Meeting 5 December 1974

Thalassæmia in Cyprus

Major C M Bate
(Queen Alexandra Military Hospital, Millbank, London SW1)

A clinic for children suffering from homozygous β thalassæmia has been in operation at the British Military Hospital in Dhekelia, Cyprus from early 1971 until the present date. Extensive clinical and biochemical data have been gathered on 64 children and the number attending the clinic continues to increase.

Clinical Features
Bone marrow expansion throughout the skeleton, in an ineffective attempt to compensate for the anæmia, produces a characteristic thalassæmic facies, with prominent malar eminences, maxillary hypertrophy and skull bossing. Affected children are stunted, with massive hepatosplenomegaly and skin pigmentation (Figs 1 & 2).

Skull radiographs demonstrate widening of the diploic space because of increased marrow content. Rearrangement of the internal bony architecture into vertical spicules to prevent the skull tables collapsing produces a striking 'hair on end' appearance (Fig 3).

Cortical thinning of the long bones and increase of marrow space give a picture of rarefaction, but pathological fractures have proved to be uncommon. Bone age is normal in early life, but is delayed by the age of 8 or 9 years.

Chest radiographs show rib expansion, often paravertebral reticuloendothelial tissue masses and, in severe cases, cardiomegaly due to anæmia and myocardial hæmosiderosis.

Some degree of delayed maturation is seen in all the affected children and growth retardation occurs for reasons which are not entirely clear. Measurement of growth hormone in 23 thalassæmic children and 11 age-matched controls showed no quantitative deficiency of the hormone with no significant variation in fasting growth hormone levels between the two groups. There was no association between growth hormone level and iron load status.

The development of secondary sexual characteristics is usually delayed, and those males who achieved puberty were shown to have azoospermia.

Measurement of gonadotrophins in 13 patients whose ages ranged from 11 to 34 produced normal results.

Iron loading as a result of both transfusion and increased absorption leads eventually to hæmosiderosis. Liver iron concentration was measured in 42 children and was shown to increase with increasing transfusion load. After the transfusion of 80 units (40 litres) or more of blood a peak concentration of about 4500 μg of iron per 100 mg of dry liver was reached and this did not increase despite further transfusion. Only 3 patients in this group were positive for Australia antigen and antibody. This suggested that iron loading and not subclinical hepatitis was responsible for liver damage. The effect of iron loading on other endocrine organs was investigated and no evidence of impaired thyroid or pancreatic function was detected in 50 patients, 17 of whom were aged 10 years or over, the eldest being 34. Adrenal function is still being assessed.

Management
Maintenance of a patient's hæmoglobin at 10 g/100 ml by transfusion suppresses his bone marrow, resulting in arrest of bony changes, or even reversal if they are early. Hepatosplenomegaly is reversed and hypersplenism often does not develop. The child becomes less susceptible to heart failure and grows normally. The quality of life approaches that of a normal child (Fig 4).

There are 57 children undergoing such a regime at BMH Dhekelia. This is obviously very demanding for patients, their relatives and the hospital staff. Considerable difficulty is experienced in obtaining supplies of blood and parents are required to obtain a civilian donor to contribute a unit of blood for the hospital blood bank before one is released for the use of the patient. Because of the paramount need to preserve peripheral veins 'cut downs' are never performed, and scalp vein needles are used to establish the transfusions.

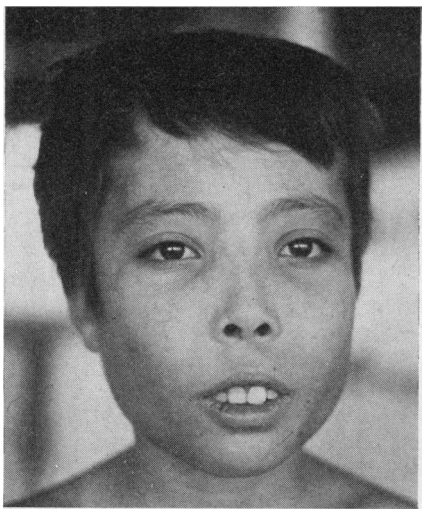

Fig 1 *Characteristic thalassæmic facies*

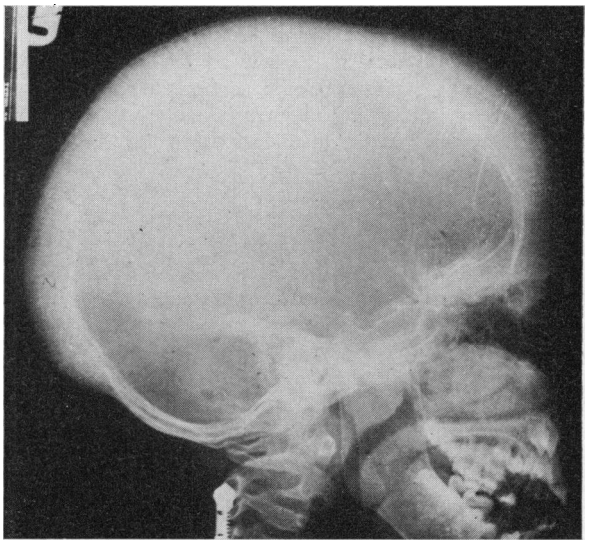

Fig 3 *Hair-on-end appearance of skull*

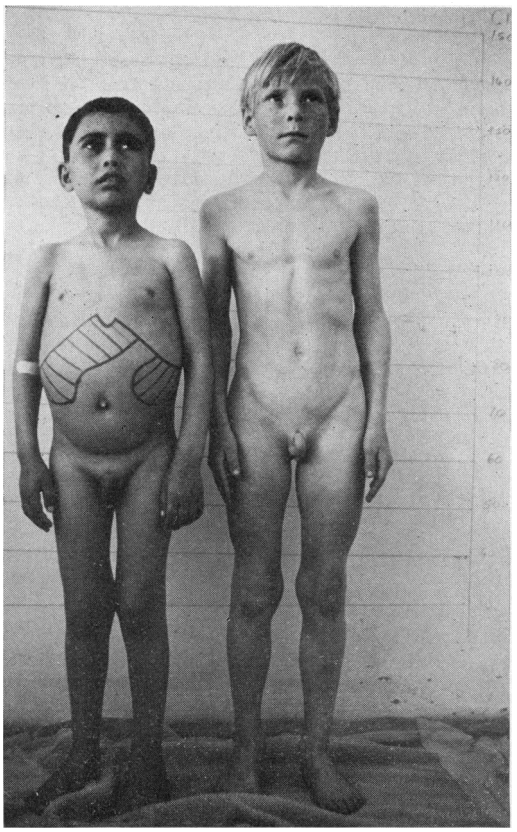

Fig 2 *Thalassæmic child compared with normal child of same age*

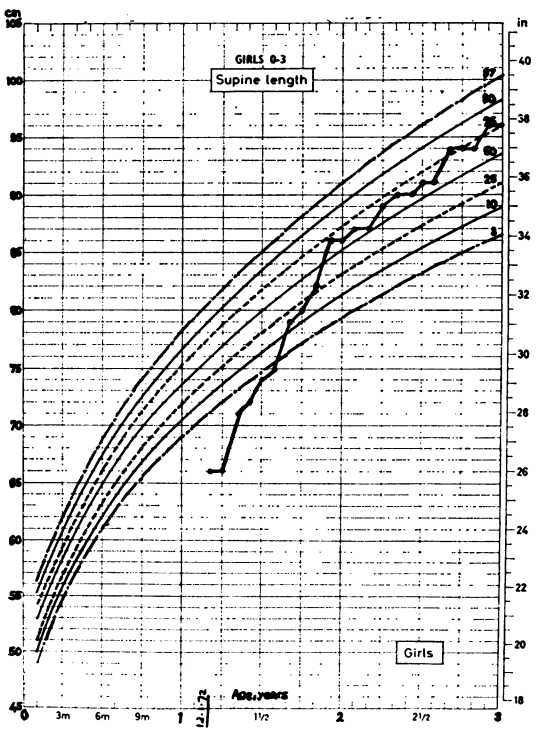

Fig 4 *Percentile chart for height in a thalassæmic child: acceleration of growth following institution of a hypertransfusion regime*

Febrile reactions are common in polytransfused patients, due to the patient forming antibodies to donor leukocytes or plasma antigens. Such reactions are abolished by intravenous hydrocortisone. Sensitization to minor blood groups can occur and is sometimes a cause of a decreasing intertransfusion period.

The risk of transmitting infections by blood transfusion is a real one, and the usual precautions are taken to prevent syphilitic, hepatitic and cytomegalic virus infection.

The extreme costliness of iron chelating agents renders their routine use to prevent hæmosiderosis impracticable in Cyprus.

Many children whose hæmoglobin is maintained below 10 g/100 ml become hypersplenic by the age of about 4 to 7 years. Splenectomies were undertaken on 13 such children, the indications being: (1) Decrease of the intertransfusion period required to maintain a given mean hæmoglobin (in the absence of red cell antibody formation). (2) Plasma volume expansion, as indicated by a failure to achieve the hæmoglobin rise expected from a patient's body weight and amount of blood transfused. (3) Massive splenomegaly not regressing on a high transfusion regime. (4) Thrombocytopenia and leukopenia. All the children subjected to splenectomy had a reduction of blood consumption (expressed in ml per kg body weight per year) of at least 50%, sometimes as high as 90%, for higher mean hæmoglobin levels. The rate of fall of hæmoglobin (expressed as a percentage of the post-transfusion hæmoglobin per day) was reduced by at least 50% in every case. The mean intertransfusion period was always increased by at least a factor of 2 for a higher mean hæmoglobin.

Splenectomy was followed by long-term prophylactic penicillin therapy, and no increase in postsplenectomy infections was noted.

The Extent of the Problem in Cyprus

With the exception of a small number of unstable hæmoglobin disorders an elevated level of circulating hæmoglobin A_2 is found only in sufferers from heterozygous β thalassæmia. Utilizing this fact a survey of 521 Cypriot men and women, 17% of whom were Turks and the rest Greeks, revealed an overall thalassæmia carrier rate of 18.5%. In other words, one out of every 118 newborn children in Cyprus is homozygous for β thalassæmia. From birth rate figures for 1963, one would expect 117 children homozygous for the gene for β thalassæmia to be born annually. To treat only the new cases born each year would cost about £29 250 for chelating agents and require about 1390 units of blood each year – a formidable public health problem. A more practical solution would appear to be to reduce the frequency of homozygotes for Cooley's anæmia by discouraging matings between heterozygotes.

Major R P Craig (*Queen Alexandra Military Hospital*) discussed thirteen operations for splenectomy in the thalassæmias, ten of which he had performed personally. Although there had been no postoperative mortality there was a very severe late postoperative blood loss from one child who had had gross preoperative thrombocytopenia, which was controlled by the placement of further skin sutures and blood transfusion.

One child who had developed obstructive jaundice which resolved after blood transfusion had been found at laparotomy two months later to have a distended gall-bladder and common duct, due to extrinsic pressure from hyperplastic extramedullary erythropoietic lymphoid tissue surrounding the duct system. A by-pass procedure had been performed with no subsequent adverse results.

Major G Humphries (*Queen Alexandra Military Hospital*) stressed that few transfusion problems and no hæmolytic transfusion reactions had been encountered in over 2000 transfusions. Two cases of hepatitis B had occurred, following transfusion of blood later found to be Australia antigen positive. It had, however, been difficult to persuade Cypriot donors to give blood.

Meeting 6 June 1974

Dr C W Kesson delivered his Presidential Address which was entitled **No Medals for Survival.**