 μg/1. (normal range 15–200). Eight patients with greatly increased (3+) splenic iron also showed greatly increased ferritin concentrations, the mean serum ferritin being 1589.6 μg/1. ($p < 0.001$).

Discussion

Our study has shown that spleens removed from our regular haemodialysis patients were siderotic. The group as a whole had received very small amounts of blood and there was no correlation between the presence of gross iron loading and volume of blood transfused. However, there was a very strong corre-

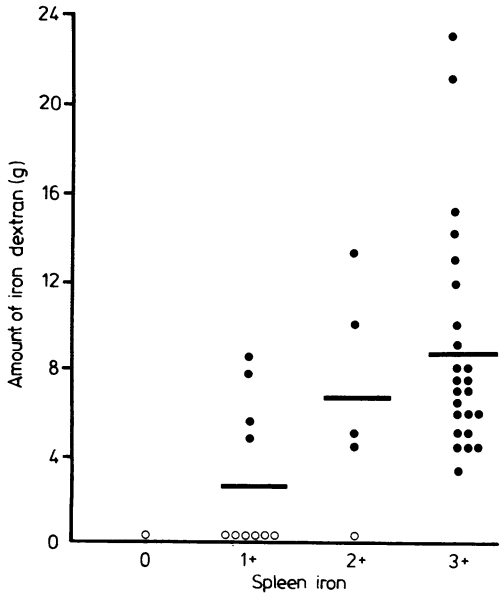

Fig. 1 *Correlation of splenic iron deposition with amount of iron dextran given in 40 haemodialysis patients. Means indicated by bars.* ○ = *patients who had never received iron dextran.*

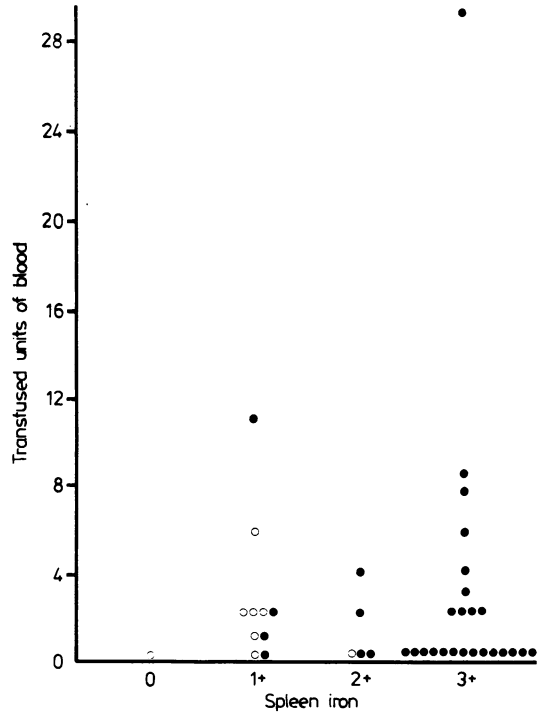

Fig. 2 *Spleen iron in relation to volume of blood transfused.* ○ = *patients who had never received iron dextran.*

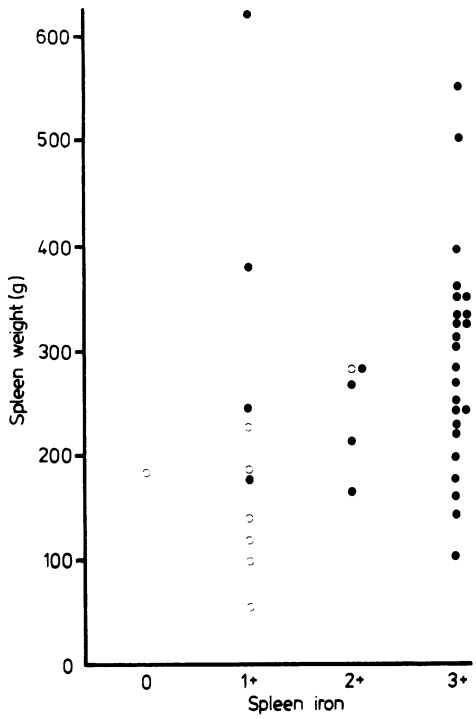

Fig. 3 *Distribution of spleen weights in relation to iron deposition.* ○ = *patients who had never received iron dextran.*

lation between iron load and amount of intravenous iron administered.

The avoidance of iron loading depends on the regulation of iron absorption, since there is no physiological route for the excretion of excess amounts.[9] The normal regulatory mechanisms controlling iron absorption are usually maintained in patients on regular haemodialysis,[10] but are bypassed when iron is administered parenterally as iron dextran or transfused blood. Only one of our eight patients who had received oral but no intravenous iron showed moderately increased iron stores in the spleen. Iron overload after oral iron therapy is extremely uncommon,[11] but we have observed one uraemic patient who had taken oral iron for many years who presented before any dialysis with a serum ferritin of 7000 μg/1. In some cases, therefore, it would appear that abnormal absorption of oral iron may account for iron loading. In general, however, oral therapy is safer than parenteral replacement with less likelihood of iron overload. One study demonstrated that oral ferrous sulphate was superior to iron dextran in terms of improvement in the haematocrit.[12]

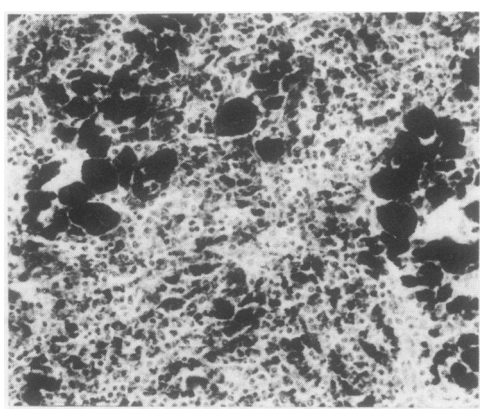

Fig. 4 *Spleen showing heavy iron deposition (Grade 3+). Perls' stain* × *50.*

Excess iron stores are undoubtedly utilised to some extent since haemodialysis patients with high ferritin concentrations after intravenous iron maintained their haemoglobin whilst the serum ferritin fell.[13] Our experience is that raised serum ferritin concentrations do not show a pronounced fall when intravenous iron is discontinued, the ferritin having been demonstrated to be a reliable determinant of iron stores in haemodialysis patients.[14,15] The patients in this study maintained or improved their haemoglobin after splenectomy but this would have been expected as many patients went on to receive a successful renal transplant. Utilisation of excess iron stores may well be transitory and there is a tendency for reticuloendothelial iron dextran stores to become progressively unavailable with time.[16] This phenomenon appears to be similar to the block in iron release seen in individuals with chronic inflammatory states. Further evidence for the impaired release of iron for effective haemopoiesis has been provided by Ali *et al*,[7] who described absent marrow iron stores in some haemodialysis patients who nevertheless had marked hepatosplenic siderosis.

Siderosis has been demonstrated previously in haemodialysis patients but there was no definite evidence of tissue damage.[2] It has been assumed that the predominant reticuloendothelial iron accumulation resulting from transfusion is less harmful than the parenchymal deposition seen with hereditary haemochromatosis.[17] Although relatively little is known of the mechanisms governing the internal distribution of iron, the storage ability of reticuloendothelial cells can easily be exceeded with subsequent parenchymal deposition. Indeed it now seems that the ultimate patterns of organ dysfunction in transfusional and hereditary iron overload are very similar despite early differences in the site of iron

distribution.[18] Schafer[19] has demonstrated important cardiac, hepatic and endocrine abnormalities in adults with transfusional iron overload. Such abnormalities, however, are difficult to assess in haemodialysis patients. Cardiomegaly and pulmonary oedema may be induced by the frequent large shifts in fluid volume. Many of our patients had abnormal liver biochemistry (usually a raised alkaline phosphatase activity), but these patients also had renal osteodystrophy. Recently changes in vitamin C status have been shown to influence the distribution of iron between reticuloendothelial and parenchymal sites.[20] All these factors suggest that reticuloendothelial iron overload may not be as innocuous as has been assumed in the past.

Haemolysis plays a role in the anaemia of chronic renal failure.[21] Reticulocyte counts are of doubtful value and haemolysis is usually only demonstrable by radioisotope studies. In keeping with previous workers[22] we have found no evidence of haemolysis in patients studied by means of absolute reticulocyte counts, serum haptoglobin, haemopexin, methaemalbumin and bilirubin concentrations.

The prominence of the red pulp in our cases is consistent with the presence of red pulp hyperplasia as previously described in haemodialysis patients. However, we have not observed the lymphoid hyperplasia described by Neiman.[3] This may be because our patients had not suffered from hepatitis since Neiman ascribed splenic enlargement in haemodialysis to chronic infection, particularly hepatitis. There was no significant difference in the weights of the spleens of the siderotic and non-siderotic groups although there was a trend for spleen weight to increase with iron loading. This study, therefore, does not support iron deposition, lymphoid hypertrophy or the presence of inorganic foreign bodies in the spleens of haemodialysis patients as causes of the splenomegaly as suggested by other workers. It would appear possible that the splenomegaly was due to red pulp hyperplasia.

The spleens in this study were a selected group removed because of clinical hypersplenism. It is, therefore, not surprising that they were enlarged. However, Platts *et al* (personal communication) have shown by radioisotope imaging of the spleens of a large population of haemodialysis patients that splenomegaly is a general finding and not seen in other uraemic patients who are either undialysed or treated by peritoneal dialysis. Hypersplenism itself can result in splenic haemosiderin deposition. However, it is not a constant finding and rarely appears heavy. In addition, the iron tends to be restricted to the sinusoidal lining cells.[23,24] Consequently we consider it unlikely that hypersplenism was the cause of the consistent and heavy iron overload seen in these patients.

On the basis of these findings we believe that parenteral iron dextran is a major factor causing iron overload in haemodialysis patients and is, therefore, an inappropriate form of therapy for this group.

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