

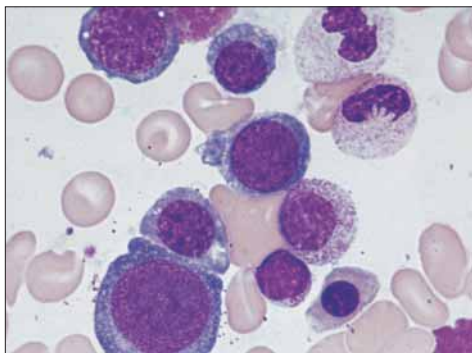
## TRANSCOBALAMIN II DEFICIENCY

### CLINICAL PRESENTATION

Patients usually present at 3–5 weeks of age with failure to thrive, weakness, hypotonia (11.31), and diarrhea, in addition to pallor due to severe progressive anemia. Some patients present with pancytopenia. Transcobalamin II is the principal transporter for B<sub>12</sub> entry into cells, and the serum vitamin B<sub>12</sub> level is normal because it is transported in the plasma by transcobalamin I. The bone marrow is severely



11.31 Transcobalamin II deficiency.



11.32 Transcobalamin II deficiency. Blood smear showing megaloblastic bone marrow.

megaloblastic (11.32) and the blood film shows macrocytosis and other features of megaloblastic anemia. Homocystinuria and methylmalonic aciduria have also been found in some cases. There is some evidence of autosomal inheritance associated with an abnormality in chromosome 22.

### DIAGNOSIS

Absence of the protein capable of binding radio-labelled cobalamin and migrating with TCII, on chromatography or gel electrophoresis.

### TREATMENT

Vitamin B12 must be kept high with systemic injections of hydroxycobalamin (IM) approximately 500–1,000 mg twice-weekly. The prognosis for neurologic abnormalities depends upon whether or not treatment is instituted early and patients must be closely monitored for any deterioration in neurologic status at which stage the vitamin B12 injections should be increased in dosage.

## FANCONI ANEMIA

### CLINICAL PRESENTATION

Usually at around 6 years of age, with hyper- and hypo-pigmentation (11.33), short stature, abnormalities of the thumbs and radii (11.34), hypogonadism, microcephaly, and microphthalmia (11.35). Renal abnormalities are also common and, being a bone marrow failure syndrome, the patients may present with bleeding and infection.

### DIAGNOSIS

Laboratory: investigations include blood count showing a single cytopenia (usually thrombocytopenia but pancytopenia may also be the presenting hematologic feature). Confirmation is by increased spontaneous chromosomal breakage induced with clastogenic agents (e.g. diepoxybutane [DEB]).

### TREATMENT

Chromosome fragility syndromes are associated with a high risk of developing acute leukemia. The progressive bone marrow failure may be temporarily managed with oxymetholone but the only curative procedure is bone marrow transplantation. Gene therapy may be a future possible treatment.

## DYSKERATOSIS CONGENITA

### CLINICAL PRESENTATION

This is a rare form of ectodermal dysplasia. Skin and nail changes are usually seen in the first decade of life, with leukoplakia in the second. All features become more extreme with age. There is a reticulated type of pigmentation of the face, neck, and shoulders, dystrophic nails (11.36), and mucous membrane leukoplakia. Aplastic anemia occurs in 50% of patients, usually during the second decade and cancer in 10% by the 3rd and 4th decade.

### DIAGNOSIS

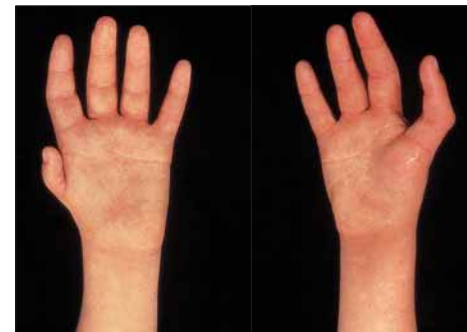
Most patients present with thrombocytopenia or anemia and then develop pancytopenia. Macrocytosis and elevated hemoglobin F are common. Chromosomal breakage studies are usually normal. The Xq28 restriction fragment length polymorphism (RFLP) might be used for prenatal diagnosis. There is an association with failure of cerebellar development (the H-H syndrome).

### TREATMENT

Some patients respond to androgens, but supportive care has been the only effective holding measure, with bone marrow transplantation the only possible chance of cure.



11.33 Fanconi anemia. Facial appearance.



11.34 Fanconi anemia. Thumb abnormalities.



11.35 Fanconi anemia. Microphthalmia.



11.36 Dyskeratosis congenita. Dystrophic nails.



**11.37** Congenital erythropoietic porphyria. Skin erosions as a result of photosensitivity.



**11.38** Congenital erythropoietic porphyria. Phototoxic damage to hands.



**11.39** Congenital erythropoietic porphyria.



**11.40** Congenital erythropoietic porphyria. Blistering on hands.

### CONGENITAL ERYTHROPOIETIC PORPHYRIA (CEP)

#### CLINICAL PRESENTATION

A rare form of porphyria; this diagnosis may be suspected when pink to dark brown stains are noted in the diaper (due to large amounts of porphyrins in the urine). At an early stage, cutaneous photosensitivity is obvious and is exacerbated by any exposure to sunlight. Initial subepidermal bullous lesions progress to crusted erosions (11.37–11.40) which heal with scarring and (usually) increased pigmentation. Hypertrichosis and alopecia are frequent and erythrodontia (red fluorescence under ultraviolet light) (11.41) are virtually pathognomonic of the disease. The patients may also display symptoms of hemolytic anemia with splenomegaly and gall stones.

#### DIAGNOSIS

Urinary porphyrins are greatly elevated due to decreased activity of uroporphyrinogen III cosynthase activity. The bone marrow shows porphyrin fluorescence in the red cells when exposed to UV light. The definitive diagnosis is a demonstration of a deficiency of uroporphyrinogen III cosynthase activity.

#### TREATMENT

Avoid sunlight and trauma to the skin. Topical sun screens may be of help, as may oral treatment with beta-carotene. The hemolysis may be mild or more severe and should be treated with blood transfusion and sometimes splenectomy. Bone marrow transplantation may be curative.



**11.41** Congenital erythropoietic porphyria. Discoloration of the teeth.

### IDIOPATHIC PULMONARY HEMOSIDEROSIS

#### CLINICAL PRESENTATION

The disease may present at any time in childhood and as early as the neonatal period. It is characterized by recurrent intrapulmonary hemorrhage. The patient may have hemoptysis and dyspnea, with a subsequent iron deficiency anemia. The sputum is characteristically 'rusty'. There may be associated fever, tachycardia, tachypnea, leukocytosis and, occasionally, abdominal pain.

#### DIAGNOSIS

The direct Coombs' test may be positive. The blood count shows microcytic hypochromic anemia. Chest X-rays vary from minimal infiltrates (11.42) to massive ones with parenchymal involvement, atelectasis, emphysema, and hilar adenopathy (11.43). Siderophages are found in the gastric aspirate and they stain positive with Prussian blue.

Lung biopsy shows alveolar epithelial hyperplasia, degeneration with excessive shedding of cells, large numbers of siderocytes, varying amounts of interstitial fibrosis and mast cell accumulation, elastic fiber degeneration, and sclerotic vascular changes.

#### TREATMENT

Steroid therapy sometimes produces a remission, and there have been alleged responses to withdrawal of milk from the diet in a few cases.



**11.42** Idiopathic pulmonary hemosiderosis. Chest X-ray showing minimum infiltrates.



**11.43** Idiopathic pulmonary hemosiderosis. Chest X-ray showing hilar adenopathy.

**BETA THALASSEMIA MAJOR****CLINICAL PRESENTATION**

Severe anemia, very often exacerbated by folic acid deficiency, which may lead to pancytopenia. At a later stage, patients who are severely affected develop overgrowth of the bones due to marrow expansion. A good example is shown in **11.44**, where the patient on the right was not transfusion-dependent and developed marrow overgrowth because of failure of marrow suppression. The patient on the left also had beta thalassemia major and developed hyperpigmentation of the skin due to iron overload from blood transfusion, but the marrow was adequately suppressed and thus maxillary and other bony overgrowth did not occur.

If patients are not transfused they develop massive hepatosplenomegaly and wasting



**11.44** Beta thalassemia major. The patient on the right has developed marrow overgrowth in the facial bones.

(**11.45**). The X-rays opposite (**11.46–11.48**) show expansion of the marrow cavity leading to a 'hair on end' appearance in the skull and expansion and thinning of the bones elsewhere.

**DIAGNOSIS**

The diagnosis depends on showing the presence of beta thalassemia trait in the parents, along with either a raised hemoglobin A2 level or the existence of a coexisting hemoglobinopathy such as hemoglobin E. The blood smear (**11.49**) shows hypochromia and microcytosis, and hemoglobin electrophoresis of the patient shows mainly HbF with some hemoglobin A2. Confirmation is either with demonstration of the lack of globin chain synthesis or by molecular methods.



**11.45** Beta thalassemia major. Hepatosplenomegaly.

**TREATMENT**

The only curative treatment at present is with bone marrow transplantation, the outcome of which is excellent if a matched sibling donor is available and the transplant is carried out in the first few years of life. Otherwise, unrelated donor transplant could be considered, but the standard treatment at present is with regular blood transfusion, splenectomy following vaccination against *Pneumococcus*, *Haemophilus*, and *Meningococcus C*, and supplementation with vitamin C, folic acid and penicillin prophylaxis (postsplenectomy).

At a later stage, iron overload becomes a major problem and regular chelation with at least five times per week subcutaneous desferrioxamine is required. If iron overload ensues, multiple endocrinopathies including diabetes mellitus occur, with eventual cardiac failure.



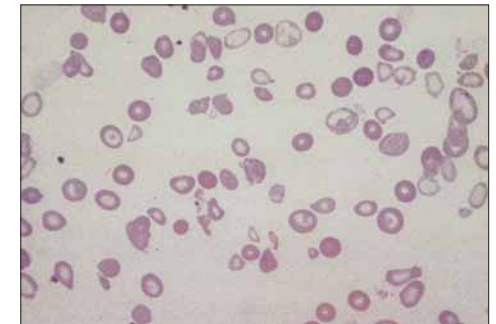
**11.46** Beta thalassemia major.



**11.47** Beta thalassemia major.



**11.48** Beta thalassemia major.



**11.49** Beta thalassemia major. Blood smear.

## PYRUVATE KINASE DEFICIENCY

### CLINICAL PRESENTATION

The child has a congenital non-spherocytic hemolytic anemia which may present with hyperbilirubinemia. Autosomal recessive inheritance is usually observed. Splenomegaly is usually present. Found predominantly in people of Northern European descent. Erythroblastopenic crisis from parvovirus B19 infection is not uncommon.

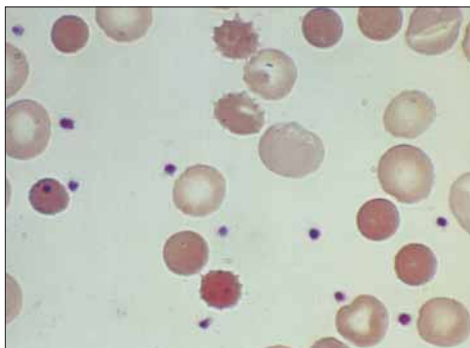
### DIAGNOSIS

Blood smear shows macrocytosis and occasional shrunken, spiculated erythrocytes (11.50). Direct measurement of the pyruvate kinase (PK) enzyme shows a reduced level and there should be a concomitant high level of 2,3-diphosphoglycerate (2,3DPG). Red cell intermediates of metabolism may be helpful in those patients with a marginally low PK level, or with a dysfunctional enzyme or very high reticulocyte count.

A severe anemia is usually present and this may be well tolerated due to a shift to the right of the oxygen dissociation curve, secondary to a raised 2,3DPG. Hyperbilirubinemia, low haptoglobins, and raised reticulocyte levels are usually found. The enzyme level may be spuriously elevated due to relatively high PK levels in the reticulocytes and the assay must be corrected for this.

### TREATMENT

The patients often tolerate a low hemoglobin of around 6g/dl very well because of the compensatory raised 2,3DPG level. Eventually the patients require splenectomy and, contrary to some previous reports, the results are usually very good. Folic acid supplementation is indicated.



## SICKLE CELL (SC) DISEASE

### CLINICAL PRESENTATION

These patients are diagnosed on hemoglobinopathy screening and by neonatal screening programs. The most common problem is a painful crisis, which may involve the hand and produce dactylitis (11.51), possibly leading to osteomyelitis (11.52, 11.53).

Sickle acute chest syndrome involves sequestration in the lungs (11.54). The patient may also present at an early age with an aplastic crisis in which red cell production is impaired by parvovirus B19 infection. Also, an early and life threatening problem is sickle cell sequestration in the spleen and a rapid drop in hemoglobin due to pooling of blood.

### DIAGNOSIS

Diagnosis is by hemoglobin electrophoresis and family studies. The electrophoretic pattern will show hemoglobin S. In hemoglobin SC



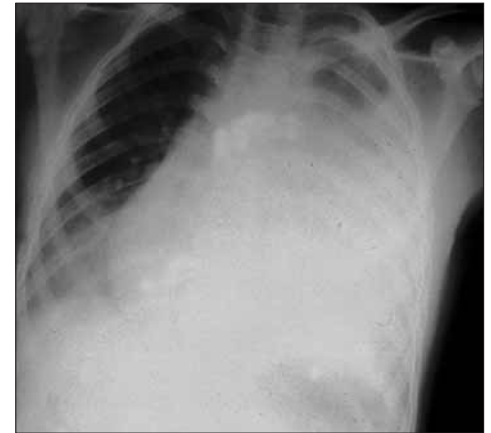
11.51 Sickle cell disease. Dactylitis.

11.50 Pyruvate kinase deficiency. Blood smear showing macrocytosis and spiculated erythrocytes.

disease, there is an extra band on electrophoresis and in hemoglobin S beta thalassemia one parent will have sickle cell trait and one parent will have beta thalassemia trait. Blood films shows the presence of sickle and target cells; the latter being more common in hemoglobin SC disease (11.55, 11.56).

### TREATMENT

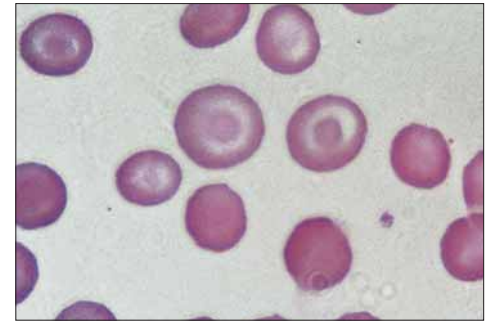
Early diagnosis is essential and may be made on neonatal screening. Early institution of penicillin prophylaxis is essential and treatment of painful crisis is with intravenous fluids and patient-controlled analgesia. For serious complications, such as chest syndrome and stroke, exchange transfusion is essential at a very early stage. Patients should be followed in a specialized Sickle Cell Center.



11.54 Sickle cell disease. Pulmonary sequestration.



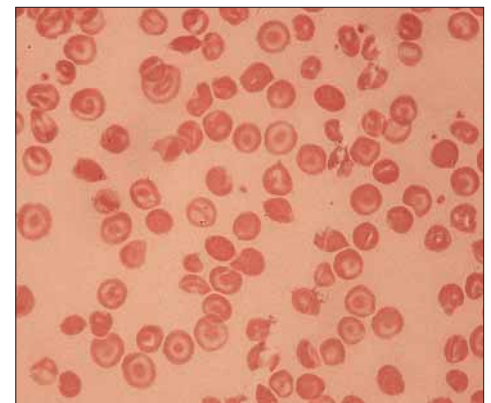
11.52 Sickle cell disease. Periosteal elevation due to osteomyelitis.



11.55 Sickle cell disease. Blood smear showing sickled cells and target cells.



11.53 Sickle cell disease. Osteomyelitis.



11.56 Sickle cell disease. Blood smear showing sickled cells and target cells.