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# Primary Acquired Sideroblastic Anaemia: Response to Treatment with Pyridoxal-5-Phosphate

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## Summary

A 72-year-old woman with primary sideroblastic anaemia showed no response to treatment with pyridoxine. When she was given pyridoxal-5-phosphate there was a prompt reticulocyte response and sustained symptomatic improvement with satisfactory control of the anaemia.

## Introduction

Primary acquired sideroblastic anaemia is a well-defined form of anaemia characterized by a heavy perinuclear infiltrate of iron-containing granules in the developing marrow normoblasts. These "ring" sideroblasts are thought to represent an unidentified defect in haem synthesis (Bessis and Jensen, 1965; Bousser *et al.*, 1967), which for some reason usually manifests itself only in the later decades of life (Macgibbon and Mollin, 1965). In contrast to the secondary type of sideroblastic anaemia no associated diseases or drug ingestion can be identified.

Pyridoxine is a necessary coenzyme for haem synthesis (Kikuchi *et al.*, 1958; Levere and Granick, 1965), and the possibility that a defect in its metabolism is responsible for sideroblastic erythropoiesis finds support in the appearance of atypical sideroblasts in pyridoxine-deficient animals (Harriss *et al.*, 1965) and in patients receiving pyridoxine antagonists such as cycloserine or isoniazid (Verwilghen *et al.*, 1965). Furthermore, treatment with oral pyridoxine may lead to haematological improvement in cases of sideroblastic anaemia. However, response to pyridoxine is almost always suboptimal and occurs in only 40-50% of patients (Macgibbon and Mollin, 1965). In addition very large doses of the drug, often 100 times the normal nutritional requirement, may be necessary.

For these reasons it has been suggested that a block in the conversion of pyridoxine to its main active form, pyridoxal-5-phosphate, is the underlying cause of sideroblastic anaemia (Hines and Grasso, 1970). This conversion, which can occur within the red cell (Anderson *et al.*, 1971), has been shown to be defective both in alcohol-induced and primary sideroblastic anaemia (Hines and Cowan, 1970; Hines and Love, 1969).

A direct corollary of this hypothesis is that pyridoxal-5-phosphate should prove therapeutically much more effective than pyridoxine in sideroblastic anaemia. The present report is of a case of primary acquired sideroblastic anaemia which was unresponsive to prolonged treatment with pyridoxine but which responded dramatically to pyridoxal-5-phosphate.

## Clinical History

The patient was admitted to the Radcliffe Infirmary in July 1968, aged 72, with a nine-month history of dyspnoea, ankle oedema, and lassitude. Apart from rheumatic fever as a child she had enjoyed good health, having been a regular blood donor until 1960. On examination she was pale and in congestive cardiac failure with evidence of mitral and aortic valve incompetence. The haemoglobin was 4.8 g/100 ml and the peripheral blood film showed a double population of hypochromic and normochromic erythrocytes, together with numerous poikilocytes and occasional nucleated red cells. Bone marrow aspiration showed erythroid hyperplasia with a disproportionate increase in early red cell precursors. Most of the later forms were shown to be ring sideroblasts on Perl's staining. These cells were negative on P.A.S. staining and marrow chromosome preparations were normal.

Results of biochemical tests were normal except for a serum bilirubin of 1.0 mg/100 ml and a plasma lactic dehydrogenase of 300 mU/ml. The plasma iron was 150 µg/100 ml, with a saturation of 48%. Ferrokinetic studies with <sup>59</sup>Fe showed an increased plasma clearance ( $t_{1/2}$  12 min.) and a reduced red cell utilization (22% on day 14). Careful investigation failed to produce evidence of any other disease.

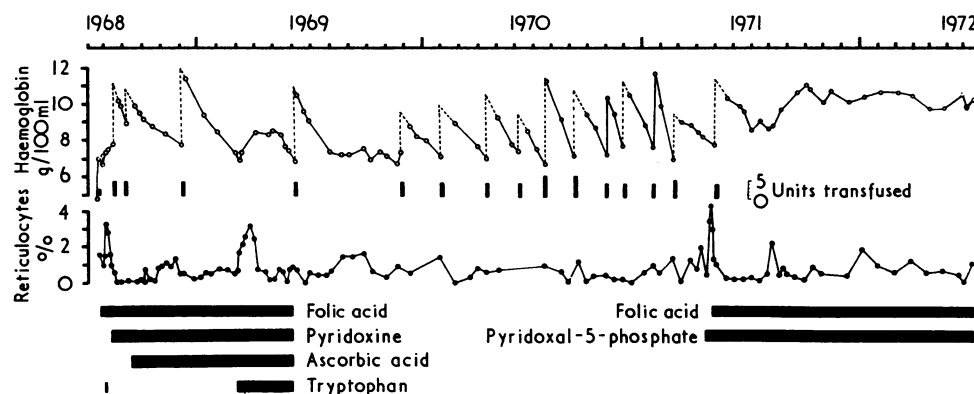
After transfusion and conventional therapy for congestive failure treatment was started with oral folate (5 mg three times a day) to which was later added pyridoxine (100 mg twice daily) and ascorbic acid (200 mg twice daily). Each drug was given continuously for several months without any evidence of haematological response (see chart). Further transfusions were given in September and December 1968 but by February 1969 the haemoglobin had fallen to 7.0 g/100 ml. At this stage, because of a transient reticulocytosis which had been noted during her first admission following a tryptophan loading test (see chart), she began taking oral tryptophan at an initial dose of 2 g daily, later increased to 4 g daily, in addition to the other haematinics. Although this new treatment appeared to cause a reticulocytosis and an increase in haemoglobin, the improvement was transient. She developed diarrhoea, and in May, after a total consumption of 280 g of tryptophan, all treatment for anaemia was stopped.

After a further transfusion she maintained a haemoglobin level of 7.5 g/100 ml until November 1969. She then required increasingly frequent blood transfusions because of recurrent episodes of cardiac failure. Although desferrioxamine treatment had been initiated in November 1968, and was given at the time of each transfusion, a bone marrow specimen in March 1971 showed an increase in storage iron, and a serum iron of 215 µg/100 ml with 75% saturation was recorded. By this time she had received a total of 62 units of blood since the diagnosis. In addition the transfusions had been complicated by the

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appearance of an anti-Kell antibody in June 1969 and increasingly severe allergic reactions necessitating transfusion with dextran sedimented blood and chlorpheniramine cover.

Treatment with intramuscular pyridoxal-5-phosphate\* was started in April 1971 at an initial dosage of 250 mg daily, later reduced to 250 mg weekly when a maximal haemoglobin response had been obtained.

A prompt reticulocyte response was noted with a peak of 4.5% on day 10, and after five months of treatment the haemoglobin had risen to 11.0 g/100 ml. From October 1971 until the time of writing a constant haemoglobin was maintained between 10 and 11 g/100 ml without further transfusion and the patient had remained well. Ferrokinetic studies repeated in November 1971 after six months' therapy still showed increased iron clearance ( $t_{1/2}$  23 min) and poor iron utilization (22% at 14 days). Bone marrow aspirations at this time and in July 1972, after 14 months of treatment, still showed the persistence of numerous ring sideroblasts.

## Discussion

This case is a typical example of primary acquired sideroblastic anaemia. No evidence of any other disorder was found; in particular the P.A.S.-negative marrow erythroid precursors (Hayhoe and Quaglino, 1960), the normal marrow chromosome pattern (Heath *et al.*, 1969), and the constancy of the sideroblastic abnormality over the course of four years all argue against an underlying leukaemic process.

Pyridoxal phosphate is necessary for the activation of glycine in the initial stages of haem production. Theoretically, therefore, a deficiency or inhibition of the phosphorylating enzyme (pyridoxal kinase) required for the conversion of pyridoxine to its active form (pyridoxal-5-phosphate) could lead to disordered haem synthesis and accumulation of iron within the mitochondria. However, the fact that there was no evidence from marrow aspiration or ferrokinetic studies that treatment had reversed the sideroblastosis suggests that additional factors other than defective pyridoxal phosphate synthesis underlay the abnormality.

From a therapeutic point of view, however, the present findings suggest that pyridoxal-5-phosphate should be tried in all cases of symptomatic primary sideroblastic anaemia which have shown no satisfactory response to pyridoxine. There is very little published information on the therapeutic value of pyridoxal-5-phosphate to date. Gehrman (1965) described the case of a 31-year-old man with acquired sideroblastic anaemia who responded rather better to small doses of pyridoxal-5-phosphate (25 mg/day) than to much larger doses of pyridoxine (300 mg/day). Hines and Grasso (1970) referred to

a patient who showed a prompt reticulocytosis when given pyridoxal-5-phosphate (20 mg/day), having been previously unresponsive to pyridoxine (100 mg/day). We could find no other reports of therapy with pyridoxal-5-phosphate in primary sideroblastic anaemia; undoubtedly the paucity of information stems in part from the fact that the drug has yet to be approved for general use in either the U.K. or the United States. We found no evidence, in the course of more than a year's treatment, of toxicity or side effects to contraindicate its use.

Finally, it should be pointed out that pyridoxal phosphate is given parenterally, whereas pyridoxine, being well absorbed from the gastrointestinal tract, is usually given by the oral route, as it was in this patient. It is therefore conceivable that in this case the failure to respond to pyridoxine, although the dose was about three times the maintenance dose of pyridoxal phosphate, was due to intestinal malabsorption. There was no evidence, however, of a malabsorption syndrome, and adequate absorption of at least one other drug, folic acid, was implied by high serum levels achieved. In addition direct evidence that resistance to pyridoxine in sideroblastic subjects may not be related to poor absorption is found in Hines and Cowan's (1970) observation that patients with alcohol-induced sideroblastic anaemia responded to intramuscular pyridoxal phosphate but not to intravenous pyridoxine.

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