Personal practice

Total management of thalassaemia major*

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Beta-thalassaemia major is a severe anaemia of childhood which is inherited as a mendelian recessive; the heterozygous (carrier) form of the condition is thalassaemia minor or thalassaemia trait. The homozygous disease, thalassaemia major, is due to defective ability to synthesize the β -chains of adult haemoglobin, which leads to gross ineffective erythropoiesis and anaemia for which blood transfusion is the only treatment. Though the prognosis is improving steadily with advances in management, it is still generally considered a fatal disease. The genetics and biochemistry of the thalassaemias have been fully reviewed by Weatherall and Clegg (1972). This article is confined to the clinical aspects of homozygous β -thalassaemia and its management, as observed in Britain.

There are now about 300 patients with thalassaemia major in Britain, mostly under 17 years of age because they are the offspring of recent immigrants, and about 13 more are born every year. Among Cypriots the incidence of β -thalassaemia trait is 15 to 18% (Banton, 1951; Modell *et al.*, 1972; Ashiotis *et al.*, 1973; C. Bate, personal communication), and the incidence of thalassaemia major is at least 5 per 1000 live births. It is therefore not surprising that about 60% of patients with thalassaemia major in Britain are children of Cypriot origin: 30% are immigrants originally from the north-western part of the Indian subcontinent, and less than 10% are from Italy and China. The majority of patients in Britain have the β^+ type of thalassaemia: the clinical picture of patients with β^0 thalassaemia may differ in several significant ways from that described here (C. Vullo, personal communication). They are generally managed by the paediatrician at the local hospital, and a partial survey of the problem has been achieved by studying the notes of many patients, with the co-operation of numerous paediatricians and haematologists.

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This survey has allowed an evaluation of the various aspects of treatment, and the results will be published in detail elsewhere.

At present there are only three main aspects of management, maintenance blood transfusion, the intensive use of iron-chelating agents to combat transfusional siderosis, and splenectomy. Since the dominating problem is the control of transfusional iron overload, the other aspects of management should be arranged around it: the data presented here provide initial criteria for transfusion, splenectomy, and iron-chelation therapy, in relation to iron overload.

Patients and methods

This article is based on a study of 196 individuals with thalassaemia major between 1 and 23 years old, 116 of whom have been fully documented in the manner described below. The majority had homozygous β^+ thalassaemia.

Thalassaemia major. 93% of homozygous β -thalassaemics born in Britain are transfusion-dependent, indications for transfusion being: inability to maintain Hb > 7g/dl, failure to gain weight, anorexia, and sleeplessness. The regular recording of height, weight, pre- and post-transfusion Hb, and amount of blood transfused in hospitals throughout Britain allows the following data to be worked out for each patient for each year (Fig. 1). (1) The pattern of Hb fall between between transfusions. (2) Mean Hb maintained by transfusion (= the average of the mean pre- and mean post-transfusion Hb). (3) Annual blood consumption, expressed as ml/blood per kg and year = ml blood transfused in the year/weight in June. (4) Growth in height and weight.

There is a wide margin of error in the routine recording of clinical data, but the measurements are repeated often enough to produce statistically acceptable figures. The information that can be derived from the routine Hb chart is discussed more fully by Modell and Bunton (1977).

Fig. 1 Diagram summarizing the routine Hb chart of a patient for 2 complete years, the one immediately before splenectomy and the one immediately after splenectomy. The curves of Hb fall in each of the 2 years have been superimposed, and a representative line drawn through all the points. The broken line represents an Hb fall of 1% of the post-transfusion Hb per day. This is the expected rate of fall in a patient subsisting entirely on donor blood, with no contribution from his own marrow and no excessive donor cell destruction. Before splenectomy mean Hb was 8.2 g/dl. The patient received 11 transfusions of 3 units each, and the annual blood consumption was 740 ml/kg per year. After splenectomy mean Hb was 8.7 g/dl. The patient received 3 transfusions of 3 units each, and the annual blood consumption was 222 ml/kg per year.

Thalassaemia intermedia. 7% of all patients with homozygous β -thalassaemia born in Britain have 'thalassaemia intermedia', i.e. they can maintain Hb > 7.5 g/dl and do not require transfusion. This is a genetically heterogeneous group in which there is wide clinical variation. The prognosis of such patients, in terms of normal sexual maturation, reproduction, and long-term survival is better than that of the patients with severe thalassaemia major (Erlandson *et al.*, 1964). The management of thalassaemia intermedia will not be discussed here.

Results

(1) Blood requirements: effects of transfusion scheme and of the spleen. The amount of blood required by patients on maintenance transfusion should be primarily related to the Hb level maintained by transfusion. This is the case in splenectomized patients with thalassaemia (Fig 2A) whose annual blood requirement is between 150 and 350 ml of blood/kg, depending on the transfusion scheme. This standard curve is very valuable for assessing the causes and extent of increased blood consumption in thalassaemia.

The standard relationship described above gener-

ally does not hold for unsplenectomized patients, whose blood consumption may be between 200 and 1200 ml/kg per year, and seems unrelated to the mean Hb maintained by transfusion (Fig. 2B, C, D). If a thalassaemic patient's observed blood consumption is divided by the expected blood consumption for his transfusion scheme (obtained from the standard curve in Fig. 2A) the resulting figure is nearly always more than 1 in unsplenectomized patients. This figure, called the 'transfusion quotient', expresses the increase in blood requirement over expectation, due to the presence of the spleen. Fig. 3 illustrates the use of the transfusion quotient in assessing hypersplenism in individual patients. This patient's blood consumption started near the normal range and then increased steadily to more than twice expectation. Splenectomy returned his blood consumption to the normal range, with a decrease of 70% in the blood requirement and hence in the rate of iron-loading. For transfused patients, routine chromium studies are less sensitive than evaluation of the blood consumption as a guide to the value of splenectomy (Fig. 4).

If the criterion of 50% increase in blood consumption is used (i.e. transfusion quotient of 2 or more) hypersplenism is extremely common in thalassaemia major. Nearly 50% of patients observed in Britain are hypersplenic at presentation (Fig. 2B). Most patients now splenectomized had a grossly increased blood requirement before they came to operation (Fig. 2C), and many patients yet unsplenectomized have a blood consumption of about twice 'basal' (Fig. 2D) even in the absence of other evidence of hypersplenism. A spleen palpable more than 6 cm. is rarely benign by this standard, and even an impalpable spleen may destroy donor cells. (In the one case where we observed this the spleen had enlarged upwards under the diaphragm.) These figures show that the spleen is a major cause of variation in the blood requirements of patients with thalassaemia major, and that it is possible to predict the effect of splenectomy on blood requirement in individual patients.

It has often been said that the beneficial effects of splenectomy are evanescent. Of the 58 splenectomized patients studied, the reduction in blood requirement was permanent in all but 3. These were all on a very low transfusion scheme, and are all now dead: none had a post-mortem examination, but one died from bleeding to thrombocytopenia. As recurrent splenic tissue has been found at post-mortem in splenectomized patients, it is thought that the very low transfusion scheme provoked hypertrophy of persisting splenic tissue in these 3 patients. This clinical picture has not been observed in patients maintained on an

Fig. 2 Relationship between annual blood consumption (ml blood received per kg per year) and mean Hb maintained by transfusion in thalassaemic patients. (A) In splenectomized patients there is a close relation between transfusion scheme and blood requirement: data from 30 splenectomized patients are included, each point representing 1 year ($r=0.74$). (B) At presentation the blood requirement is already raised due to the presence of the spleen, in 34 out of 69 patients. Each point represents the first full year on transfusion of a single patient. (C) Blood consumption may be grossly raised and is unrelated to transfusion scheme in hypersplenic patients. Each point represents the last presplenectomy year in each of 24 patients. (D) Even in patients not suspected of hypersplenism on other grounds, blood consumption may be substantially raised: each point represents the most recent year for each of 29 such patients. 1.5 times the average blood consumption for splenectomized patients is indicated by the broken line. We consider splenectomy on grounds of iron economy in patients whose blood consumption is above this level for more than 2 years running.

intermediate or high transfusion scheme after splenectomy, nor have we ever observed the liver to take over the role of the spleen in destroying red cells.

(2) **Effect of transfusion scheme on rate of onset and severity of hypersplenism.** In the β^+ population of thalassaemics studied in London the majority of patients have in the past become hypersplenic (i.e. transfusion quotient > 1.5 – 2.0) by 6 years of age (Modell and Bunton, 1977). However, it has been suggested that high transfusion from the beginning should prevent the onset of hypersplenism (Piomelli *et al.*, 1974). Fig. 5 shows the transfusion quotients of patients at 6 years of age, related to the

transfusion scheme for the first 6 years. It is clear that in general the higher the transfusion scheme the lower the incidence of hypersplenism.

(3) **Transfusional iron overload: rate and clinical consequences.** The minimum rate of intravenous iron loading in splenectomized patients of average stature on high and low transfusion schemes (calculated from the standard curve of blood consumption in (Fig. 2A) and the growth chart), is shown in Fig. 6. By the age of 18 a transfusion-dependent thalassaemic patient on a low scheme has usually received 35 g iron and one on a high scheme 60 g of iron intravenously. Long-standing severe hypersplenism can of course greatly increase

Fig. 3 The use of the transfusion quotient, (observed blood consumption)/(expected blood consumption), in assessing hypersplenism in thalassaemic patients. This patient's blood consumption started near the expected range but rose steadily and was restored to expectation by splenectomy.

Fig. 4 Relationship between blood consumption and the result of routine ^{51}Cr -tagged donor red cell studies in patients with thalassaemia major. $\blacktriangle$ =patients with positive chromium studies. It is clear that this method, as routinely used, picks up only gross red cell destruction.

the amount of iron received, and there is also good evidence of excessive gastrointestinal iron absorption in patients on low transfusion schemes (Erlandson *et al.*, 1962). Considering this massive rate of iron loading (the normal body iron stores are only 1–2 g) it is surprising that signs of iron toxicity appear as late as they do.

The majority of patients maintained on high transfusion schemes are superficially indistinguishable from normal children until at least 13 years old, but in fact there is usually gradual retardation of

Fig. 5 Relationship between transfusion-scheme and hypersplenism. Hypersplenism, as indicated by the transfusion quotient at 6 years of age, is plotted against mean Hb maintained by transfusion for the first 6 years of life. There is a clear correlation between low transfusion and the severity of hypersplenism. The lower horizontal line shows the upper limit of the normal range; the upper line shows the dividing line between moderate and gross hypersplenism.

Fig. 6 Theoretical rate of cumulative intravenous iron-loading in nonhypersplenic patients on low (mean Hb 8.5 g/dl) and high (mean Hb 11.5 g/dl) transfusion schemes. The values are calculated from the standard curve in Fig. 2A, for a patient growing on the 50th centile, and without a pubertal growth spurt. No allowance is made for gastrointestinal iron absorption.

growth starting at 9–11 years (Johnston *et al.*, 1966; Logothetis *et al.*, 1972), and failure of puberty is very common, especially in boys. In high-transfused patients it is the first clinical manifestation of iron toxicity: it is profoundly depressing and calls for investigation and replacement therapy. Data on 35 patients from 14–20 years are summarized in Table 1.

In girls, pubertal growth and sexual development often occur but may be retarded. Breast develop-

Table 1 Presence of puberty in 35 British and Australian thalassaemics over 14 years of age

Diagnosis	No. studied	No. with puberty	%
<i>Female</i>			
Thalassaemia major	10	9	
Thalassaemia intermedia	4	3	
Total	14	12	85
<i>Male</i>			
Thalassaemia major	18	4	
Thalassaemia intermedia	3	2	
Total	21	6	29

ment may be adequate but periods may be irregular and scanty. Complete failure of puberty in a girl is a poor prognostic sign. In boys, by contrast, there is usually complete or partial failure of pubertal growth and sexual development. A preliminary endocrinological study has shown no evidence of gonadal or pituitary failure, so it is possible that the cause of the problem lies in defective hypothalamic maturation (N. McIntosh, B. Modell, and N. Barnes in preparation), and the best replacement therapy may prove to be hypothalamic releasing factors, if these become available in an acceptable form (Mortimer *et al.*, 1976). The effect of life-long high transfusion on this picture remains to be worked out, but there is so far no evidence of any beneficial effect. By contrast there is some evidence of improved pubertal development in patients receiving long-term treatment with desferrioxamine. In those patients achieving sexual maturity, secondary impotence and amenorrhoea due to gonadal iron overload may occur (Canale *et al.*, 1974; M. Constantoulakis, personal communication).

As most patients in Britain are still under 18 years of age we do not yet know the average life expectancy of the high-transfused patient in whom no steps are taken to counteract the accumulation of iron. The average age of death from iron-overload in a multicentre study in Britain, Australia (Melbourne), and the USA (New York Hospital) was between 16 and 24 years. In Britain 10 deaths could

be attributed directly to iron overload (Table 2). The patients' ages ranged from 12 to 23 years, the amount of iron loaded as blood ranged from 29 to 82 g, and none had been on long-term desferrioxamine therapy. Death was due to cardiac failure in all. 2 deaths were acute in relatively young patients who had received unusually large amounts of blood because of long-standing severe hypersplenism; hepatic, renal, and endocrine failure seemed to be precipitated by an episode of acute cardiac failure: the clinical picture suggested that hypoxia released iron in an active form within the cells where it had accumulated, thus causing widespread organ damage. The remaining 8 patients died after 5 days to 10 years of progressive cardiac failure, complicated in a minority of cases by overt diabetes, hypoparathyroidism, and adrenal failure. There was complete absence of puberty in all 10.

These observations suggest that the pathology caused by severe iron overload and the manner of death are fairly consistent. However, they give only the earliest age of death, not the average life-expectancy, as there are a number of patients in the same range of age and iron load who are clinically well, but these individuals must be considered at serious risk.

(4) **Use of desferrioxamine.** The only useful iron-chelating drug at present commercially available is desferrioxamine, which is expensive and has to be given parenterally (Sephton-Smith, 1962). Because it offers the only hope of an improved long-term prognosis it has been used regularly in many British and Australian patients in doses of from 0.5–1 g daily with or without vitamin C for up to 9 years (Barry *et al.*, 1974; Seshadri *et al.*, 1974; Modell and Beck, 1974).

Iron excretion in response to desferrioxamine is directly related to the body iron load (Fielding *et al.*, 1966), so in thalassaemia it increases with the total units of blood transfused, and therefore increases with age. The continuous line in Fig. 7 shows the

Table 2 Pathology of patients dying of iron overload in thalassaemia major

Case no.	Age (years)	Mean Hb (g/dl)	Volume of blood transfused (600 ml units)	IV, Fe (g)	Duration (years) of				Adrenal failure
					Cardiac failure	Hypoparathyroidism	Diabetes mellitus	Puberty	
1	12	12.5	218	44	2 m	—	—	Absent	+
2	16	7.7	151	30	4	—	—	"	—
3	19	5.5	145	29	3	+	—	"	+
4	16	9.8	200	40	6	+	—	"	—
5	18	11.0	240	48	2	1	2	"	—
6	20	11.5	270	54	1	—	—	"	—
7	18	11.5	340	68	2 m	—	—	"	—
8	21	11.3	370	74	9	+	6	"	—
9	23	11.8	402	81	10	8	6 m	"	—
10	21	9.1	409	82	1	—	—	"	—

Fig. 7 Average daily amount iron received IV, and response to desferrioxamine in patients newly starting chelation therapy. The daily iron increment received IV as blood increases with age (weight). The solid line shows the daily increment in mg for a splenectomized high-transfused patient, calculated from the blood consumption chart, Fig. 2A. To bring a patient into iron balance, desferrioxamine must remove this amount of iron per day, of which approximately two-thirds would appear in the urine, the remaining third being excreted in the stool (Cumming *et al.*, 1969). The mg of iron that must be excreted in the urine each day to bring about balance is therefore shown by the broken line. The points represent the average daily iron excretion of hitherto unchelated patients starting on regular daily injections of desferrioxamine 500 mg IM. Balance is rarely achieved in children <20 kg (6 years of age); on average such children have received <100 units of blood. Negative balance is the rule in patients above this age, most of whom have received >100 units of blood. Therefore long-term treatment with an appropriately weight-related dose of desferrioxamine should hold the body iron at the level it reaches in the 6-year-old unchelated patient. Intensifying treatment should push down the age and body iron load at which balance is achieved. ▲=poor responses in 2 older patients who were severely depleted of ascorbic acid, but showed a dramatic increase in response when given oral ascorbic acid 200 mg daily.

average daily amount of iron received as blood by nonhypersplenic thalassaemic patients of different ages on a high-transfusion scheme. The figures are derived from the standard blood consumption curve for splenectomized patients (Fig. 2A), and the growth chart (50th centile) on the assumption that each unit of blood received per year (420–450 ml) deposits 0.59 to 0.63 mg iron per day i.e. if a child receives 18 units of blood in a year, the average amount of iron deposited per day will be 10.6 to 11.3 mg. For hypersplenic patients the daily average would be higher, and for those on lower transfusion schemes it would be lower.

If desferrioxamine is to bring a patient into iron

balance, it must bring out each day the amount of iron shown on the chart for patients of each age (weight). But a maximum of 70% of iron excreted in response to desferrioxamine appears in the urine, the rest emerges in the stool (Cumming *et al.*, 1969); so the approximate amount of iron that should appear in the urine daily to keep a patient in iron balance is shown by the lower dotted line in Fig. 8. Higher values for urine iron probably represent negative balance, and lower values probably indicate positive iron balance.

Fig. 8 Average daily amount of iron received IV and response to desferrioxamine in patients after 2 years or more of long-term desferrioxamine therapy. In most of the patients the daily dose of desferrioxamine was 750–1000 g, and all were taking regular ascorbic acid 200 mg daily. In most patients the daily iron excretion approximates to the balance level, illustrating the point that whatever method of long-term treatment is selected, the iron excretion will finally settle at the balance level. Fall-off of response towards this level is an indication not of resistance to the drug, but of the success of treatment in reducing the chelatable body iron load. The success of treatment is to be judged therefore not by the amount of iron that can be removed at the initiation of the therapy, but by the body iron load at which balance is reached. This may be best assessed by iron estimation in a liver biopsy, or by serum ferritin level. ▲=patient known to take his injections only about 3 times weekly: his body iron load has remained raised well above the balance level.

Patients treated with desferrioxamine can be observed in two situations. Firstly, at the onset of the treatment urine iron excretion reflects total accumulated body iron, so the initial response to treatment is primarily age-related. The response of patients to 500 mg desferrioxamine intramuscularly at the start of regular treatment is shown in Fig. 7. Most patients under 6 excrete less than the balance amount of iron, while the majority of older patients are brought promptly into negative iron balance by

this dose. It can be concluded that this dose of desferrioxamine, i.e. 25 mg/kg, given daily should prevent or seriously retard further accumulation of iron after 6 years of age. This clear type of information can be obtained only in patients recently started on iron chelation therapy.

The second situation in which patients can be observed, is when they have come into equilibrium on long-term treatment. Older patients started on long-term desferrioxamine certainly enter negative iron balance, but marked negative balance continues for only 1 to 2 years. Fig. 8 shows that the majority of patients treated for more than 2 years are then in approximate iron balance. An increase in the daily desferrioxamine dosage causes increased daily iron excretion until the chelatable iron load has fallen, when daily excretion falls off to the balance level once more.

(5) Vitamin C and desferrioxamine. It has been shown that iron-loaded patients become ascorbic-acid depleted (Lynch *et al.*, 1967), and that ascorbic acid supplements increase the urinary iron excretion with desferrioxamine (Wapnick *et al.*, 1969). In 12 patients in this study, 200 mg oral ascorbic acid once daily increased the average iron excretion by 100%, and those patients over 6 years old who were usually in positive iron balance came into negative balance. This situation continued for 6 months to a year when iron excretion in all the patients had returned to balance level. It was permanently improved in the initial 'poor responders', who were also those with the lowest original white cell ascorbate levels (Modell and Beck, 1974).

(6) Survival and long-term desferrioxamine. Thalassaemic patients over 14 years of age must be considered at risk of death from iron overload. Almost all British patients over this age have been included in this study. Of 58 patients over 14 years, nearly half have been on long-term chelation, and the mortality to mid-1976 in the two groups is shown in Table 3. 9 out of 31 unchelated patients have died, while only 1 out of 27 chelated patients has died, even though the dosage of desferrioxamine used has commonly

been less than optimal (see Discussion). Though promising, these data have not yet been examined sufficiently closely to allow a firm conclusion to be drawn.

Discussion

The objective of this work is to provide evidence for rational choice of treatment in thalassaemia, and the results will therefore be discussed under the headings of splenectomy, transfusion scheme, and iron chelation therapy.

Hypersplenism and splenectomy. The extent of hypersplenism is best measured by the transfusion quotient, i.e. the relationship of the observed blood requirement to the blood requirement of a splenectomized patient on the same transfusion scheme. This method is more sensitive than studies using ^{51}Cr -labelled donor red cells (Fig. 4), and has the advantage of being noninvasive. Using this criterion severe hypersplenism in which the blood consumption is increased to twice basal or above, is extremely common in the β^+ population of thalassaemics studied. In addition, low transfusion seems to precipitate hypersplenism, and high transfusion from the outset may moderate it in many cases (Fig. 5). It is noteworthy that in the predominantly β^0 population of thalassaemics in Ferrara (Bargellesi *et al.*, 1967) hypersplenism is uncommon and less severe (C. Vullo, personal communication). This may be because the more seriously affected β^0 cells do not survive to emerge from the bone marrow and involve the spleen.

In Britain we have not so far encountered any cause other than hypersplenism for a chronically increased blood requirement in thalassaemia major. Serious clinical problems due to blood group incompatibility have been reported (C. Vullo, personal communication; Beard *et al.*, 1969) but have not arisen in any of the patients studied here; in 3 patients with increased blood consumption and non-specific cold agglutins, splenectomy still reduced the blood consumption as predicted.

When a decision has to be made about splenectomy, the main indication should be the effect of the spleen on blood requirement and hence on iron loading. The decision to remove the spleen is rarely difficult when the blood requirement is grossly raised, e.g. Fig. 4, especially when there is associated severe thrombocytopenia, in itself an absolute indication for splenectomy since it can cause fatal bleeding. The decision is less clear-cut in the many patients not suspected of hypersplenism on other grounds, who also have increased blood consumption (Fig. 2D). The spleen may to some

Table 3 Survival and long-term chelation therapy in thalassaemic patients more than 14 years of age

	Chelated	Unchelated*	Total
Living	26	22	48
Dead	1	9	10
Total	27	31	58

* This group includes some patients who had intermittent or only preterminal desferrioxamine therapy. The evidence is strong that only continuous and intensive treatment is effective.

extent protect against iron overload by extending the reticuloendothelial iron stores but if, using the standard curve in Fig. 2A, the spleen is found to be increasing the blood requirement by 50% or more, its destructive effect probably outweighs its value in reducing iron toxicity. This level of hypersplenism is chosen as our current indication for splenectomy, but the assumptions about iron balance on which it is based require experimental investigation. After splenectomy it is wise to withhold transfusion until it has become clear that the patient really cannot do without it, as the operation occasionally unmasks a thalassaemia intermedia.

The risks of splenectomy vary significantly in different parts of the world. In the United States, in Thailand (S. Pootrakul, personal communication), and probably also in Australia (R. Matthews, personal communication) there is a high risk of overwhelming postsplenectomy infection, usually streptococcal or pneumococcal, especially meningitis or peritonitis, and risk continues indefinitely after splenectomy (Smith *et al.*, 1964). In Greece the incidence of rheumatic fever is significantly increased in thalassaemics after splenectomy (M. Constantoulakis, personal communication). In Britain there have been some similar infections but no deaths from them (B. Modell, in preparation). There have, however, been 2 deaths from staphylococcal pneumonia in young splenectomized patients receiving prophylactic penicillin. All patients suffering serious infection were on a low transfusion scheme at the time (mean Hb < 10 g/dl).

The indications for prophylactic penicillin after splenectomy are therefore unclear. But at present, in view of the evidence from other parts of the world, it still seems wise to protect thalassaemic patients by giving prophylactic penicillin 125 mg twice daily or 250 mg daily, *indefinitely*, after splenectomy. Prophylactic treatment for malaria should also be given indefinitely in endemic areas.

Choice of transfusion scheme. Once it is clear that a child requires maintenance transfusion, nothing can be gained by trying to hold his blood requirement to the minimum compatible with life. Such a policy produces a chronically sick child in a chronically anxious family, without apparently increasing the life expectancy. A more satisfactory objective is to obtain the best quality of life, and this requires that Hb be maintained approximately in the normal range (Wolman, 1964). If Hb is raised regularly from 9 up to 14 g/dl, giving a mean of about 11.5 g/dl, the stimulus to unlimited bone-marrow expansion which causes so much of the pathology (Nathan and Gunn, 1966; Modell, 1974), is reduced and most of the undesirable physical manifestations of the

disease, such as poor exercise tolerance, cardiomegaly, stunting of growth, facial deformity, hepatosplenomegaly, and pathological fractures, are suppressed. Thalassaemic children treated in this way are superficially indistinguishable from normal ones up to about 13 years of age, when the effects of the iron overload may begin to appear.

The observations summarized here, and reported fully elsewhere, support the choice of a high transfusion scheme as they show it has the following important additional advantages. (1) If started at the outset it may prevent, or moderate, the severity of hypersplenism, thus allowing some patients to retain their spleens as an extra protection against iron overload, and against overwhelming infection. (2) It suppresses the excessive gastrointestinal absorption of iron that occurs on lower schemes (Erlandson *et al.*, 1962); this may compensate for the increased rate of intravenous iron loading on high transfusion schemes (Modell and Bunton, 1977). (3) The expanded blood volume present in patients on low schemes is restored to normal, thus relieving the load on the heart (Modell and Bunton, 1977). (4) Severe infections are less common in patients on high transfusion schemes, whether or not they are splenectomized (B. Modell, in preparation).

The only complication of high transfusion is that in severely hypersplenic patients it may grossly increase the rate of iron loading, and lead to early death from cardiac failure. This can be avoided by careful monitoring of the blood requirement as described here, and removing the spleen as soon as the transfusion quotient rises above 1.5–2.0.

Iron chelation therapy (desferrioxamine). It has been shown that chronic desferrioxamine therapy can bring about iron balance and stabilize the body iron load. The higher the daily dose of desferrioxamine, the lower the total body iron load retained when balance is achieved. Until recently in Britain patients have usually been treated with a standard dose of 500 mg daily. Although this policy is bound to produce decreasing returns as patients grow, it nevertheless protects the liver against iron toxicity (Barry *et al.*, 1974; Risdon *et al.*, 1975) and appears to improve long-term survival: this last conclusion will be subjected to more rigorous examination in the near future. This makes it likely that a properly weight-related dose will more effectively protect against iron toxicity, and indeed reversal of established cardiac and hepatic pathology has been observed clinically in older patients on appropriately high desferrioxamine doses (Seshadri *et al.*, 1974).

Treatment should be started at about 3 years of age, because substantial iron excretion is not in-

Table 4 Recommended weight-related dosage of desferrioxamine (DF) (approximately 25 mg/kg)

Weight range (kg)	Age (years)	Dose DF (mg)	Distilled water (ml)	Comment
15-20	3-6	500 mg	1.5-2	Usually acceptable
20-35	7-12	75 mg	2	Usually acceptable
35-45	13-puberty	1000 g	2-3	May be some difficulties
45-65	Post pubertal if normal stature (uncommon)	1500 g	4	Hard to tolerate

duced before that time (Fig. 7), with a dose of 25 mg/kg. Iron balance is usually achieved around 6 years of age, and further increase in body iron load should be prevented if this dose is maintained. A suggested dosage scheme is set out in Table 4. The smaller doses are usually well accepted by younger patients, but older patients may find the larger injections hard to tolerate. The dose should always be adapted to suit the individual patient, even if this involves some concessions. The drug is injected intramuscularly, by the child himself, a parent, or the district nurse. An insulin gun* is found helpful by many patients. Pain is experienced only if the injection is subcutaneous rather than intramuscular, if the solution is too concentrated or, in older patients, if the volume is too large. Such problems, which may be encountered when a patient is first started on the injections, can usually be solved by careful attention from the physician. In addition, 2 g desferrioxamine should be added to each unit of blood transfusion.

The adequacy of a patients' response to desferrioxamine may be monitored by urine iron estimation, using the standard chart in Fig. 7. The duration of the initial negative iron balance can be followed; if the initial response is inadequate this can usually be corrected by giving oral vitamin C (see below). In the later years, a response above the line representing balance usually means that the patient is not taking his injections regularly and has allowed the body iron load to creep up. A response of less than the balance level may indicate inadequate desferrioxamine dosage, or unusually large gastrointestinal excretion, or a continuing need for ascorbic acid supplements.

Patients should be warned that they may occasionally suffer an acute reaction. These effects have been observed in 5 of our patients receiving intramuscular doses of desferrioxamine above 500 mg daily, apparently when some of the drug entered a vein (blood was actually seen in the syringe on two occasions). There may be prickling sensations, feelings of coldness or heat, bradycardia, hypertension, rigors, headache, and photophobia. The patient is alarmed. Most of the manifestations last

*Palmer Injector, manufactured by McGregor & Alves Limited, Hillington, Scotland.

only a few minutes, but the headache may last hours. Treatment was discontinued in all 5 patients and restarted cautiously under supervision in 4 with no ill effect. Similar reactions have been observed by others (V. C. Canale, personal communication) but in no case has a patient come to harm, nor has there been any evidence for an allergic basis for the reaction. After desferrioxamine administration, cataracts were reported in 2 patients who were both also receiving long-term steroids (Brown, 1976). Patients should therefore have annual slit-lamp examinations of the eyes, though no cataracts have yet been observed in thalassaemic children in England or abroad.

Induction of chelation therapy in older patients. Older, heavily iron-loaded patients are brought into negative iron balance by the doses of desferrioxamine recommended above, but after 1 to 2 years the iron excretion has fallen to about the balance level, after a net excretion of no more than 4 to 8 g. This suggests that a large part of the body iron load, which may be 40-70 g in such patients, is relatively inaccessible to desferrioxamine, which must react with a smaller chelatable iron pool. It seems unwise to ignore these large iron stores, especially in patients who have measurable cardiac pathology, as there is evidence that intensive treatment can reverse such pathology, though probably nothing can help in the terminal stages (A. W. Nienhuis, personal communication).

It has been shown that though there is a limit to the amount of iron that can be removed by increasing the dose of desferrioxamine administered intramuscularly, continuous IV infusion of massive doses of the drug may remove very large quantities of iron (Modell and Beck, 1974; Propper *et al.*, 1976). If it is desired to start long-term desferrioxamine therapy in an older patient about whom there is anxiety because of either age or physical condition, it would seem reasonable, in addition to prescribing the recommended daily dose of desferrioxamine, to admit the patient for week-ends or occasional whole weeks of continuous IV or subcutaneous infusion of 10 g desferrioxamine daily, or to arrange for regular overnight subcutaneous infusions at home. This should be continued for 1 to 2 years, or until the urine excretion in response to this treatment

falls off significantly. Propper *et al.* (1976) have shown that chronic subcutaneous infusion of large doses of desferrioxamine from a portable light-weight pump is both feasible and as effective as intravenous infusion, and when suitable equipment becomes available, this will probably be the ideal way of inducing treatment in older suitable patients.

Vitamin C and desferrioxamine. There is general agreement that vitamin C taken by mouth enhances the effectiveness of desferrioxamine therapy; but there is some anxiety that large doses could also enhance iron toxicity, especially in older patients because it may work by releasing iron from relatively harmless storage, e.g. in reticuloendothelial cells. The suggestion that the effect of vitamin C was due to coincidentally increased iron absorption has been disproved (Nienhuis *et al.*, 1976). More work needs to be done on the mechanism of the vitamin C effect, but present treatment should be firmly based on the principle that the more iron is removed, by whatever means, the better. Therefore, ascorbic acid should probably be added into all treatment schemes, but only after the patient has already been receiving desferrioxamine for at least a month. In patients with measurable pathology, it should be introduced cautiously and discontinued at the first sign of cardiac arrhythmia. The dose should probably not exceed 200 mg/day in these patients, and possibly should be adjusted to maintain the urine iron excretion at a maximum, or the white cell ascorbic acid level within the normal range.

In conclusion, the accumulated evidence for the effectiveness of desferrioxamine in iron overload in thalassaemia now indicates that all patients should receive daily injections from the age of 3 years, with vitamin C supplements. Rigorous treatment may even reverse established pathology (Seshadri *et al.*, 1974) so treatment should not be withheld from older patients on the supposition that they are beyond recovery.

Social aspects. Most of the suffering caused by thalassaemia, as by many other chronic childhood diseases, arises from the anxiety of the child and the parents. One of the most important aspects of treatment is to support the family by ensuring continuity of care by the same individual as far as possible, ease of access to expert medical advice, time for discussion, efficient service, and the minimum possible number of hospital visits once the patient is well-controlled. In such a setting the majority of families can cope with one thalassaemic child, but in any setting 2 such children may prove an intolerable burden.

The pattern of management recommended here for Britain is impracticable in many countries in the Mediterranean area, the Middle and the Far East, where thalassaemia is a major public health problem. In these communities immense distress is caused by difficulty in obtaining blood for treatment of the hundreds of affected children, and desferrioxamine is too expensive to be used to counteract iron overload. The observation that splenectomy appreciably decreases the blood requirement in the majority of β^+ patients over 4 years of age may be valuable in this context. In areas where desferrioxamine is hard to obtain, treatment should probably be postponed until it is known to be most effective, i.e. at 6 years of age onwards. In addition, new oral iron chelators such as 2, 3 dihydroxybenzoic acid are being developed (Graziano *et al.*, 1974). If they prove effective and can be manufactured cheaply, such drugs could transform the outlook for the majority of patients in countries where the disease is most common. However, in all communities prevention by population screening, antenatal diagnosis, and selective abortion seems the long-term solution, and this will probably become a possibility in the near future (Kan *et al.*, 1975; Alter *et al.*, 1976; D. V. I. Fairweather *et al.*, in preparation).

Summary of recommendations for management

The following guidelines, which include some points not discussed in the body of this paper, are suggested to clinicians entrusted with the care of thalassaemic patients.

(1) Care should be taken in the differential diagnosis of thalassaemia intermedia and major (Erlandson *et al.*, 1964). To start a patient with thalassaemia intermedia on maintenance transfusion is at present a serious error.

(2) Patients requiring maintenance transfusion do better in every way on a high transfusion scheme (mean Hb 11.5 g/dl), but the detection and treatment of hypersplenism becomes especially important for patients on such schemes.

(3) Splenectomy reduces the blood requirement significantly and permanently in the majority of patients with β^+ thalassaemia major. The results of the operation can be precisely predicted from an analysis of the blood requirement of individual patients as described here. The operation carries risks and should not be undertaken without careful evaluation of the expected advantage.

(4) Prophylactic penicillin 125 mg twice daily should be given indefinitely after splenectomy.

(5) Long-term iron-chelation therapy with intramuscular desferrioxamine 500 mg–1.5 g daily according to weight, is safe and feasible and can bring patients into iron balance albeit at a high body iron load. Desferrioxamine protects the liver from toxic effects of iron, and appears to prolong life. All patients who can, should now receive this drug.

(6) Any severe illness probably carries a risk of death from acute iron toxicity, since hypoxia and acidosis apparently release iron from storage complexes (Modell and Matthews, 1976). Any thalassaemic patients with an acute illness, in addition to therapy indicated for the intercurrent disease, should be treated as follows. (a) If there is the least possibility of septicæmia, give high dosage intravenous antibiotics until the diagnosis is disproved. A combination of ampicillin 200–400 mg/kg per 24 h and cloxacillin 200 mg/kg per 24 h is suggested. (b) Antagonize iron toxicity with slow intravenous desferrioxamine (up to 250 mg/kg per 24 h is safe in iron-loaded patients). (c) Transfuse to Hb 14 g/dl to correct hypoxia: this is especially important if the patient is in cardiac failure. (d) Protect against adrenal insufficiency with hydrocortisone 100 mg immediately and daily as long as the patient is severely ill. (e) Monitor the blood urea, bilirubin, glucose, and serum calcium.

(7) In giving a prognosis to the parents of a new patient presenting with thalassaemia, it is realistic to promise good health to 13 years, to give a minimum prognosis of 20 years, and to point out how much time this leaves for progress in the control of iron overload, and in bone marrow transplantation, the use of artificial blood substitutes, and in molecular biology, all active and promising research areas.

(8) The immediate family should be screened for thalassaemia trait, and genetic counselling offered to carriers. The risks of having further affected children should be discussed with the parents and advice on contraception given. If they wish to have further children, the possibility that antenatal diagnosis of the fetus will become available in the near future should be considered.

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Erratum—The table below replaces that on page 497, June issue, in the article ‘Total management of thalassaemia major’ by B. Modell (pp. 489–500). There was an error in column 3, desferrioxamine (DF) dosage.

Table 4 *Recommended weight-related dosage of desferrioxamine (DF) (approximately 25 mg/kg)*

<i>Weight range (kg)</i>	<i>Age (years)</i>	<i>Dose DF (mg)</i>	<i>Distilled water (ml)</i>	<i>Comment</i>
15–20	3–6	500	1·5–2	Usually acceptable
20–35	7–12	750	2	Usually acceptable
35–45	13–puberty	1000	2–3	May be some difficulties
45–65	Post pubertal if normal stature (uncommon)	1500	4	Hard to tolerate