Erythropoiesis, iron stores and tissue iron exchange in man

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Summary
1. The exchange of iron between plasma and erythroid and non-erythroid tissues was measured in 14 normal subjects, 17 iron-deficient patients, nine patients with primary idiopathic haemochromatosis and in 13 patients with haemolytic disorders.
2. The two main factors determining tissue iron turnover were shown to be the level of iron stores and the erythropoietic activity of the bone marrow.

Key words: erythropoiesis, iron exchange, iron stores.

Introduction
The flow of iron from plasma to erythroid cells in the marrow dominates internal iron kinetics. Although iron is present in all non-erythroid tissues, both as a storage component and in a variety of functional forms, it has been generally assumed that in patients with normal or increased erythropoiesis uptake of iron from plasma transferrin into non-erythroid tissues is negligible (Finch, Deubelbeiss, Cook, Eschbach, Harker, Funk, Marsaglia, Hillman, Slichter, Adamson, Ganzoni & Giblett, 1970). However, experiments in vitro have shown that liver cells (Morton & Tavill, 1975), monocytes, lymphocytes and polymorphonuclear leucocytes can take up iron from transferrin (Summers & Jacobs, 1976). Similarly, such diverse tissues as skin, muscle and synovium can accumulate iron from transferrin in extravascular fluid in vivo (Beamish, Jobbins & Cavill, 1971; Cavill & Jacobs, 1971; Wilkins, Williams & Cavill, 1977). In addition, non-erythroid iron exchange has been shown to play a part in plasma iron kinetics (Ricketts, Jacobs & Cavill, 1975). We have measured the flow of iron between the plasma and non-erythroid tissues and examined the extent to which this is influenced by variation in the amount of storage iron and erythropoietic activity.

Subjects and Methods
We studied 14 healthy adults and 39 patients, whose haematological and iron status are given in Table 1. All gave informed consent to the study. The 17 iron-deficient patients were women suffering from menorrhagia. The nine patients with idiopathic haemochromatosis enabled iron overload to be studied without the possible complicating factors of recent blood transfusion. One of these patients with idiopathic haemochromatosis was studied at presentation, the remaining eight having had all or part of their excess iron stores removed by venesection, which was discontinued during the 10 days preceding the study. The effect of changes in erythropoietic activity were studied in a group of patients with haemolytic disorders who had no other haematological abnormalities. Their erythrocyte life spans ranged from 11 to 71 days, as measured by the method of Ricketts et al. (1975). In five of the patients with haemolysis this arose from a prosthetic heart valve, whereas in eight there was either autoimmune disease or an intrinsic erythrocyte abnormality.

A 5 ml sample of defibrinated plasma from
either the patient or from a healthy hepatitis B, antigen negative (radioimmunoassay) donor was mixed with $^{59}$Fe ferric citrate. The $^{59}$Fe not bound to the plasma transferrin was removed by an anion-exchange column (Cavill, 1971) and the specifically labelled plasma, containing not more than 10 $\mu$Ci, was injected intravenously. The clearance of the $^{59}$Fe from the plasma was measured over the subsequent 10 to 14 days (Cavill, Ricketts, Napier, Jacobs, Trevett & Bishop, 1976) and the fraction of the injected dose in the circulating erythrocytes was measured on the final day of each study. Analysis of the clearance curves (Ricketts et al., 1975) enabled the total plasma iron turnover to be subdivided into the amount destined for erythropoietic tissue, the amount flowing through the extravascular circulation and the amount exchanged with non-erythroid tissues. Iron stores were assessed by measurement of the serum ferritin concentration (Jones & Worwood, 1975).

Results
In the normal subjects total plasma iron turnover ranged from 89 to 156 $\mu$mol day$^{-1}$ 1$^{-1}$ of blood (Table 2). Although most of this (67 to 96%), was involved in erythroid iron turnover, between 0 and 18% left the plasma and exchanged with iron in non-erythroid tissues. The iron-deficient patients showed a similar range of plasma iron turnover, although the mean was slightly lower than in the normal subjects. Tissue iron turnover (TIT) in these patients was not significantly different from that seen in the normal subjects (Fig. 1), accounting for up to 18% of the total plasma iron turnover. In the patients with idiopathic haemochromatosis the mean plasma iron turnover was significantly greater ($P < 0.001$) than in the normal subjects, TIT representing 7 to 33% of the total iron turnover through the plasma. Increased TIT in these patients was associated with increased iron stores (Fig. 2) and there was a significant correlation between serum ferritin concentration and TIT ($r = 0.96, P < 0.001$). Transferrin saturation ranged between 23 and 100% but it was not significantly correlated with TIT. In the 15 patients with shortened erythrocyte life span erythropoietic activity was increased and TIT ranged from normal to a value greater than that seen in haemochromatosis (Fig. 1). The mean value was significantly greater than normal ($P < 0.002$) and there was a significant correlation ($r = 0.84, P < 0.001$) between TIT and marrow iron turnover (Fig. 3). Although long-standing haemolysis had increased the iron stores in many of these patients (Table 1),
Tissue iron turnover

Figs. 1, 2 and 3. Effect of variation of iron stores, measured by serum ferritin concentration, on the amount of tissue iron turnover in the patients with haemochromatosis.

Discussion

This study shows that non-erythroid tissues take up a small but significant amount of iron from the plasma in all subjects and this must be taken into account in any investigation of plasma iron kinetics. The tissue iron turnover calculated from an analysis of the plasma $^{59}\text{Fe}$ clearance curve is a measure of all the iron which leaves the plasma, enters non-erythroid tissues and does not return within the period of study. Part of this iron maintains the equilibrium between the plasma and tissue iron pools while a proportion represents iron loss from the body. The total amount of iron leaving the plasma must be balanced by an equal inflow, which is made up either from iron stores or by absorption. The proportion contributed by each will be determined by their relative availability (Cavill, Worwood & Jacobs, 1975).

Iron turnover through non-erythroid tissues was related to increased iron stores in patients with idiopathic haemochromatosis. However, despite a 300-fold range in iron stores the exchange with plasma varied only fivefold. Although the level of iron stores is likely to affect non-erythroid tissue iron turnover in other conditions, its effect will be negligible in patients with normal or decreased iron stores. For example, in the iron-deficient patients there was no detectable reduction in the amount of non-erythroid iron turnover. Despite the requirements of the iron-starved marrow the total plasma iron turnover was divided normally between erythroid and non-erythroid tissues, and there was no significant correlation between TIT and their serum ferritin concentration.

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no evidence of preferential delivery of iron to the marrow. However, when marrow iron turnover was increased, as in the patients with haemolytic disorders, this had a major effect on the rate of iron turnover through all other tissues, which was seen even when the marrow activity was only moderately increased. For example, a doubling of the marrow iron turnover raised tissue iron turnover to between 34 and 79 μmol day⁻¹ l⁻¹ of blood (Fig. 3). Iron stores produced a similar effect only when the serum ferritin concentration was between 1380 and 3400 μg/l (Fig. 2).

It has been suggested that the serum iron concentration is the main determinant of the amount of non-erythroid iron turnover (Cook, Marsaglia, Eschbach, Funk & Finch, 1970). However, we found only a weak correlation between the plasma iron concentration and non-erythroid iron turnover ($r = 0.33$) and this appeared to be a secondary reflection of the effect of iron stores on tissue iron turnover. When all 53 subjects were considered there was a significant multiple correlation between tissue iron turnover, marrow iron turnover and serum ferritin concentration ($r = -16.3 + 0.02 \text{ ferritin} + 0.22 \text{ marrow iron turnover}; n = 53$, multiple correlation coefficient $= 0.86$, $F = 71.2$; reduction in sum of squares due to ferritin $= 41.4\%$, partial correlation coefficient $= 0.62$; reduction in sum of squares due to marrow iron turnover $= 32.6\%$, partial correlation coefficient $= 0.75$). The two major factors determining tissue iron turnover are therefore iron stores and erythroid activity.

References


