Today's Treatment

Blood and Neoplastic Diseases

Toxic Anaemia

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This form of anaemia, also called "the anaemia of chronic disorders," is associated with chronic infection, connective tissue disorders, and malignant disease. It is common, especially in patients in hospital, and worldwide in distribution. The anaemia is usually mild, normochromic, and normocytic. When the infection is severe and protracted the anaemia may be appreciable, hypochromic, and microcytic.

Chronic Infection

Mild and shortlasting infections are seldom accompanied by anaemia. Severe infections, particularly when they are accompanied by fever are, however, rapidly followed by disturbances of iron metabolism, and later by the development of anaemia. This is especially so where there is suppuration or severe systemic upset with fever. Such anaemias are common and do not respond to treatment with haematinics, seldom being affected or relieved until the infection is controlled. The blood elements then regenerate in association with a reticulocytosis, as with other treated anaemias.

The mechanism by which the anaemia occurs is complex and ill understood. Within the first day of the illness the plasma iron and transferrin levels diminish, to about 20 mg/100 ml and 150 mg/100 ml respectively (normal 75-175 mg and 250-410 mg/100 ml), and return to normal only when the infection and its associated fever subside. With persistent infection the serum iron and transferrin levels remain low, and do not respond to treatment with oral iron. The low plasma iron levels is out of proportion to the low transferrin level, and is not due to it. After parenteral iron therapy the plasma iron level attained is limited by the plasma transferrin level but giving transferrin by intravenous injection will not return the plasma iron level to normal. The intake of iron is reduced by anorexia, and its absorption from the gut is impaired, but once absorbed iron is rapidly removed from the plasma and diverted to storage sites—particularly the liver, spleen, and bone marrow. This results in increased amounts of iron in the depots and of haemosiderin in the bone marrow. The utilization of this iron is, however, reduced and its rate of incorporation into red cells is diminished in relation to the severity and chronicity of the infection. The persistent low level of iron in the blood is due to a com-

bination of decreased intake, impaired absorption, increased diversion to storage sites, and failure of the tissues—and particularly the reticulo-endothelial cells—to release into the plasma iron resulting from degradation of haemoglobin from destroyed or aged red cells. This results in a diminished flow of iron from storage sites to the bone marrow.

These abnormalities of iron metabolism are associated with complex haemopoietic derangements. The anaemia that ensues has several causes, but reflects a combination of mild haemolysis and toxic inhibition of erythropoiesis. The marrow erythropoiesis rate is normal or slightly increased, so that the marrow is depressed in proportion to the demand being placed on it. Haemoglobin synthesis is impaired at the stage of iron insertion into the protoporphyrin molecule. Abnormalities of globin synthesis and of red cell stroma formation also occur. The resultant anaemia is usually unaccompanied by blood loss or appreciable haemolysis, though both may arise as complicating factors in some infections—for example, typhoid fever or malaria. The anaemia is generally mild to moderate and accompanies such chronic infections as empyema, chronic osteomyelitis, brucellosis, tuberculosis, bronchiectasis, lung abscess, bacterial endocarditis, chronic pyelonephritis, amoebic liver abscess, and some chronic fungal infections. If these chronic debilitating infections occur in a patient who is already malnourished the anaemia may become hypochromic and severe.

The end result of all these derangements is a normochromic anaemia which develops within the first month of the illness, progresses slowly over several months, and then becomes stationary with a haemoglobin level around 9 g./100 ml. The clinical features of the infection generally dominate the picture, though the anaemia may itself be the presenting feature. This variety of anaemia must be treated by trying to eradicate the infection by suitable antibacterial therapy, for haematinics are ineffective. In patients with empyema, chronic osteomyelitis, hepatic, subphrenic, or other large abscesses, surgical drainage of pus must be undertaken, for no other measures will permanently alleviate the anaemia. In these patients the transfusion of fresh packed red cells ought to be considered immediately before surgery, the operation also being covered by parenteral bactericidal antimicrobial therapy.

Patients with established cardiovascular, cerebrovascular, or chronic pulmonary disease in whom a persistently low haemoglobin level would be deleterious should be transfused with fresh packed cells under diuretic cover, given together with appropriate antimicrobial therapy. Eradication of the infection will, however, be almost invariably followed by a return of the blood to normal, though the regeneration process may sometimes be slow. General supportive measures are necessary throughout treatment in all patients, supplemented by a high protein and calorific intake during convalescence.

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If the haemoglobin level becomes stationary after a while in spite of control of the infection, then a four-week course of oral iron therapy should be given.

In the developed countries a higher standard of community health and readily available antibacterial therapy have undoubtedly reduced the incidence of this form of anaemia. In underdeveloped countries the anaemia of infection remains common, and in Britain it still arises frequently in children and the elderly; moreover, it is important to recognize that the presence of infection will impair the response of patients to the treatment of other anaemias.¹⁻³

Connective Tissue Disorders

The cause of the connective tissue disorders remains unknown, but they have in common abnormalities of immune mechanisms often associated with an underlying vasculitis. The commonest of these disorders is rheumatoid arthritis, and its most frequent extra-articular manifestation is anaemia.

The anaemia of rheumatoid arthritis is usually normochronic or mildly hypochromic and normocytic, and results mainly from a reduction in the red cell count, with only a modest reduction in the mean corpuscular haemoglobin concentration. The degree of anaemia correlates more closely with the activity of the disease such as the systemic manifestations, particularly fever, the erythrocyte sedimentation rate, and the degree of active joint involvement, than with its duration. The plasma iron is low and inversely related to the erythrocyte sedimentation rate, while the iron binding capacity is not increased, differentiating this type of anaemia from true iron-deficiency anaemia. Iron absorption from the gut is mildly impaired and the lowered serum iron level cannot be corrected by oral iron. There is diminished release of iron to the plasma from the reticuloendothelial cells an abnormality that can be corrected by treating the patient with corticosteroids. Adequate iron stores exist, though the bone marrow contains less iron than in non-anaemic controls. Mild haemolysis and a degree of haemodilution occur, but have relatively unimportant roles in the production of the anaemia, except in patients with Felty's syndrome. Blood loss from the effects of salicylates and other anti-inflammatory drugs may complicate the picture further. The important factors in the development of this type of anaemia are an impaired response of the bone marrow to anaemia, an impaired flow of iron from reticuloendothelial stores to the marrow, and shortened survival of the red cells.

The anaemia rarely responds to oral iron but parenteral iron therapy will increase the haemoglobin concentration in most patients, probably doing so by overcoming the avidity

of the reticuloendothelial system for iron. The marrow is consequently presented with adequate quantities of utilizable iron. It is more important, however, to control the activity of the underlying disease process with bed rest, splinting, and salicylates and other anti-inflammatory analgesics, and in suitable cases the use of corticosteroids and penicillamine. A combination of these measures and parenteral iron therapy will usually improve or correct the anaemia of rheumatoid arthritis.⁴

Malignant Disease

Of the wide variety of haematological abnormalities associated with cancer, anaemia is by far the commonest. Anaemia is almost invariable with metastatic disease, but also arises frequently in localized cancer. Indeed, it is rare for any malignant disease to run its natural course without haematological complications.

The anaemia of malignancy has many causes, including haemorrhage, deficiency states, haemolysis, haemodilution and leuco-erythroblastosis—and may be further complicated by chemotherapy. Dyserythropoietic anaemias arise with localized and metastatic malignancy and may closely mimic that seen in chronic infection or inflammation. This is well recognized, but its cause remains largely conjectural.

The anaemia is usually mild and develops gradually. It may sometimes be the presenting feature, though the primary cause more often dominates the clinical picture. The red cells are normochromic and normocytic, though they may be hypochromic and microcytic, particularly if there is bleeding. There is no reticulocytosis. The serum iron and iron-binding capacity are reduced, and marrow hemosiderin often increased. This iron is poorly utilized, however, the red cell precursors having poorly haemoglobinized cytoplasm without siderotic granules. Ferrokinetic studies confirm the presence of dyserythropoiesis, red cell production remaining uninfluenced by the stimulus of anaemia. Haematinics are ineffective, though the anaemia will often respond to treatment of the disease by surgery, radiotherapy, or chemotherapy.⁵ Transfusion may be necessary before surgery and repeated transfusions of fresh packed cells are often necessary during or after courses of chemotherapy.

References

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