MEDICAL PRACTICE

Today's Treatment

Blood and Neoplastic Diseases

Blood Formation and the Pathogenesis of Anaemia

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The definition of anaemia is somewhat arbitrary, and "normal" haemoglobin values in various western population studies have been rising gradually for several years. A safe rule would be to regard as abnormal a haemoglobin level below 13g/dl in men and below 12g/dl in women, and to investigate its cause in the context of the patient's complaints.

The visual estimation of haemoglobin is notoriously difficult and can lead to large mistakes in both directions. The colour of the face is particularly deceptive, though a history of onset of pallor of the face is significant in anaemia. Pallor of the mucous membranes may indicate only the grosser degrees of anaemia. The skin creases in the palms are the best guides to significant pallor, but even these may be colourless only when the haemoglobin level is 7g/dl or below. Any routine medical examination should include a check on the blood when there is the remotest suspicion of anaemia on the grounds of history and physical findings.

The symptoms of anaemia are extremely non-specific, and all of them vary greatly, and depend on several connected factors:

(1) The causative disorder will modify the picture, perhaps greatly.

(2) The speed with which the anaemia has developed is a prime factor in determining the nature and severity of the symptoms. In contrast to the obvious disability of fairly acute blood loss, symptoms of very chronic anaemia may be absent,

or very minor, even when the haemoglobin level is well under 7g/dl.

(3) The pre-existing state of the cardiorespiratory system in particular is obviously important. Even mild anaemia will aggravate angina, the breathlessness of lung disease or cardiac failure, or intermittent claudication.

PREVALENCE

Probably 10% of females have anaemia at the age of 15, over 30% between 30 and 40, about 20% at 50, rising to 30% again at the age of 70. Under 5% of males are affected until 50, and then the proportion rises to over 20% in the 70's.

The old nomenclature of primary and secondary anaemias has now been superseded, since every anaemia has a cause which ought to be found before treatment is given. Probably 90% of all anaemias are of iron-deficiency type. Megaloblastic anaemia due to vitamin B₁₂ or folate deficiency, or both, may account for 7%, and haemolytic and other anaemias (including leukaemia) for 3% of the total. All of these figures are only approximations, since no complete survey has been done in the general population, but they give some idea of the relative numerical importance of the types of anaemia found in a British general practice over the years.¹ Being very selected, the types of anaemia seen in hospital differ of course in relative frequency, the emphasis being on the more severe and rarer types needing hospital investigation and treatment. Moreover, probably there is a good deal of undiagnosed and untreated anaemia in the community.

Red Cell Physiology

Maintenance of normal blood values depends on the balance between production and destruction of red and white blood

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cells. The average red blood cell life is 120 days and a 70 kg man has about 770 g of haemoglobin circulating in his red cells, containing about 3 g of his total of 5 g body iron. In health the turnover in destruction and production of red cells affects about 6.5 g of haemoglobin daily, with the reticulocytes (young red cells newly released from the marrow) accounting for up to 2% of the total red cells.

This haemoglobin yields about 20 mg of iron daily and also 250 mg of protoporphyrin and 6.2 g of globin daily. The iron and globin are modified and used anew in the bone marrow, providing good examples of natural recycling of valuable materials. The protoporphyrin is changed into bilirubin, which is carried unconjugated to the liver where it is conjugated and excreted, giving rise to the urinary and faecal urobilinogen. The normal bone marrow can respond to anaemia, notably from blood loss or haemolysis (increased breakdown), with an increase of seven to ten times its normal resting output. With such an active normal response, anaemia will arise from haemolysis only when the red cell life span has fallen below about 15 days, as measured by labelling of the cells with chromium-51.

Ferroketic studies of iron uptake and turnover using radioactive iron (^{59}Fe) can give a fair estimate of the avidity of the marrow for iron, the rate of formation of new haemoglobin and red cells within the marrow, and of the discharge of red cells into the circulation. Radioactive chromium can be used to measure the life span of the red cell, and to discover the site of abnormal red cell destruction, usually the spleen. These are useful supplementary procedures in the study of the more obscure aplastic or haemolytic anaemias—such as hypersplenism, in which red cells (as well as white cells and platelets) may be sequestered and destroyed at an excessive rate in an enlarged spleen.

Pathways to Anaemia

Anaemia arises from one or more of three mechanisms: (1) reduced formation of blood from marrow hypoplasia or aplasia, replacement of the normal marrow by abnormal tissue, or metabolic upset of erythropoiesis, "dyserythropoiesis," as in nutritional deficiency or faulty marrow metabolism of free iron as in sideroblastic anaemia; (2) blood loss, acute or chronic, and often occult; and (3) increased blood destruction (haemolysis), which also may be overt or occult. Any one of these mechanisms alone may lead to anaemia, but sometimes two or all three are involved (fig. 1).

REDUCED BLOOD FORMATION (FIG. 2)

Marrow failure can result from various causes giving rise to the production of too few or defective red cells. So-called idiopathic aplastic anaemia, in which the normal red marrow is replaced by non-functioning fatty tissue, perhaps has an autoimmune cause. Marrow destruction may be caused by various drugs, either directly or through hypersensitivity mechanisms.

Some of these drugs can be shown to act like antimetabolites. Marrow failure may result also from invasive change in leukaemia, myeloma, reticulosis, and secondary carcinoma. In all of these there are, of course, other mechanisms which also cause anaemia—notably haemolysis and blood loss as well as metabolic factors so far poorly understood. It is not simply a case of the blood-producing cells being crowded out.

Iron deficiency is the chief cause of dyserythropoietic anaemia, and here the red cell numbers are reduced less than the circulating haemoglobin mass. Megaloblastic anaemia, another excellent example of dyserythropoiesis—with defects also in the white cells, platelets, and all epithelial cells—is a condition where far too few red cells are produced and released by the marrow.

Megaloblastic anaemia is classified as a nutritional deficiency, though it may result from various absorptive and metabolic defects. In general, megaloblastic haemopoiesis results from lack of vitamin B₁₂ or folic acid, or both, and these substances, together with iron, are the most obvious nutritional requirements for normal blood formation. Pure nutritional lack of vitamin B₁₂ is rare in western countries, occurring only in severe vegetarians ("vegans"), though folate lack in the diet may not be so uncommon, especially in the elderly and in alcoholics. Lack of these two vitamins is more often "conditioned" by disease of or operations on the stomach or gut, or by conditions with high cellular turnover, such as psoriasis or hyperthyroidism, which accentuate any folic acid lack. The best-known example of megaloblastic anaemia in Britain is Addisonian or pernicious anaemia, where the primary alimentary defect is in the stomach, causing failure of the absorption of vitamin B₁₂ in the ileum.

Trace elements like cobalt and copper are needed as well in normal red cell formation, though no anaemia due to copper or cobalt deficiency has been found in man, nor has any anaemia due to other vitamin B lack except that of pyridoxine (vitamin B₆), which is rare. Some forms of sideroblastic anaemia respond to pyridoxine whether or not there is demonstrable deficiency of this vitamin. Protein deficiency must be gross, as in kwashiorkor, before it causes anaemia and this degree is probably unknown in Britain. Anaemia due to ascorbic acid deficiency (scurvy) is also rare, though when severe it can cause megaloblastic anaemia, since vitamin C is necessary for the metabolism of folic acid to the active form folinic acid.

Other examples of faulty erythropoiesis illustrate how these classifications serve convenience chiefly, and that there are overlapping factors. In lead poisoning a defective and vulnerable red cell is produced which is broken down too readily, and in the congenital haemolytic anaemias such as hereditary spherocytosis or the haemoglobinopathies (when the red cell contains an abnormal type of haemoglobin) an unusually fragile red cell is produced. Hence all these could also be considered forms of dyshaemopoiesis, though the most striking mechanism of anaemia is the haemolytic one. An acquired example of such a red cell defect occurs in paroxysmal nocturnal haemoglobinuria which, at different stages in the disease, may show predominantly aplastic or mainly haemolytic features.

BLOOD LOSS

Blood loss may be obvious but is often occult, and has a multitude of causes. They include epistaxis; haemorrhoids; peptic ulcer; gastric or colonic carcinoma; drugs such as aspirin and many anti-inflammatory agents; bleeding from the uterus or urinary tract, or into the lung and serous cavities; as well as thrombocytopenic purpura and other disorders of haemostasis. The important loss to the body in chronic haemorrhage is of iron.

Iron loss is one of the most important and commonest causes of anaemia and is an obvious factor in menstruating women, when the balance between iron loss and intake can be so easily made unfavourable, even when the diet is relatively good and

contains more than 10 mg of iron daily. Blood loss is often a hidden and treacherous condition, and may continue from some unsuspected site when the most obvious sources have been investigated and found apparently normal. Bleeding from the caecum is notoriously likely to escape early detection. Aspirin is a frequent cause of either acute haemorrhage or anaemia from mild chronic loss; it also produces fairly profound and long-standing changes in the haemostatic mechanisms so that mild mucosal breaches may be more apt than normal to bleed. Haemorrhage—either acute or recurrent into serous cavities or into tissues such as the lung—may occur even to the extent of causing jaundice from haemoglobin breakdown. In tropical countries many additional causes have to be remembered; hookworm infestation is the commonest cause of chronic blood loss at present in the world.

OVERT OR OCCULT HAEMOLYSIS

Though some degree of increased red cell destruction is a component of many kinds of anaemia, in haemolytic anaemias it is the predominant or only abnormality, and may be severe. Once again there are many causes—including intrinsic defects of, or injury to, the red cells, or destruction of the cells by antibodies circulating in the blood or coating the cell itself. Intrinsic cell defects may be inherited such as hereditary spherocytosis and the various haemoglobinopathies, or acquired as in paroxysmal nocturnal haemoglobinuria. Autoimmune haemolytic anaemias, usually with a positive direct antiglobulin (Coombs) test, are caused by antibodies with many varying characteristics, and are often though not invariably responsive to treatment with adrenocortical steroids or other immunosuppressive agents. Sometimes these acquired autoimmune haemolytic anaemias arise with apparent spontaneity, but on other occasions they are secondary to diseases such as chronic lymphatic leukaemia or systemic lupus erythematosus.

Various drugs may cause a haemolytic state: alaphamethyldopa

often gives a positive direct antiglobulin test without overt haemolysis, and much more rarely a haemolytic anaemia responsive to steroids. With phenacetin and other drugs, the mechanisms are rather different. Hypersplenism has been mentioned as a cause of haemolysis. Purely mechanical buffeting of red blood cells in damaged blood vessels may be responsible for very obvious haemolysis, as in some forms of arteritis, sometimes in malignant hypertension, and also when heart valves (especially the aortic valve), have been replaced by artificial prostheses.

MIXED MECHANISMS

Though often very obvious and clinically important, the anaemia of many severe pathological processes is still obscure and certainly complex in its causation. This applies to the anaemia of infection or severe chronic inflammation and to that of malignant disease and renal failure. In all of these the red cell survival time is diminished and the capacity of the bone marrow to respond to blood loss or destruction is impaired. In chronic inflammatory diseases such as rheumatoid disease there appears also to be an inability of the marrow to utilize iron properly so that, though the stores are full, the serum iron is low and the red cells hypochromic. In renal and malignant disease the main mechanism, whatever its detail, appears to be an unfavourable balance between red cell destruction and replacement. In renal failure lack of renal erythropoietin may be an important factor.

The more important and common of these processes and their treatment, in their clinical setting, will be considered in the articles that follow in this series.

References

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General Practice Observed

Awareness and Experience of General Practitioners of Selected Drug Interactions

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Summary

The awareness of general practitioners of selected adverse drug interactions has been assessed. The drugs studied included adrenergic neurone blockers, warfarin, antidiabetic agents, and monoamine oxidase inhibitors. The findings must

be interpreted with caution but they suggest that there is a clear need to improve the effectiveness of communication of information about adverse drug interactions if unnecessary iatrogenic disease is to be avoided.

Introduction

There is a clear need to ensure that information about clinically important adverse drug interactions is communicated effectively to those doctors who are starting treatment with drugs known to carry such risks. This study aimed to find out whether a group of general practitioners was aware of some of the potential drug interactions involving five groups of drugs—adrenergic neurone blockers, warfarin, antidiabetic agents, monoamine oxidase inhibitors, and sedatives. An attempt was

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