

## XIII. MANAGEMENT OF THE ANAEMIC PATIENT IN GENERAL PRACTICE

E. B. ADAMS, B.Sc. (S.A. AND OXON.), M.B., B.Ch. (RAND), M.R.C.P. (LOND.)

*Professor of Medicine, University of Natal*

Anaemia is one of the easiest conditions to recognize, yet in spite of this patients are frequently mismanaged. Treatment with iron, liver extract, folic acid or vitamin B12 is often prescribed prematurely without a precise diagnosis being made, not infrequently in the form of proprietary preparations containing combinations of all these substances. When such haphazard treatment is followed by improvement, further investigations are often not undertaken and underlying disease is missed. It is always worth while for the doctor to try and answer the question: Why did this patient become anaemic?

## CLINICAL APPROACH

The type of anaemia should first be determined. A full history and physical examination will help to eliminate conditions such as nephritis, chronic sepsis and tuberculosis, in which anaemia may be a secondary feature of the disease. The physical findings, a normal leucocyte count, and the absence of primitive white cells in the blood, will exclude leukaemia, while haemolytic anaemia is unlikely without obvious jaundice. When there is significant anaemia due to haemorrhagic diseases such as haemophilia and the purpuras, the history and clinical features may often point to the diagnosis, but full pathological investigations are necessary in order to

separate the various disease entities. Many of the blood dyscrasias need special investigations in a hospital or clinic, but even so the long-term responsibility falls rightly on the general practitioner. On the other hand, types such as the iron-deficiency anaemia, can be handled entirely in domiciliary practice.

In South Africa there is a racial variation in the incidence of blood diseases which is useful in diagnosis. Chronic iron-deficiency anaemia is uncommon in Africans (probably because of their excessive tissue-iron deposits) but it occurs quite frequently among Europeans and Indians. Unlike the children of other races, Indian children are often afflicted with hookworm anaemia. Pernicious anaemia is practically confined to Europeans, whereas megaloblastic anaemia of pregnancy and the puerperium is not uncommon among African and Indian women in Durban, although it is seen only occasionally in Europeans.

In general practice, it is worth while becoming familiar with the microscopic appearance of thin blood-films properly made and adequately stained. (Reference should be made to the descriptions of Dacie<sup>1</sup> or Whitby and Britton<sup>2</sup> for technical details.) Normally red cells appear round in shape with little variation in size and form, and they are well filled with haemoglobin, the centres appearing a little paler than the periphery.

Using a simple method for haemoglobin estimation (such as the Sahli technique), the white-cell count and the microscopic appearance of the blood cells, the larger categories of anaemia can often be sorted out without more detailed investigations of the peripheral blood or the bone marrow.

#### A. IRON-DEFICIENCY ANAEMIAS

Here the red cells are small (microcytosis), somewhat varied in size (anisocytosis) and shape (poikilocytosis), and show a characteristic rim of cytoplasm round the periphery of the cells, the centres of which are very pale (hypochromia). (See Fig. 1.) These appearances are

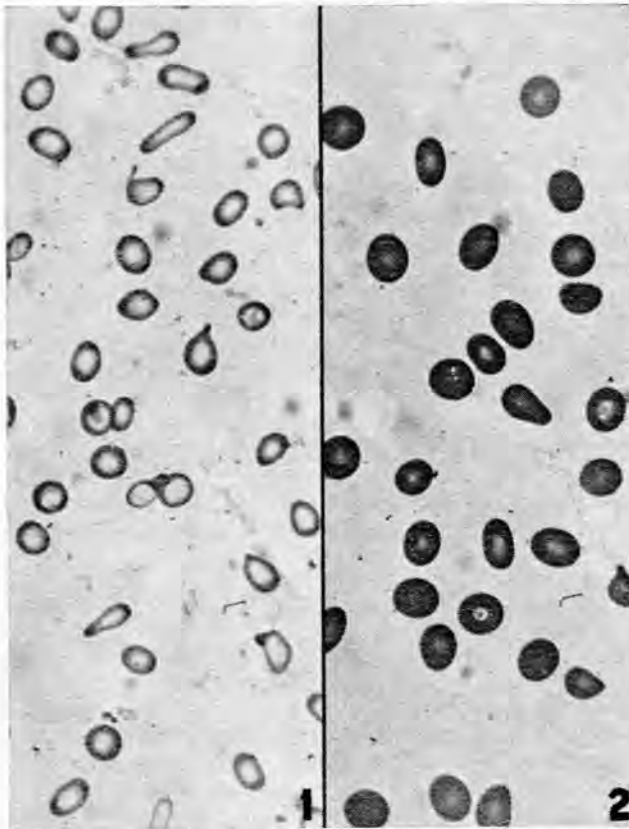


Fig. 1. Blood film: iron deficiency anaemia. The red cells are small and hypochromic, and vary in size and shape.

Fig. 2. Blood film: megaloblastic anaemia. The red cells are large and well filled with haemoglobin, and vary in size and shape. Same magnification for both films.

sufficient evidence on which to diagnose iron-deficiency anaemia. If fuller investigations are available, it will be found that the red-cell count has dropped not nearly as much as the haemoglobin (giving a colour index well below 1.0); the mean corpuscular haemoglobin concentration (MCHC) will be low and the mean corpuscular volume (MCV) decreased.

A useful principle upon which to work is that iron-deficiency anaemia in male patients is almost invariably due to chronic blood loss. In women there is a more

delicate balance between dietary intake, absorption of iron, and blood loss, due to the additional factor of menstruation. The iron stores are, therefore, more readily depleted in the female. Gastric hydrochloric acid converts dietary organic iron into the ferrous state, its most absorbable form. Dietary fads, achlorhydria and menstrual loss contribute towards idiopathic iron-deficiency anaemia in women, which is less commonly seen in South Africa than in Britain. Menorrhagia, however, is a frequent cause of iron-deficiency anaemia and a full menstrual history and pelvic examination are essential. Slight continuous bleeding from haemorrhoids, peptic ulceration or carcinoma of the stomach or large bowel often leads to a considerable degree of anaemia and such cases may actually present with the signs and symptoms of anaemia. A diligent search for such a lesion is therefore always necessary—including proctoscopy, radiology of the alimentary tract and sigmoidoscopy. It is not sufficient to ask the patient if he has passed blood in his stools, it is better to test for the presence of occult blood. Stools should also be examined microscopically, since chronic blood-loss from hookworm infestation may lead to severe hypochromic anaemia. On the other hand, anaemia is not usually a feature of infestation with other parasites such as *Entamoeba histolytica* and *Schistosoma mansoni*, nor is it often seen in urinary schistosomiasis.

In addition to iron therapy for the anaemia, treatment of these underlying conditions is obviously of the utmost importance. In women in whom no source of blood loss can be found, idiopathic hypochromic anaemia must be diagnosed and iron treatment continued indefinitely. Ferrous sulphate (3 gr. *t.d.s.*) is usually very effective and well tolerated. Occasionally, larger doses are necessary before there is a response. Ferrous sulphate has the advantage of cheapness over proprietary preparations, but sometimes there are digestive disturbances such as gastritis, colic or diarrhoea, and in these cases another form of oral iron should be prescribed before resorting to the intravenous route. Good results are obtained with iron and ammonium citrate (20 gr. *t.d.s.*), care being taken to advise the use of a straw since this preparation blackens the teeth. It is well to remember that iron salts are toxic. Coated tablets are attractive to children because of their appearance and sweet taste, and fatalities have occurred in infants ingesting 30 gr. of ferrous sulphate. Care should therefore be taken with the tablets in the home.

#### Intravenous Iron Therapy

There are not many indications for the intravenous injection of iron, but it may be necessary when there is intolerance to iron by mouth and for cases refractory to oral treatment. It is most useful in iron-deficiency anaemia discovered late in pregnancy, especially if there has been vomiting earlier on. In these cases time is limited and it is necessary to achieve as rapid a rise in haemoglobin as possible before delivery.

Administration may present difficulties. Intravenous injection of the dark-coloured solution of saccharated iron oxide requires particular care. It should not be attempted unless the veins are good, for it will cause tissue necrosis if extravasated. Moreover, it may be

followed by thrombo-phlebitis, but given slowly it is well tolerated in doses not exceeding 100 mg. Occasionally it produces tachycardia, flushing, syncope, headache, backache, substernal pain and collapse. It should therefore only be used when there are objections to the oral route.

Saccharated iron oxide (ferrivenin) is dispensed in 5-ml. ampoules each containing 100 mg. of iron. If small initial injections of 25 mg. and 50 mg. give rise to no untoward effects, 100 mg. may be given daily. The total dosage for a course of injections should be calculated on the basis that each 100 mg. of iron will produce a rise of 4% haemoglobin.

Recently a dextran-iron complex has become available for intramuscular injection, but it is too early to assess its place in iron therapy. Preliminary reports are encouraging. However, it is uncommon to find a patient who cannot be adequately treated by oral iron (the cheapest and easiest route) or by intravenous injection.

#### B. MEGALOBlastic ANAEMIAS

As a group these are not seen as frequently as iron-deficiency anaemias. The appearance of the red cells in thin blood-films is quite different, for they are well filled with haemoglobin, many are larger than normal and oval forms are common (Fig.2). Nucleated red cells and nuclear remnants such as Howell-Jolly bodies are sometimes seen. Variation in size and shape is a more striking feature here than in iron-deficiency anaemia, and bizarre poikilocytes are often seen.

These cases should always be more fully investigated. Complete blood counts will reveal high values of the MCV (macrocytosis), with the MCHC within the normal range.

A distinction should always be made between macrocytic anaemias which are megaloblastic and those which are not, for the finding of macrocytic anaemia alone is not sufficient indication for treatment with folic acid, liver extracts or vitamin B12. These are only indicated in the megaloblastic anaemias; in other varieties of macrocytic anaemia, such as aplastic anaemia and the type associated with liver diseases, treatment with these substances has no value. A common error is to start treating a macrocytic anaemia before it has been decided whether it is megaloblastic or not. In megaloblastic anaemias a typical change occurs in the red-cell precursors in the bone marrow. This characteristic appearance disappears shortly after treatment with liver extracts, vitamin B12 or folic acid; so these substances should be withheld until blood investigations are complete. Undue haste in starting therapy, before there is a definite diagnosis, makes subsequent management more difficult. If anaemia is severe the pathologist may find megaloblasts in the peripheral blood, and then examination of the bone marrow is unnecessary; but if they are absent the pathologist should be asked to aspirate a specimen of marrow by sternal puncture.

Gastric analysis is essential if megaloblastic anaemia is diagnosed, but it can be carried out after treatment has commenced. After withdrawing resting juice from the empty stomach, 0.5 mg. of histamine phosphate is

injected subcutaneously and specimens of gastric juice obtained 30 minutes and 1 hour later.

When there is histamine-fast achlorhydria, Addisonian pernicious anaemia is present. Such a diagnosis should not lightly be made, for it means treatment for life. Best results are obtained with vitamin B12. Given by intramuscular injection, 100  $\mu$ g. at weekly intervals will be followed by an excellent response. Once a normal haemoglobin level has been reached, less frequent injections are necessary to maintain good health. Usually 100  $\mu$ g. of vitamin B12 monthly will suffice. Patients should always be carefully examined for evidence of subacute combined degeneration of the cord, in which peripheral subjective sensations and loss of vibration sense appear early on. When there are neurological complications, weekly injections of 100  $\mu$ g. of vitamin B12 should be continued after the restoration of a normal blood picture to ensure as much neurological improvement as possible. Folic acid should not be prescribed for pernicious anaemia, for it does not prevent the onset of cord lesions.

A diagnosis of pernicious anaemia is untenable if free acid is present, as it usually is in the megaloblastic anaemia of pregnancy and the puerperium, and in the nutritional type. Megaloblastic anaemia is occasionally seen in malnourished African children, in whom gastric analysis is not necessary since pernicious anaemia is extremely rare in infancy. The treatment of choice in these cases is folic acid, given in oral doses of 5 mg. 3 times a day until the blood picture is normal. In addition, an adequate protein diet should be provided.

#### TRANSFUSION TREATMENT

Blood transfusion is more urgently indicated in some anaemias than in others, and there are occasions when transfusion is by no means the treatment of choice.

Usually the need for blood transfusion is directly related to the rate at which blood has been lost. Rapid bleeding amounting to 1,500-2,000 ml. may prove fatal, but considerably more can be lost over 24 hours without a fatal outcome. After a severe haemorrhage, haemoglobin estimated from the peripheral blood may leave the doctor with a false sense of security, for it will often be surprisingly high, especially when there has been insufficient time for the restoration of blood volume. Thus immediately after a large haematemesis the haemoglobin may only have dropped to 70%, but as fluid passes from the tissues into the circulation to make up the blood volume the haemoglobin will drop to considerably lower levels. *The decision to transfuse should be made on the clinical state of the patient rather than on the haemoglobin level.* When in doubt in conditions such as haematemesis, where bleeding is difficult to arrest and may be recurrent, it should always be borne in mind that another haemorrhage may be fatal. There should therefore be no delay in transfusion; whole blood has been lost and whole blood ought to be given.

When blood loss is slow there is ample time for compensatory changes in the cardiovascular system, and treatment is not so urgent. In chronic anaemias with faulty blood-formation (such as pernicious anaemia or aplastic anaemia) similar compensatory changes take

place, and patients are sometimes surprisingly active despite haemoglobin levels of 30% or less; if put to bed there is little danger in delaying treatment for a day or two while the type of anaemia is being sorted out.

Once a firm diagnosis has been made, treatment with the appropriate haematinic is usually very effective in severe iron-deficiency and megaloblastic anaemias. Blood transfusion offers no advantages. Within a matter of days these patients will remark upon how much better they feel, and the haemoglobin will be found to increase at the rate of about 1% a day.

Severe chronic anaemias may be associated with the signs and symptoms of congestive cardiac failure. Here blood transfusion is a hazardous procedure. Failure is of the high-output type and unless blood is transfused slowly, and preferably as packed cells in small amounts, there will be a significant rise in the venous filling pressure, and a consequent lowering of the cardiac output and worsening of the degree of failure. Reactions in these patients, too, seem to be particularly dangerous, and transfusion is therefore best avoided if the anaemia is of a type which is known to respond to other treatment.

*Case 1.* An Indian child aged 9 years was admitted to hospital with severe dyspnoea, marked pallor of the mucous membranes, tachycardia, engorged neck veins, enlarged tender liver, oedema of the ankles and crepitations at the lung bases. The onset had been insidious, without a history of haemorrhage. Examination of the blood revealed a severe iron-deficiency anaemia with 10% haemoglobin. The test for occult blood in the stools was positive and ova of hookworm were detected. Blood transfusion was withheld because of the signs of congestive cardiac failure. The patient responded very well to ferrous sulphate by mouth and later on, when his haemoglobin had risen considerably and the signs of congestive cardiac failure had cleared, a vermifuge was administered. Recovery was complete.

*Case 2.* A European woman aged 70 years complained of dyspnoea on exertion, tiredness and marked pulsations in the neck. She had been told that she had an aneurysm of the carotid artery. Pallor was striking, her finger nails were spoon-shaped, and there were signs of congestive cardiac failure. Haemoglobin was 25%, the white cells were normal and the blood film showed typical changes of iron-deficiency anaemia. Response to complete rest in bed and ferrous sulphate by mouth was excellent. Investigations for a source of haemorrhage revealed a large diaphragmatic hernia, for which surgery was not advised because of her age. In this condition the mucosa may become constricted and congested, leading to a slow loss of blood. Recovery from anaemia was complete and she remains well on a maintenance dose of iron.

*In a personal series of 34 cases* of severe megaloblastic anaemia of pregnancy and the puerperium in Africans and Indians, haemoglobin values on admission to hospital ranged from 2.1 g. % (14%) to 6.5 g. % (44%), with a mean of 3.7 g. % (25%); 9 were in congestive cardiac failure. Treatment with folic acid gave very satisfactory results and blood transfusion was avoided. In this series 32 patients recovered and 2 died. One of these showed gross pyonephrosis at autopsy, which was considered to be the cause of death; the other was admitted *in extremis*, with 2.5 g. % haemoglobin (17%), congestive cardiac failure, and multiple bilateral retinal haemorrhages and exudates.

#### THE MANAGEMENT OF OTHER ANAEMIAS

There are of course many anaemias for which there is no specific treatment. In these transfusion is invaluable. Symptoms of anaemia associated with Hodgkin's

disease and leukaemia can be alleviated by blood transfusion, which is also often necessary in haemolytic anaemias and after prolonged bleeding in thrombocytopenic purpura. Anaemia which is associated with other diseases and with infection is usually not severe, and will only respond to iron treatment if it becomes hypochromic in type. It usually clears up when the underlying disease has been treated. A good dietary supply of protein is probably more important than extra iron in restoring normal blood counts after sepsis and severe infections.

Substances containing a benzene ring may cause a wide range of blood disorders, affecting the red cells, the leucocytes and the platelets, and there are other substances such as the heavy metals which are known to have similar effects. Toxic causes of agranulocytosis are commonly known, but they are sometimes found in aplastic anaemia, in thrombocytopenic purpura and in acquired haemolytic anaemia. It is therefore wise to enquire closely into the occupation and habits of patients suffering from these diseases, and to find out what drugs are being taken. In aplastic anaemia a close search for possible bone-marrow poisons is particularly important, for withdrawal from exposure offers the only hope of recovery. I have seen a severe case of this disease in a child cured by withholding mesantoin, which was being administered for epilepsy. Usually, however, a toxic cause cannot be detected in aplastic anaemia, and repeated blood transfusion, preferably with packed cells, is the only effective treatment, although it is not curative.

#### SUMMARY

In the management of the anaemic patient in general practice an attempt should always be made to sort out the type of anaemia and find its cause.

Iron-deficiency anaemias frequently follow chronic blood loss, possible sources of which must be investigated.

Premature treatment of a macrocytic anaemia with vitamin B12, folic acid or liver extract is ill-advised before it has been established whether or not it is of the megaloblastic variety. Vitamin B12 is the treatment of choice in pernicious anaemia, while folic acid is usually more effective in other types of megaloblastic anaemia.

The relative need for blood transfusion in various anaemias is discussed and attention drawn to the possible dangers in severe cases with congestive cardiac failure.

In unexplained anaemias such as acquired haemolytic anaemia, thrombocytopenic purpura and aplastic anaemia, possible toxic causes should always be sought, for their removal may provide the only chance of recovery.

I should like to thank Dr. S. Disler, Medical Superintendent of King Edward VIII Hospital, for permission to publish details of cases; Drs. N. A. Rossiter and J. K. Drummond for access to patients; and Mr. C. R. Stuart for the photomicrographs.

#### REFERENCES

1. Dacie, J. V. (1950): *Practical Haematology*, p. 39. London: J. & A. Churchill, Ltd.
2. Whitby, L. E. H. and Britton, C. J. C. (1953): *Disorders of the Blood*, 7th ed., p. 701. London: J. & A. Churchill, Ltd.