Iron Metabolism in the Anaemia of Chronic Renal Failure. Effects of Dialysis and of Parenteral Iron

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Summary: Serial studies of iron transport in patients on maintenance dialysis showed normal or raised values in almost all subjects and a transient increase soon after the start of dialysis in three. These patients, who were seldom or never transfused, had low serum iron levels and normal iron-binding capacity with low saturation. Iron transport was substantially increased by parenteral iron-dextran treatment. Tracer studies showed good iron utilization, with transport to the marrow rather than to the liver. In these circumstances iron therapy is safe and beneficial, and a useful rise in red cell mass was shown to result from it. The packed cell volume was found to be a valid index of red cell mass in these patients. Red cell loss in the dialysers was insufficient to account for the observed reduction in red cell survival.

Introduction

Chronic renal failure is accompanied by anaemia characteristically resistant to haematinics. This anaemia has been attributed to reduced red cell survival (Emerson and Burrows, 1949), to reduced red cell production (Chodos, 1956), or to a combination of both mechanisms (Joske *et al.*, 1956). The reduction in erythropoiesis may be attributable to lack of erythropoietin production by the kidneys (Mann *et al.*, 1965), but probably the biochemical disturbances of severe uraemia also influence bone marrow activity. Dialysis has been followed by an initial increase in erythroid iron turnover (Kurtides *et al.*, 1964; Mann *et al.*, 1965), but the studies of Eschbach *et al.* (1967) failed to show any clear-cut effect of dialysis on iron utilization in patients who were already on maintenance dialysis. It is probably relevant that these patients were routinely transfused in order to maintain packed cell volumes above 24%.

The purpose of the present study was to investigate the pattern of iron kinetics in patients treated by intermittent dialysis without transfusion. By means of an isotope of short half-life (^{59}Fe , half-life 8.2 hours) serial studies of plasma iron clearance could be made in these patients to try to discern any effect of dialysis and of the administration of therapeutic doses of iron compounds. The packed cell volume is often used as a guide in the assessment of anaemia in dialysed patients. The rapid changes in plasma volume which may occur in patients treated by dialysis, however, cast doubt on the validity of using the packed cell volume as a guide to erythropoietic adequacy. We have therefore studied the relation between red cell mass and packed cell volume at various intervals between dialysis.

Clinical Data

The details of the 15 patients studied are summarized in Table I. In each of them a Teflon-Silastic arteriovenous shunt had been inserted. They were dialysed twice or thrice

weekly by means of the two-layered low-volume Kiil dialyser with PT150 cuprophane membranes for a minimum total of 28 hours per week. A few patients had previously been dialysed for a short period (one to three months) on coil dialysers which had been primed with blood. The Kiil dialysers were primed with saline, and blood transfusion was given only when severe symptoms of anaemia or blood loss necessitated it. None of the patients, however, required transfusion during the period of the study. Some were investigated at the time of admission to the dialysis programme or as soon as possible thereafter. These patients were reinvestigated at intervals to assess the effect of dialysis on iron transport. Another group of patients were investigated before, during, and after a period during which parenteral iron-dextran (Imferon) had been injected into the venous line at the end of each dialysis; 2 ml. of this, equivalent to 100 mg. of elemental iron, was given on each occasion.

TABLE I

Case No.	Sex and Age	Diagnosis	Mean Value of Blood Urea at Start of Each Dialysis (mg./100 ml.)	Serum Iron before Study ($\mu\text{g./100 ml.}$)	Duration on Dialysis at First Study	Transfusion before Study
1	F 21	GMN	170	20	9 months	Frequent till 3 months before study. Only once since then
2	F 34	CPN	120	69	7 weeks	One unit only
3	M 37	GMN	115	82	Nil	None
4	M 55	GMN	150	82	12 months	Frequent till 3 months before. None since
5	M 20	Alport's syndrome	120	46	1 day	4 units, 4 weeks before
6	M 47	Polycystic kidneys	170	60	7 months	None
7	F 30	CPN	105	60	2 weeks	4 pints (2.3 litres) one month before
8	F 30	CPN	80	64	6 months	None
9	F 27	CPN	110	50	7 days	None
10	M 47	Analgesic nephropathy	100	42	4 weeks	None
11	M 43	GMN	100	43	Nil	None
12	M 35	CPN	110	45	4 months	None
13	M 49	GMN	150	70	11 months	Twice (two units each)
14	M 31	Polycystic kidneys	100	52	3 months	None
15	M 30	Malignant hypertension	115	38	3 weeks	None

GMN = Glomerulonephritis. CPN = Non-obstructive chronic pyelonephritis.

Methods

For serial studies of iron clearance and red cell mass the following procedure was adopted at each study. The patient came to the hospital at about 5 p.m. and a medication rubber insert was placed between the two limbs of the shunt followed by an injection of 2,000 units of heparin. The venous end of this medication rubber insert was used for all injections and the arterial end for all sample-taking during the study to obviate any discomfort and risk of damage to potential shunt sites.

Seventeen millilitres of blood was withdrawn into 3 ml. of acid citrate dextrose and the red cells were separated by centrifuging at 1,000 r.p.m. Five microcuries of ^{59}Fe was added

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to 10 ml. of plasma and allowed to stand for 15 minutes at room temperature; a weighed amount was then reinjected. A further weighed amount was kept as a standard. Blood samples for serum iron estimation were taken at 20, 40, and 60 minutes after reinjection. The radioactivity of the samples was determined 100 minutes¹ after the last sample was taken; the results were expressed as half-clearance time and iron transport (Lajtha, 1961).

As soon as the plasma had been set to incubate with the ⁵²Fe the separated red cells were washed in 3% plasma saline (made with the surplus of the patient's own plasma), packed by centrifuging at 1,000 r.p.m., and the supernatant discarded. Enough ⁸⁶RbCl₃ was added to give a final uptake of between 5 and 10 μ Ci,¹ and the mixture was incubated at 37° C. for 60 to 75 minutes. After incubation the cells were washed twice with plasma saline at 4° C. and resuspended in this. A weighed amount was reinjected and a further amount retained as standard. A final sample was withdrawn 10 to 15 minutes after reinjection for estimation of red cell mass. This and the standard were counted in a well crystal counter four days later. The delay allowed complete decay of ⁵²Fe while resulting in only moderate loss of rubidium activity (half-life 14 days).

Long-term studies with ⁵⁹Fe and ⁵¹Cr were carried out in the usual manner (Lajtha, 1961). Serum iron and iron-binding capacity were estimated on the AutoAnalyzer with Tripyridyl and by a manual method using Bathophenanthroline. Both methods were often used on the same samples, and close agreement was obtained. Conventional methods were used for estimating urea, creatinine, packed cell volume, reticulocytes, and haemoglobin.

Blood loss was estimated by labelling the patients' cells with ⁵¹Cr (Lajtha, 1961) and collecting the fluid left in the Kiil dialyser, together with the membranes and connecting lines. These were all placed into a 1-litre wide-mouthed bottle at the end of dialysis. They were counted in a large-volume scintillation counter against a standard composed of a known amount of the patient's blood, which had been taken towards the end of dialysis and diluted to a similar volume in water and in an identical type of bottle.

Results

Packed Cell Volume as Index of Red Cell Mass

In patients maintained by dialysis a close correlation exists ($r=0.94$, S.E.=0.21) between arterial blood haematocrit values measured at varying times between dialyses and the red cell mass (in ml./kg.) as determined by labelling cells with ⁸⁶Rb or ⁵¹Cr (Fig. 1). The correlation was less exact before maintenance dialysis was started because of a relative expansion of plasma volume.

FIG. 1.—Red cell mass determinations related to arterial haematocrit reading. The correlation coefficient is 0.94 and the line is the calculated regression line, the equation of which is P.C.V.=1.61×red cell mass (ml./kg. body weight)−2.2. Only patients receiving regular maintenance dialysis are represented on the graph.

¹ For details see appendix concerning the use of ⁵²Fe and ⁸⁶Rb.

Iron Metabolism

In most of the group of non-transfused patients on maintenance dialysis who were studied by us the plasma iron transport was within the normal range (Fig. 2). Studies made shortly after dialysis had begun indicated that a sharp rise in iron transport might occur during the early days of the treatment, but that if so the effect would be transient (Fig. 3). After the first two months of dialysis the plasma iron transport had returned to predialysis levels. Though in most patients studied the transport was normal or raised, in some it was slightly below normal. It has not been possible to relate this difference to differences in the adequacy of dialysis as assessed by serum urea or creatinine levels.

FIG. 2

FIG. 3

FIG. 2.—Distribution of plasma iron transport values in dialysed patients not receiving iron therapy. FIG. 3.—Effect of beginning regular dialysis treatment on iron transport. ○—○ Case 5; ×—× Case 3; △—△ Case 11; □—□ Case 2; ■—■ Case 9; ●—● Case 7.

Plasma iron levels in these patients were nearly always low (42 to 86, mean 60 μ g./100 ml.) before treatment with iron, whereas the iron-binding capacity was normal (range 228 to 468, with mean of 22 observations=368 μ g./100 ml.; saturation 13 to 27%, mean 18.8%). The administration of iron-dextran raised the plasma iron level and produced a concomitant increase in plasma iron transport (Fig. 4), which was

FIG. 4.—Effect of parenteral iron therapy on serum iron and iron transport in patients well established on maintenance dialysis. ●—● Case 1; ×—× Case 4; △—△ Case 8; □—□ Case 13; ○—○ Case 12.

largely explained by the change in plasma iron level rather than by an abnormal variation in clearance time. Values of serum iron and iron transport fell again after the course of injections was stopped.

Studies with ^{59}Fe in four patients showed that with or without parenteral iron therapy there was a normal pattern of accumulation of iron in the bone marrow and no abnormal accumulation in other organs. Red cell iron utilization was efficient in three of the four patients (Case 9 96%, Case 12 86%, Case 13 84%, Case 5 67%; normal 70 to 90%). Most of those treated with parenteral iron also showed a rise in haemoglobin levels consistent with the increase in plasma iron levels and transport (Fig. 5). Nevertheless, it was only in the two patients with polycystic disease of the kidneys that the haemoglobin levels rose to nearly normal. After the administration of parenteral iron had been discontinued the plasma iron levels often fell quite rapidly; this was followed by a fall in haemoglobin, but not necessarily in mean corpuscular haemoglobin concentration. In most patients the haemoglobin concentration did not rise above the range of 6 to 9 g./100 ml. despite therapy. All of these patients had normal or raised serum vitamin-B₁₂ levels. Where folate levels were low—as was commonly the case before dialysis was begun—folic acid was administered, but no convincing effect on erythropoiesis or haemoglobin levels was seen.

FIG. 5.—Response to parenteral iron therapy in patients on maintenance dialysis without blood transfusions. ○—○ Case 5; ●—● Case 7; ×—× Case 6; △—△ Case 8; □—□ Case 1; ■—■ Case 12.

Red Cell Survival and Red Cell Loss in Dialyser

Red cells were labelled with ^{51}Cr in four patients, and the results of survival studies indicated a slight to moderate reduction in red cell life in these patients. The figures obtained were: Case 2 52 days, Case 7 76 days, Case 15 75 days, Case 14 90 days (normal 110 days). In all the patients the observations made virtually corresponded to a straight-line relationship between time and percentage survival. This suggests that the reduced red cell survival is due to an intrinsic defect rather than to random loss or destruction. Clear-cut evidence of reduced survival was also seen during the ^{59}Fe study on Case 5. In the studies on Cases 12 and 9 falls in circulating red cell iron activity occurred after the seventh day, suggesting that survival was impaired, but not great enough to be conclusive. No such effect was seen in Case 13. It must be appreciated that iron utilization studies are a much less sensitive way of detecting reduced red cell survival than chromium labelling.

Some of the observed reduction in red cell survival could be explained by loss in the dialyser owing to blood remaining in the apparatus at the end of dialysis. Losses were measured as described above on six consecutive occasions in two patients who were on twice-weekly dialysis (Table II). From these it is clear that the excess turnover of red cells exceeds that due to natural destruction at normal rates by an amount which is too great to be explained by dialyser losses alone. Nor is it explicable by the small amounts taken for laboratory studies,

since these did not exceed 15 ml. per week during the period of investigation.

TABLE II

		Case 14	Case 15
Losses in dialyser in ml. whole blood	1	9.2	7.2
	2	7.2	13.0
	3	13.0	9.8
	4	25.0	10.5
	5	12.5	15.5
	6	10.0	5.3
Mean loss		12.8	10.2
Loss per week		25.6	20.4
Blood volume (ml.)		4,750	4,850
Red cell survival (days)		90	75
Whole blood regenerated with respect to red cells per week (ml.):			
At normal survival		296	346
At observed survival		365	480
Difference		69	134
Excess over losses incurred on dialysis		43.4	113.6

Discussion

This study confirms the validity of using haematocrit values as a guide to red cell mass in patients on maintenance dialysis, despite the possibility that plasma volume may change according to variations in the state of hydration. A mild haemolytic element is present in most of these patients (Joske *et al.*, 1956; Eschbach *et al.*, 1967), and is in addition to the inevitable blood loss at the end of each dialysis. With the newer pattern of Kiil dialyser this loss is very small, being considerably less than the values observed by Lawson *et al.* (1969), who used comparable techniques with coil dialysers.

The changes in iron transport after dialysis therapy has been started may explain the discrepancy between the data of Eschbach *et al.* (1967) and those of Kurtides *et al.* (1964). The latter found that erythropoietic activity increased as a direct result of a single haemodialysis in previously undialysed patients, whereas Eschbach's group could find no consistent effect in patients who had already been maintained on dialysis for varying but appreciable periods. Even so, several of their patients did show an increase in erythrocyte iron turnover over periods of 10 to 35 months.

In this study we have not measured plasma erythropoietin levels. Previous workers have found reduced or zero levels of erythropoietin in the plasma of patients with renal failure, though the Seattle workers (Eschbach *et al.*, 1967) found raised levels in two patients. It has been suggested, therefore, that there may be extrarenal sites of erythropoietin production (Hampers and Schupak, 1967; Mirand *et al.*, 1968). Our findings are consistent with the absence of significant erythropoietin production in most patients in this series. It is noteworthy that in only two patients with polycystic disease (in whom there is probably significant residual functioning renal tissue) did parenteral iron raise haemoglobin to nearly normal levels.

The initial stimulus to increased plasma iron transport, which occurs at the beginning of dialysis, is most probably the partial correction of the biochemical abnormalities inhibiting marrow activity, thus permitting increased erythropoiesis. Later there may be loss, by dialysis, of substances necessary for adequate erythropoiesis, leading to deficiency effects (MacKenzie *et al.*, 1969). In our patients folic acid deficiency was excluded and deficiency of other factors was not evident. Thus it is not clear why iron transport should revert to pre-treatment levels after this initial increase. Biochemical control tends to be better after a few weeks of dialysis therapy than at the outset, and one might expect the higher level of transport to be maintained.

We have also found that the haemoglobin level often rises under these circumstances, though it still remains subnormal. This higher level of haemoglobin is maintained in patients who

have not received haematinics. It may therefore be that the apparently transient nature of this increment in useful iron transport is artifactual. One possible explanation is that transport of iron to the liver (observed by Eschbach *et al.*, 1967) may be present in uraemic patients, and may be replaced by the normal physiological transport to the bone marrow after therapy is established. Another explanation may be that ineffective erythropoiesis occurs in these patients before dialysis is begun. Further studies will be needed to investigate these hypotheses. In either instance the utilization of iron transported will be improved, and increased erythropoiesis can be maintained on the same level of transport.

Several authors have drawn attention to the development of iron deficiency in patients receiving maintenance dialysis without transfusion (Crockett *et al.*, 1968; Wright *et al.*, 1969) and have indicated the need for iron therapy, often over prolonged periods. Curtis *et al.* (1969), however, have cautioned that parenteral therapy may lead to hepatic haemosiderosis and have therefore cast doubt on how far iron deficiency is responsible for the anaemia in these patients. These workers found an increase of iron granules in the bone marrow of most of their patients and a fairly high saturation of the iron-binding capacity of the plasma. Many of their patients had received regular blood transfusions until 1966, since when they were given blood only when symptoms of anaemia became distressing. Oral iron produced no improvement in haemoglobin level, and the anaemia in their patients, as in ours, was normochromic. In our patients the saturation of the iron-binding capacity was appreciably lower than in theirs, and oral iron was found to be inconsistent in its effects. Transfusion was an exceptional event in these patients from the outset of their maintenance dialysis, and parenteral iron resulted in partial amelioration of the anaemia in most of those studied.

Our policy was to administer parenteral iron only until serum iron was raised to normal levels and no further rise in haemoglobin resulted. A fall in serum iron and a reversion of haemoglobin to pretreatment levels occurred after discontinuing iron therapy. We have found plasma iron transport to be increased in dialysed uraemic patients when the serum iron is raised by therapy, and studies with ^{59}Fe have shown that this therapeutic iron is well utilized in haemoglobin formation. Useless and potentially harmful accumulation in the liver, however, has not been found.

The enhancement of iron utilization achieved when the serum iron level in our patients was raised remains unexplained, but suggests the possibility of inhibition of iron utilization in the developing erythron, which can be overcome only by increasing the concentration of available iron. With increased saturation of transferrin more of the "erythron-orientated" binding sites will be occupied, and the transfer of iron to the developing red cell thereby facilitated (Fletcher and Huehns, 1968). Sideroblasts are not a feature of uraemic bone marrow. This fact would suggest that if there is a defect it is one of transfer of iron to the developing erythron rather than one of incorporation of iron into the haem molecule. The finding of increased iron granules in the marrow (Curtis *et al.*, 1969) suggests the administration of iron beyond a certain level of transferrin saturation will increase the non-erythroid iron utilization, with the diversion of iron into a less available storage form. Patients who have received few blood transfusions may have true iron deficiency. We agree with Curtis *et al.* that parenteral iron should be given to maintenance dialysis patients with caution, but we think that it definitely improves erythropoiesis even when iron deficiency, as usually defined, cannot be found, and certainly prevents the development of such deficiency from a combination of restricted diet and dialyser blood loss.

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Appendix

Studies with ^{52}Fe

This isotope, which has a half-life of 8.2 hours, decays via ^{52m}Mn (half-life 20 minutes). It was shown by Maynard and Fink (1956) that intravenous manganese is rapidly cleared from the plasma (within a few minutes of injection), and this was confirmed for ^{52m}Mn by Anger and Van Dyke (1964). By making use of the special circumstances of these patients, we have also been able to confirm these observations directly.

A 3-feet (91-cm.) length of sterile plastic tubing was inserted into the arteriovenous shunt of two patients, and this was coiled four times round a 2-in. (5-cm.) scintillation crystal to give a continuous flow counter. This was coupled to a chart-recording rate meter. The ^{52}Fe was injected on the venous side of the detector and a continuous record of activity obtained over the first five minutes after injection. With the use of pulse height analysis it was possible to minimize detection of ^{52}Fe while recording ^{52m}Mn . A multicomponent exponential curve was obtained, which agreed closely with the findings of Maynard and Fink. It is therefore necessary to allow the ^{52}Fe in blood withdrawn from the patient to return to equilibrium with its daughter isotope before it can be compared with the in-vitro standard in which no physical separation of Mn and Fe has taken place, unless recourse is had to complex counting procedures using more than one channel. Fortunately five half-lives—that is, 100 minutes for ^{52m}Mn —suffices to ensure this.

Studies with ^{86}Rb

Preliminary studies showed that uptake of Rb was greater when blood had been taken into the acid citrate dextrose than when heparin was used as anticoagulant. Uptake depended on the volumes of cells and fluid present and on time of incubation, as well as temperature and agitation of the samples. Conditions were controlled with respect to the last two and the volume of fluid added, so that the uptake could be predicted for a given time and volume of cells. It was usually about 40%.

The rate of elution of the label from the cells in vivo was found to be such that no significant difference was recorded in two patients between samples taken at 10, 20, and 30 minutes; and thereafter, to minimize the amount of blood taken from the patients, only a single 10- to 15-minute sample was withdrawn. No detectable ^{86}Rb could be found in the blood of patients three weeks after a study. These findings are in agreement with the values for biological half-life of ^{42}K and ^{86}Rb of 36 to 40 hours recorded by Yalow and Berson (1951) and Tudhope and Wilson (1956). Thus the rubidium ion must be efficiently removed by haemodialysis.

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Neurological Disease after Partial Gastrectomy

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Summary: Clinical and laboratory signs of neurological disease were found in 14 patients many years after partial gastrectomy. Vitamin B₁₂ deficiency occurred in most patients, but only those three who had signs of subacute combined degeneration of the cord and no osteomalacia responded well to treatment.

Introduction

There have been relatively few reports of serious neurological disease as a complication of partial gastrectomy. The first description of "subacute combined degeneration of the cord" following a Billroth II partial gastrectomy was recorded by

Knox and Delamore (1960), and since then there have been fewer than 10 other cases reported. Nevertheless, Olivarius and Roos (1965) suggested that such neurological complications are much more common; from a variety of Scandinavian sources they were able to review 26 cases of "myelopathy" associated with low serum vitamin-B₁₂ levels after gastrectomy. In these patients the average time of onset of neurological symptoms was more than 10 years after operation.

Present Series

In a five-year period in our centre we have seen and treated 14 patients with neurological disease after partial gastrectomy. In many of these the response to treatment has been poor and some are permanently incapacitated with an irreversible neurological disorder. (Although relatively rare this is obviously an important clinical problem.) The findings in these patients are summarized in Table I.

TABLE I.—Findings in 14 Patients after Partial Gastrectomy

Case No.:	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Sex	F	M	M	M	M	M	M	F	M	F	F	M	M	M
Age (years)	51	55	50	57	56	63	63	68	68	76	54	67	41	55
Ulcer site	G	D	D	G	D	G	G	G	G	G	D	D	G	D
Operation	BII	BII	BII	BII	BII	BII	BII	BI	BII	G.E.	BII	BII	BII	BII
Time interval (years)	14	5	5	12	16	10	10	12	14	37	11	12	14	13
Symptoms:														
Unsteadiness	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Weakness	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Paraesthesia	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Numbness	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Depression or psychosis	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Loss of consciousness	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Signs:														
Wasting in legs	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hypotonia	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Plantar response	Fl	Ex	Ex	Fl	Fl	Ex	Ex	Fl	Fl	Fl	Ex	Ex	Ex	Fl
Loss of position sense	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Loss of vibration sense	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Loss of pin-prick sensation	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Associated deficiencies:														
Weight loss	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Poor diet	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alcoholism	+	+	+	+	+	+	+	+	+	+	+	+	+	+
B ₁₂ deficiency	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Iron deficiency	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteomalacia	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Steatorrhoea	+	+	+	+	+	+	+	+	+	+	+	+	+	+

G = Gastric. D = Duodenal. BII = Billroth II. BI = Billroth I. G.E. = Gastroenterostomy. Ex = Extensor. Fl = Flexor. + = Present. - = Absent.