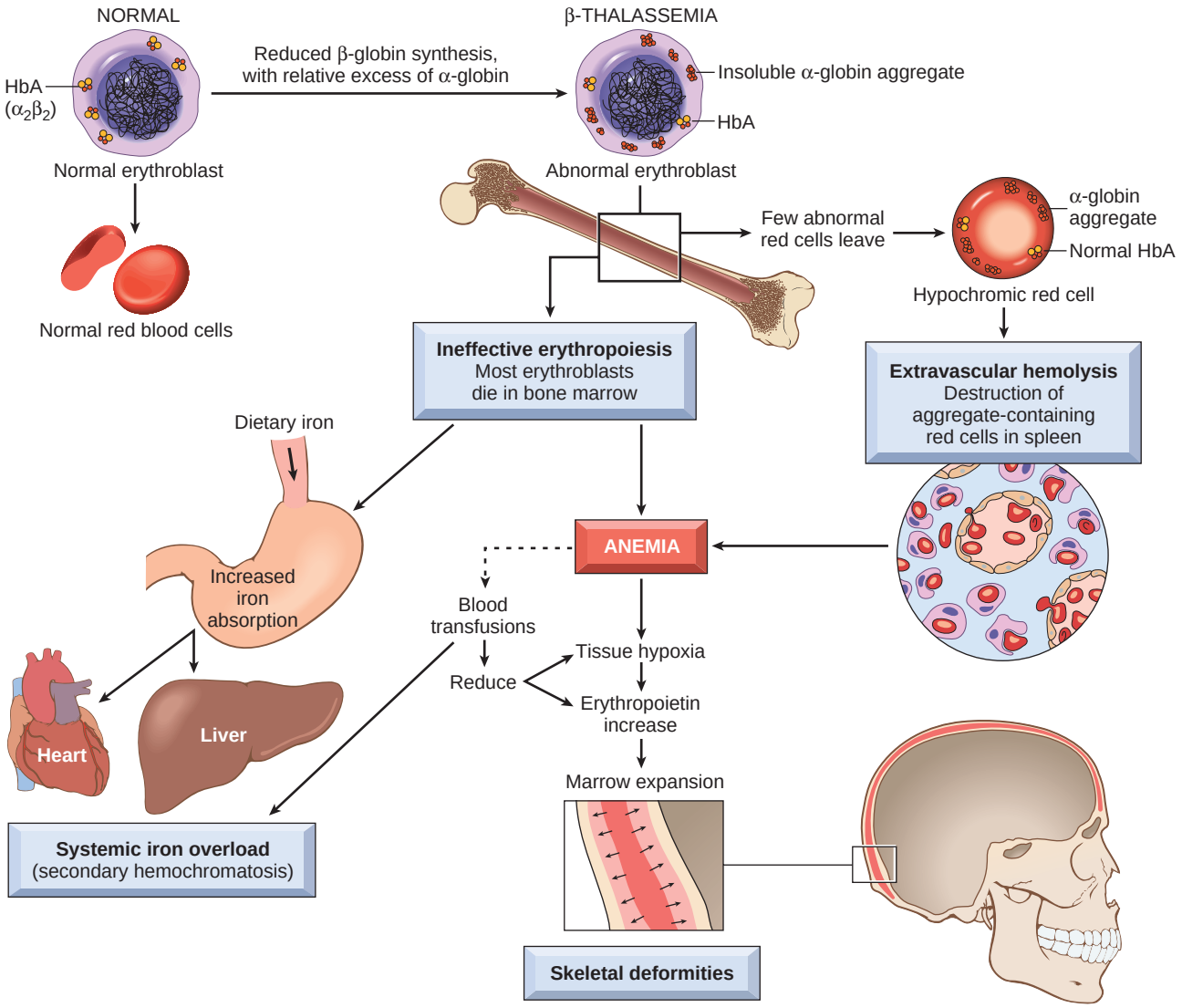

Figure 14-12 Pathogenesis of β-thalassemia major. Note that the aggregates of unpaired α-globin chains, a hallmark of the disease, are not visible in routinely stained blood smears. Blood transfusions are a double-edged sword, diminishing the anemia and its attendant complications, but also adding to the systemic iron overload.

β-Thalassemia Major. β-Thalassemia major is most common in Mediterranean countries, parts of Africa, and Southeast Asia. In the United States the incidence is highest in immigrants from these areas. The anemia manifests 6 to 9 months after birth as hemoglobin synthesis switches from HbF to HbA. In untransfused patients, hemoglobin levels are 3 to 6 gm/dL. The red cells may completely lack HbA (β^0/β^0 genotype) or contain small amounts (β^+/β^+ or β^0/β^+ genotypes). The major red cell hemoglobin is HbF, which is markedly elevated. HbA_2 levels are sometimes high but more often are normal or low.

MORPHOLOGY

Blood smears show severe red cell abnormalities, including marked variation in size (**anisocytosis**) and shape (**poikilocytosis**), **microcytosis**, and **hypochromia**. Target cells (so called because hemoglobin collects in the center of the cell), basophilic stippling, and fragmented red cells are also common. Inclusions of aggregated α chains are efficiently removed by the spleen and not easily seen. The reticulocyte count is elevated, but it is lower than expected for the severity of anemia because of the ineffective erythropoiesis. Variable numbers of poorly hemoglobinized nucleated red cell precursors (normoblasts) are seen in the peripheral blood as a result of "stress" erythropoiesis and abnormal release from sites of extramedullary hematopoiesis.

Other major alterations involve the bone marrow and spleen. In the untransfused patient there is a striking expansion of hematopoietically active marrow. In the bones of the face and skull the burgeoning marrow erodes existing cortical bone and induces new bone formation, giving rise to a "crewcut" appearance on x-ray studies (Fig. 14-13). Both phagocyte hyperplasia and extramedullary hematopoiesis contribute to enlargement of the spleen, which can weigh as much as 1500 gm. The liver and the lymph nodes can also be enlarged by extramedullary hematopoiesis.

Hemosiderosis and secondary hemochromatosis, the two manifestations of iron overload (Chapter 18), occur in almost all patients. The deposited iron often damages organs, most notably the heart, liver, and pancreas.