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THE MANAGEMENT AND TREATMENT OF THE ANAEMIAS

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Anaemia is produced by a wide range of diseases, some of which affect the blood-forming organs directly while in others remote systems are primarily affected. Successful treatment can begin only when an accurate diagnosis of the cause of the anaemia has been made. One way in which the anaemias may be classified is according to the morphology of the red corpuscles,[1] into megalocytic, microcytic hypochromic, and normocytic normochromic anaemias, and this classification of anaemias is a broad guide to treatment. Thus, the megalocytic group respond to vitamin B_{12} and folic acid and the microcytic hypochromic group respond to iron. The normocytic normochromic group, on the other hand, include a wide range of general diseases as well as haematological disorders and may present difficult diagnostic problems.

Many therapeutic measures are available for the treatment of the anaemias and some of those in common use will be considered.

Iron

The commonest anaemias met with in general practice are the iron-deficiency or hypochromic microcytic anaemias. Most of these occur during pregnancy, when there are excessive demands for iron. Another very important cause is chronic blood loss. Usually the recognition of the source of bleeding presents no difficulty but some patients may not be aware of blood loss, especially when this arises from the gastro-intestinal tract. It is extremely important to consider conditions such as chronic peptic ulcer, carcinoma of the stomach, and bleeding haemorrhoids. Carcinoma of the stomach and the caecum are notorious for giving relatively mild gastro-intestinal symptoms and presenting as problems in anaemia: to treat such patients for anaemia only (and they may respond) may be to miss the diagnosis until it is too late. The test for occult blood in the stool is easily performed; it is very valuable in screening such patients and barium studies should be undertaken when indicated.

Once the diagnosis of iron-deficiency anaemia has been made, and abnormal bleeding has been arrested, the treatment is with iron and iron alone, and excellent results may be anticipated. Vitamin B_{12} and folic acid are ineffective in the treatment of hypochromic anaemias.

In the majority of patients oral iron is all that is needed. Many patients believe they cannot take iron by mouth, largely as a result of what they have heard or read. The incidence of side-effects is low; these are mild gastro-intestinal symptoms such as nausea, abdominal discomfort, occasional vomiting and diarrhoea which, contrary to general belief, is found more often than constipation. In a recent 'double-blind' series it has been suggested by Kerr and Davidson[2] that the incidence of side-effects with iron tablets in conventional dosage is no higher than with placebo tablets. In any case there is a wide choice of preparations and, if the dose to start with is small, there should be very few patients for whom one cannot find some source of iron which suits them.

Ferrous salts are better absorbed than ferric salts, and in order of potency iron preparations may be graded as follows: Ferrous salts, scale preparations, ferric salts, organic compounds.

A list is given below of daily therapeutic requirements of various common iron preparations.[3]

Ferrous Salts		*Ferric Salts*	
Ferrous chloride	0·25 – 0·5 g.	Liq. ferri perchlor.	8 ml.
„ sulphate	0·6 g.	Ferric citrate	2 g.
„ lactate	1·5 g.	Colloidal ferric hydroxide	5·25 – 10·5 ml.
„ carbonate	3 – 4 g.	*Complex Ferric*	
„ gluconate	1·2 – 2·4 g.	Ferri et ammon. cit.	4 – 8 g.
„ succinate	0·45 – 0·9 g.		

A case can be made out for combining iron salts with vitamin C because it has been shown that vitamin C increases the absorption of iron. Unfortunately, there are many preparations on the market in which iron is combined with other vitamins and haematinics such as vitamin B_{12} and folic acid, and these have nothing to recommend them.

Occasionally it may be necessary to give iron parenterally, but this should be reserved for cases of severe gastro-intestinal disease, for late stages of pregnancy, and for rare cases of refractory iron-deficiency anaemia. For intravenous use, a 5% solution of saccharated oxide of iron is available: 5 ml. contains 100 mg. of elemental iron, and this amount will raise the haemoglobin by 4%. The usual dose is 2 ml. the 1st day, and thereafter 5 ml. every 2nd or 3rd day until the calculated dose has been given; an extra 4 or 5 injections may be given to replenish the iron stores. There is a considerable incidence of toxic effects. There may be local thrombophlebitis, and general reactions include headache, precordial discomfort, tachycardia, faintness, feelings of intense warmth, nausea and vomiting. Intramuscular injections are less toxic and for these a dextran-iron preparation is used. The average dose is 5 ml., containing 250 mg. of elemental iron. There may be pain at the site of injection. The utilization of the iron is less complete than with intravenous injections, and volume for volume the intramuscular dextran preparation is given in the same doses as the intravenous preparation of saccharated iron oxide.

Cyanocobalamin (Vitamin B_{12})

This is usually given parenterally, by intramuscular injection. It is of particular value in pernicious anaemia, where it supplies complete replacement therapy. It will help other macrocytic anaemias, but for these it has usually to be given with folic acid. The minimal daily dietary needs of vitamin B_{12} are 0·6 — 2·8 μg.[4] and the effective (intramuscu-

lar) dose is 1·0 — 1·5 μg. daily. Excellent haematological response can be obtained in pernicious anaemia by treating patients with such doses. Some authorities consider that for patients in relapse larger amounts should be given, e.g. 1,000 μg., not only to produce haematological remission but also to replenish the body stores. If this is given as a single dose, much is lost by excretion. A satisfactory programme is 10 injections of 100 μg. over the course of 2—3 weeks, followed by maintenance treatment of 100 μg. per month. A good response can be prophesied from the reticulocytosis which starts on the 2nd or 3rd day of treatment and subsides by the 14th day. It is rarely necessary to transfuse patients with pernicious anaemia unless there are special complications such as cardiac failure, or severe mental deterioration, or when emergency surgery is contemplated. Patients should have their blood examined at 3-monthly intervals, and it is important to maintain normal values, particularly if there are symptoms of subacute combined degeneration of the cord. If the patients do not respond as well as expected, this may be due to complications such as arteriosclerosis or intercurrent infection, and then larger or more frequent doses of vitamin B_{12} are needed. Occasionally iron deficiency is present as well, and full blood values will only be reached when iron is given in addition to vitamin B_{12}. There is a close relationship between pernicious anaemia and carcinoma of the stomach. Carcinoma of the stomach may occasionally produce a picture resembling that of pernicious anaemia, which may even respond to vitamin B_{12}. Moreover, patients with pernicious anaemia are more than usually prone to develop carcinoma of the stomach as the result of the atrophic gastritis which is a feature of the disease. Every patient, therefore, should be subjected to a barium-meal examination at the beginning of treatment.

Pernicious anaemia can be treated successfully with oral vitamin B_{12}. At first it was thought that very large doses were necessary unless a source of intrinsic factor was added to promote absorption. It has recently been shown, however, that vitamin B_{12} in moderate doses can be absorbed in amounts large enough to maintain normal blood values both after relapse and as maintenance treatment. Chalmers and Shenton[5] have recommended 100 μg. daily by mouth. It is generally agreed, however, that parenteral treatment is preferable to oral because with injections there is no doubt about absorption and, more important, the patients can be kept under observation.

Liver Extracts

Vitamin B_{12} has entirely replaced parenteral liver, of which it is the active principle. Compared with liver extracts, it has the great advantages of constant potency, small bulk, relative cheapness, and almost complete absence of sensitivity reactions.

Folic Acid

Folic acid is not the treatment of choice for pernicious anaemia. Haematological response is sub-optimal and what is more important, it fails to protect patients against the development of subacute combined degeneration of the cord. Indeed, some patients have developed neurological changes for the first time while receiving folic acid. It has been suggested that folic acid depletes the body stores of vitamin B_{12}, which is necessary for the metabolism of the central nervous system. However, for megaloblastic anaemias other than pernicious anaemia, folic acid is the treatment of choice; indeed, it is usually more effective than vitamin B_{12}, though sometimes both are needed. For example, folic acid produces full haematological remission in sprue, adult steatorrhoea, and pernicious anaemia of pregnancy. The dose of folic acid is 10—30 mg. daily, given orally, until the blood is normal. In certain conditions a small maintenance dose is required, e.g. 3—5 mg. daily. In pernicious anaemia of pregnancy, no further treatment is needed after delivery.

Thyroid Extract

Patients with myxoedema look pale because of their yellowish complexions and they may be anaemic as well, though often not to such a degree as their appearance suggests. The anaemia of hypothyroidism is usually not very severe; it is usually normocytic, although occasionally macrocytic. It responds to the administration of thyroid extracts but not to vitamin B_{12} or folic acid.

Ascorbic Acid

The anaemia of scurvy, which is usually normocytic and normochromic, responds only to ascorbic acid.

Other Haematinics

Cobalt, riboflavin and pyridoxine have interesting theoretical implications, but their practical value has not been fully established.

Treatment of Underlying Diseases

Anaemia is a symptom of many chronic diseases, and the correct treatment is that of the underlying disease, if this is treatable. If it is not, blood transfusion will give temporary relief. Patients with chronic renal disease show a normocytic normochromic anaemia. Sometimes uraemia develops very insidiously, for example in chronic pyelonephritis, and patients with this condition may actually present as problems in anaemia. Although the ultimate prognosis is poor, active working life may be prolonged and the patient made very much more comfortable by correction of the anaemia with blood transfusions.

Chronic infections may be associated with normocytic normochromic anaemia. An important example is subacute bacterial endocarditis, which may be very elusive when the cardiac lesion is not classical. This condition should always be remembered in unexplained anaemia, particularly in young persons where there is associated pyrexia, and careful search should be made for confirmatory points. It is important to delay treatment with antibiotics until cultures have been taken, though not necessarily until they have been reported on; even a small amount of antibiotic may render the cultures sterile. Disease of the reticulo-endothelial system such as Hodgkin's disease and leukaemia usually present no difficulty in diagnosis if the classical histology of the glands and the blood findings are both present. Occasionally, however, anaemia is the presenting symptom and the diagnosis may then be very difficult to establish. Lymphadenopathy and increased leucocyte count may be absent.

Removal of Toxic Agents

The aplastic or refractory anaemias are a complex group in which there is lack of regeneration of one or all of the 3 main elements of the blood, viz. erythrocytes, leucocytes, and platelets. In some cases no cause can be found, but in others toxic agents and drugs are responsible and the list of these becomes longer every year. There are some substances (or

rays) which regularly produce aplasia of the bone marrow if a big enough dose is received; examples are X-radiation, radio-active substances, the nitrogen mustards, and myleran. There are other substances, moreover, which produce aplasia of the marrow, though only occasionally, as the result of idiosyncrasy. Some of these are in common use and it is extremely important to be aware of their dangerous potentialities, though happily most patients suffer no ill effects. Chloramphenicol, some of the hydantoin compounds used for the treatment of epilepsy, anti-thyroid drugs such as thio-uracil, and phenylbutazone are notorious offenders. It is essential, therefore, to make detailed enquiries about any medicines the patient has taken. Removal of the offending agent may lead to dramatic improvement.

Blood Transfusion

It is impossible to consider here the practical details of blood transfusion. Obviously, blood transfusions play an important role in the treatment of anaemia. They are indicated when the degree of anaemia is such as to endanger life, and especially when the diagnosis is obscure and therefore no specific therapy can be started, for example in patients with aplastic anaemia. If specific therapy is available, as in pernicious anaemia, blood transfusions will naturally not be given unless there are special indications, such as emergency surgery. They may be given quite apart from the degree of anaemia to supply some factor which is deficient in the blood, as in haemophilia or thrombocytopenic purpura.

As a general rule, it is better to under-transfuse than to over-transfuse, because where one is dealing with patients with chronic anaemia, circulatory overloading is a real danger. For this reason, too, red-cell suspensions are often to be preferred to whole blood, if the former are available.

Splenectomy

The condition which splenectomy is most likely to benefit is hereditary spherocytosis (acholuric family jaundice), in which almost uniformly beneficial and lasting effects are obtained. Good results are also obtained for chronic or recurrent attacks of idiopathic thrombocytopenic purpura. It is generally advised that splenectomy should not be done during the first 6 months of the illness, because some cases will revert to normal during this period, with or without steroid therapy. Splenectomy is also indicated in selected cases of acquired haemolytic anaemia and in hypersplenism. In acquired haemolytic anaemia where steroids have not produced lasting remissions, the results after splenectomy are much less predictable than they are in the familial type.

Steroids

Adrenocorticotrophic hormone (ACTH) and the steroid hormones are very useful agents for the control of acquired haemolytic anaemia, in which the patients have acquired auto-immune antibodies which haemolyse their own red cells. Steroids are used for idiopathic thrombocytopenic purpura in the early stages of the disease, that is roughly for the first 6 months, though their value is difficult to assess since some cases undergo spontaneous remissions. They are of value in very acute cases with severe bleeding when, together with blood transfusion, they tide the patients over either until spontaneous recovery occurs or until splenectomy is decided on. Steroids may also produce remissions in acute leukaemia, especially in children. The best results have been obtained with acute lymphoblastic leukaemia; in acute myeloblastic and acute monoblastic leukaemia they are very disappointing. There is no uniform dose of steroid for these haematological disorders, but the one in commonest use at present is prednisone, of which the usual daily dose is 40—60 mg. in divided doses until response has occurred, when the dose is reduced. Some authorities, however, advise very much bigger doses.

Before any treatment is started an accurate blood count should be made, because even small amounts of haematinics may so alter the blood picture as to make it difficult to interpret. Examination of the bone-marrow by sternal puncture is not necessary in every case before starting treatment; however, when the diagnosis of pernicious anaemia is suspected, sternal puncture should be carried out before treatment is started, because even small amounts of vitamin B_{12} may alter the bone-marrow picture completely and, as patients with pernicious anaemia have to receive treatment for the rest of their lives, it is important to establish the diagnosis firmly.

A Warning

A final word should be said about 'shotgun' anti-anaemic remedies which are widely advertised and very expensive, and contain mixtures of haematinics, vitamins and trace elements in surprising combinations. The main objections to them are (1) that if the patient improves it is impossible to know to which component this is due, and how to proceed thereafter, and (2) that these compounds do not contain enough of any one haematinic to be really effective if it is needed. Wintrobe rather unkindly remarks that there are three advantages to this type of therapy: No diagnosis is required, neurasthenics may be temporarily improved, and finally a puzzling patient may seek a better physician.

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