preferred the freedom to work outside the home to the rigours of a large family.

Abortion in the first trimester is normally done by suction evacuation, as an outpatient, with no anaesthetic. The patient occasionally has an analgesic or she may be given acupuncture. Since none of the legal procedures required in Britain apply to termination it is possible in most cases to perform a suction-aspiration abortion very early in pregnancy, and indeed possibly without waiting for a diagnostic pregnancy test. The methods used for mid-trimester abortion varied. In Peking the gynaecologists were using prostaglandins but in Kwangchow they were still using intrauterine injection of hypertonic saline; indeed the use of prostaglandins was not even being considered. This emphasized to me the size of the country and the apparent lack of communication between major centres.

Sterilization is easily available for men and women, though I gather that there is a certain amount of reluctance among men to have the operation. Again I was not able to get accurate figures but was told that sterilization is quite common in women with two children.

Reasons for Success

The decentralized system for delivering medicine in China means that the whole population has access to contraceptive advice and to abortions and sterilizations. However, experience throughout the world has shown that simple provision of contraceptive technology by itself does little to affect population growth. The success of China's policy is that it is unequivocal and direct—there are no warring factions as there are in Britain. The policy is based on the acceptance by the people of the three main principles: no sex before marriage, only two children to the family, and abortion for any unintended pregnancies.

So far as we could see, these messages are constantly repeated by the posters and in the political thought sessions that are a major feature of life in China. Whenever we discussed the concepts and methods with doctors, workers, or patients we were impressed by their positive attitude. What would in the West be thought of as severe restrictions on individual liberty are evidently not seen in that light in China.

Today's Treatment

Blood and Neoplastic Diseases

Megaloblastic Anaemia

A. V. HOFFBRAND, A. LAVOIE

British Medical Journal, 1974, 2, 550-553

Introduction

Megaloblastic anaemia is one of the most satisfactory of all disorders to treat. A patient with a life-threatening anaemia can often be restored to full health. Nevertheless, correct management depends not only on recognizing that megaloblastic anaemia is present, but also on diagnosing its underlying cause, and failure of full investigation and of adequate follow-up account for most cases of incorrect therapy or subsequent relapse. Early clinical or haematological signs of vitamin B₁₂ or folate deficiency should always be taken seriously; otherwise the anaemia will progress and irreversible neurological damage may also occur.

Diagnosis

Though megaloblastic anaemia may be suspected clinically because of anaemia, jaundice, glossitis, neuropathy, or presence of a disease known to predispose to vitamin B₁₂ or folate deficiency, ultimately the diagnosis depends on the laboratory findings. Megaloblastosis is suggested by macrocytes and hyper-

segmented polymorphs in a peripheral blood film and is confirmed by characteristic changes in the bone marrow. The introduction of electronic red cell counters has facilitated early recognition of macrocytosis and any patient found to have a mean corpuscular volume (M.C.V.) greater than 100 fl should be suspected of vitamin B₁₂ or folate deficiency even in the absence of anaemia. Other causes of macrocytosis include haemolytic anaemia, blood regeneration, liver disease, alcoholism, myxoedema, aplastic anaemia, myeloma, sideroblastic anaemia, and leucoerythroblastic anaemia. The higher the M.C.V. the more likely is megaloblastic anaemia to be present. But when iron deficiency and megaloblastic anaemia are combined the M.C.V. may be normal; nevertheless, the blood and bone marrow still show some of the morphological characteristics of megaloblastic anaemia.

Causes

The anaemia may be due to vitamin B₁₂, folate deficiency, or rarely another cause. Vitamin B₁₂ is present only in foods of animal origin and is absorbed through the terminal ileum, a process mediated by gastric intrinsic factor and limited to a few microgrammes daily. Adult daily requirements are about 2-3 µg and stores 3-4 mg, sufficient for a few years. In Britain deficiency is usually due to malabsorption and pernicious anaemia is by far the most important cause of this. Resection of the stomach or ileum, a stagnant-loop, or some other small intestinal disease are less frequent causes. Veganism commonly leads to vitamin B₁₂ deficiency in areas of Britain where there are many Hindu immigrants.

Folate is present in both vegetable and animal foods, particularly in greens and liver, but, unlike vitamin B₁₂, folate is

Department of Haematology, Royal Postgraduate Medical School, London W12 0HS

A. V. HOFFBRAND, D.M., M.R.C.P., Senior Lecturer (Present appointment: Professor of Haematology, Royal Free Hospital, London, NW3 2QG).

A. LAVOIE, M.D., Research Fellow in Haematology (Supported by the Medical Research Council of Canada)

easily destroyed in cooking. It is absorbed through the duodenum and jejunum, the amount increasing in parallel to the amount ingested. Adult requirements are 100-200 μg and body stores 10-12 mg, enough for only three to four months. Mild folate deficiency is common, since it may occur through reduced appetite in patients chronically ill from almost any cause. Severe nutritional folate deficiency is particularly likely to occur in the aged, poor, and psychiatrically disturbed, and may be associated with alcoholism or scurvy. Other major causes of megaloblastic anaemia due to folate deficiency are malabsorption because of coeliac disease or tropical sprue; increased demands caused by pregnancy, haemolytic anaemias, myelosclerosis, or chronic inflammatory and malignant diseases; drugs—for example, anticonvulsants, barbiturates, or alcohol; and increased losses brought about by dialysis or liver disease.

Megaloblastic anaemia may also arise because of impaired DNA synthesis from causes other than vitamin B₁₂ or folate deficiency. In practice, erythroleukaemia, acute myeloid leukaemia, and primary acquired sideroblastic anaemia are the conditions most likely to be confused with megaloblastic anaemia due to vitamin B₁₂ or folate deficiency and are sometimes only diagnosed when the anaemia fails to respond to both vitamin B₁₂ and folic acid. Antimetabolite drugs such as cytosine arabinoside and methotrexate and the congenital illness, orotic aciduria, may also lead to a failure to respond to vitamin B₁₂ and folic acid.

Investigation

It is essential to establish whether the anaemia is due to vitamin B₁₂ or folate deficiency and to ascertain the exact cause of the deficiency in every case. In anaemic patients tests and treatment are best initiated in hospital but non-anaemic ones can usually be investigated and treated as outpatients. The tests needed include firstly those to establish the diagnosis of megaloblastic anaemia (full blood count—including red and white cells, platelets, and reticulocytes—and examination of blood film; bone marrow aspiration including iron stain; testing serum iron, bilirubin, proteins, LDH, urea, and electrolytes. The second group of tests is to differentiate vitamin B₁₂ and folate deficiency—for example, serum vitamin B₁₂, serum and red cell folate; urine methylmalonic acid excretion after valine load;* and therapeutic trial. Finally, there are tests to establish the cause of the deficiencies. In all cases there should be a barium meal and follow-through examination of the small intestine; chest x-ray examination; urine analysis; and a diet and drug history. If it is appropriate tests for the following should also be conducted: serum antibodies to parietal cells, intrinsic factor, thyroid, reticulins, serum immunoglobulins; vitamin B₁₂ absorption with and without intrinsic factor; gastric secretion of acid and intrinsic factor, gastric biopsy; jejunal biopsy, xylose absorption, faecal fat; as well as tests for other suspected diseases.

The tests in the first two groups should be performed before treatment is started since rapid reversal of the blood and biochemical changes occur with therapy. Measurement of the serum vitamin B₁₂ level is particularly important and should always be carried out in cases suspected of vitamin B₁₂ neuropathy, irrespective of the haematological findings. Tests for the cause of the deficiencies can be delayed, if necessary, until treatment has started and the patient's condition has improved.

Treatment

If the patient is extremely ill large doses of both vitamins are often given immediately after the bone marrow aspiration has been examined. Nevertheless, when possible treatment should begin with the appropriate vitamin suggested by the clinical and laboratory findings.

VITAMIN B₁₂

Vitamin B₁₂ deficiency is treated with six injections of 1,000 μg of hydroxocobalamin given over a few weeks to replenish body stores. Cyanocobalamin, the form of vitamin B₁₂ previously used, is now obsolete since it is less well-retained in the body than hydroxocobalamin. Several different maintenance regimens are available but we have found 1,000 μg hydroxocobalamin once every three months satisfactory in all cases. Others use as little as 500 μg hydroxocobalamin every three months. There is no evidence that patients with vitamin B₁₂ neuropathy benefit from larger doses. Maintenance vitamin B₁₂ treatment is usually needed for life since it is usually not possible or practicable to reverse the cause of severe vitamin B₁₂ malabsorption. Vegans with megaloblastic anaemia due to vitamin B₁₂ deficiency should initially be loaded with parenteral vitamin B₁₂, in the same way as cases of pernicious anaemia. Subsequently, recurrence should be prevented either by increased intake of animal foods—for example, milk, eggs, cheese, fish, or of vegetable foods with added vitamin B₁₂, by oral vitamin B₁₂ (5-10 μg daily), or by maintenance parenteral vitamin B₁₂.

Oral vitamin B₁₂ in large (500-1,000 μg) doses daily can be used in the patients with malabsorption of vitamin B₁₂ unable or unwilling to receive injections, since a few microgrammes may be absorbed by non-physiological routes through the buccal, gastric, and upper small intestinal mucosae. Combinations of vitamin B₁₂ with commercial intrinsic factor should not be used as resistance to the foreign protein soon develops. The widespread use of vitamin B₁₂ injections in conditions other than vitamin B₁₂ deficiency has no scientific basis; even so, the injections are remarkably non-toxic.

FOLIC ACID

A dose of 5 mg folic acid daily by mouth is sufficient to replenish stores in all cases of megaloblastic anaemia due to folate deficiency, even those with jejunal disease and malabsorption. This should be continued in the first instance for about four months. In many folate-deficient patients, the cause of the deficiency is reversible by measures such as an improved intake of foods of high folate content such as liver, greens, and yeast, or a gluten-free diet for coeliac disease. Nevertheless, nutritional folate deficiency shows a definite tendency to relapse and regular follow-up is needed. In other cases, the cause of severe folate deficiency is self-limiting—for example, pregnancy or prematurity. Long-term folic acid is needed in those patients with an irreversible underlying disease—for example, congenital haemolytic anaemia or myelosclerosis. Vitamin B₁₂ deficiency should always be excluded by measuring the serum vitamin B₁₂ level before giving folic acid in large doses and at yearly intervals in patients maintained on life-long folic acid; otherwise vitamin B₁₂ neuropathy may be precipitated. Folic acid therapy should also be avoided, if possible, in patients with malignant disease since it may theoretically "feed" the tumour. It has been suggested that folate therapy aggravates the frequency of fits in epileptics and causes psychiatric changes even in normal subjects but these effects have not been substantiated by controlled trials. Parenteral folic acid is reserved for patients unable to swallow tablets, or when rapid complete saturation of body stores is needed—for example, before a folic acid absorption test.

Therapeutic Trial

Therapeutic trial is not widely practised now that measurements of serum vitamin B₁₂ and folate are widely available. It is still useful in establishing the main cause of megaloblastic anaemia in patients with low serum levels of both vitamin B₁₂ and folate and is carried out by observing the response to a physio-

*Test of body stores of vitamin B₁₂ not widely available.

logical dose of vitamin B₁₂ (1-2 µg) or of folic acid (100-200 µg) given daily for 10 days. Larger doses of the vitamins may produce cross responses—for example, the anaemia in untreated pernicious anaemia may respond to folic acid, 5 mg daily. The therapeutic trial cannot be used in severely ill patients, in whom the possible delay in correct treatment is unwarranted, and it is impractical in mildly anaemic or non-anaemic patients in whom the reticulocyte response is difficult to monitor, and in patients with complicating disorders—for example, infection or malignancy, which inhibit the marrow response.

Monitoring the Haematological Response

The response to treatment should be followed carefully in all patients, whether they are receiving physiological or large saturating doses. The patient is clinically better within 24-48 hours after starting correct treatment with improved appetite and a feeling of well-being. The reticulocyte response begins on the second to third day with a peak at six to seven days, the height proportional to the initial severity of anaemia. The serum iron falls within 24-48 hours and the serum L.D.H. begins to fall within a few days. A poor response indicates an underlying disease, infection, iron deficiency, double deficiency of both vitamins, or incorrect treatment or diagnosis. In predisposed patients, gout may be precipitated during the response owing to increased purine synthesis and breakdown.

Problems

In many patients with megaloblastic anaemia, treatment other than vitamin B₁₂ or folic acid is unnecessary. In some patients particular therapeutic problems arise and these are discussed next.

IRON DEFICIENCY

When iron and vitamin B₁₂ or folate deficiencies occur in combination, iron should be given first while the cause of the combined deficiencies is being investigated. Shortage of iron may also develop during the response of megaloblastic anaemia, or during subsequent maintenance therapy. Iron deficiency in pernicious anaemia may be due to atrophic gastritis but the possibility of an associated disease—for example, carcinoma of the stomach causing haemorrhage—must always be considered.

HEART FAILURE

Heart failure should be treated by the standard measures—diuretics and digitalis. Blood transfusion must be avoided and specific treatment started as soon as the first blood and bone marrow samples have been taken.

POTASSIUM

A single report has suggested that hypokalaemia during the response to treatment may be a significant cause of death in patients with megaloblastic anaemia. Hypokalaemia was ascribed to the entry of potassium from plasma into rapidly proliferating haemopoietic cells in the marrow coinciding with cessation of release of intracellular potassium from dying (ineffective) marrow cells into plasma. The clinical importance of this phenomenon, and the exact indications for potassium treatment in megaloblastic anaemia are still uncertain. Meanwhile, it may be wise to give oral potassium supplements during the first 10 days of treatment to patients with extreme anaemia or heart failure, to those with hypokalaemia before treatment has started,

and to those who develop hypokalaemia during the haematological response.

INFECTION

A mild fever which resolves within a few days of starting correct treatment occurs in most patients with megaloblastic anaemia even without infection. In some patients, however, an infection—viral or bacterial—aggravates or even precipitates megaloblastic anaemia in patients with pre-existing vitamin B₁₂ or folate deficiency. "Aplastic" arrest of haemopoiesis with severe, rapidly progressive pancytopenia has been described. Infections especially of the respiratory and urinary tract should be sought and, if present, treated with appropriate antibiotics.

UNDERLYING DISEASE

The disease causing vitamin B₁₂ or folate deficiency must be diagnosed in each case and treated wherever necessary. Gastric carcinoma is particularly important in patients with pernicious anaemia, while folate deficiency may be the first sign of otherwise unsuspected adult coeliac disease.

BLOOD TRANSFUSION

In most cases the heart and circulation have adapted to a slowly progressing anaemia. The benefit of rapidly increasing the haemoglobin level is outweighed by the danger of overloading the heart and precipitating heart failure so transfusion should be avoided whenever possible, particularly in the elderly. Nevertheless, when anaemia is extreme or when it is essential to raise the haemoglobin rapidly—for example, before an urgent operation or in late pregnancy—transfusion may be given slowly, with one to two units of packed cells, and the patient observed carefully for signs of heart failure. Simultaneous removal of blood from the other arm and administration of a diuretic help to reduce the risk of circulatory overload.

THROMBOCYTOPENIA

Steroids have been given to the exceptional patient with purpura or haemorrhage due to thrombocytopenia. Platelet transfusion and specific treatment now seem more appropriate for this emergency. Though megaloblastic anaemia can be improved with steroids in some patients with, for example, pernicious anaemia or coeliac disease, these drugs should not be used routinely for this purpose.

Management of the Non-anaemic Patient

With improved haematological and biochemical screening, many cases of vitamin B₁₂ or folate deficiency are now diagnosed even before megaloblastic anaemia has developed. Further investigations are always needed to elucidate the cause of the deficiencies. Low serum vitamin B₁₂ levels almost always indicate body depletion of vitamin B₁₂ and are usually associated with morphological haematological changes. The patient will usually require vitamin B₁₂ treatment in exactly the same way as a patient with severe pernicious anaemia. Nevertheless, it is not established that vegans and other subjects with low serum vitamin B₁₂ levels without haematological changes due to the deficiency benefit from vitamin B₁₂ therapy. On the other hand, in many patients with low serum folate levels, these do not indicate severe folate deficiency. Only when there are blood or bone marrow changes, or a low red cell folate should the patient be fully investigated and treated as a case of megaloblastic anaemia due to folate deficiency.

Prophylaxis

Hydroxocobalamin should be given in maintenance dosage from the time of operation to patients undergoing total gastrectomy or terminal ileal resection. Prophylactic folic acid is now widely given in pregnancy, chronic haemodialysis and peritoneal dialysis, and to patients with severe congenital haemolytic anaemia—particularly thalassaemia major and sickle cell anaemia—and it may well be of value in very premature infants for the first month or so of life.

Follow-up

Many patients with severe megaloblastic anaemia have suffered previous episodes of the same anaemia or shown minor blood or neurological changes in the past. Proper investigation and follow-up of all cases of megaloblastic anaemia and also of non-anaemic patients with vitamin B₁₂ or folate deficiency are needed to prevent subsequent relapse. Management of pernicious anaemia and other conditions in which the cause of vitamin B₁₂ or folate deficiency cannot be corrected is facilitated if the patient clearly understands that the anaemia may recur if treatment is stopped.

Any Questions?

We publish below a selection of questions and answers of general interest

Multiple Caries in Children

In children with multiple caries how safe is the practice of multiple simultaneous dental extractions before and after the eruption of the first permanent molar? Is there any danger of producing serious dental malposition of the permanent teeth?

Premature loss of deciduous teeth usually aggravates tendencies, whether genetic or acquired, to overcrowding of the permanent dentition. A tendency towards forward drifting of the molar teeth is likely to be most pronounced if the extractions were undertaken immediately before the eruption of the first permanent molar tooth. If at all possible, it is therefore desirable to postpone the extractions of the deciduous teeth until after the full eruption of the first permanent molar teeth.

Premature loss of only the deciduous incisors and canines is not likely to cause malposition of the permanent teeth. Premature loss of all or most deciduous teeth will sometimes result in overclosure of the jaws and an accompanying marked overjet of the permanent anterior teeth when they erupt. However, the prognosis after premature loss of deciduous teeth is a complex one^{1,2} and is influenced by many other factors, including the relation of the two dental arches, the habits of the patient, and any already existing tendencies to overcrowding of the teeth. It is therefore advisable to consult an experienced orthodontist regarding the prognosis.

The loss of many deciduous teeth will reduce the efficiency of masticating food and will encourage the child to eat soft foods, many of which are not as nutritious and tend to predispose to caries. It is possible to provide dentures but these will need frequent replacement with the growth of the jaws and with the eruption of permanent teeth.

¹ Clinch, L. H., *Dental Practitioner and Dental Record*, 1959, 9, 109.

² Richardson, M. E., *Dental Practitioner and Dental Record*, 1965, 16, 111.

Human Tetanus Immunoglobulin

Our practice no longer gives antitetanus horse serum to injured patients. If a patient has not been immunized against tetanus he receives wound toilet, an antibiotic, and a course of tetanus toxoid. Now that human tetanus immunoglobulin is available—though expensive—should this be used initially instead of starting the patient on a course of tetanus toxoid?

The practice of giving horse tetanus antitoxin to non-immune patients with tetanus-prone wounds has greatly declined dur-

ing the last ten years. It was previously a recommended routine procedure¹ and a doctor who had not given horse antitoxin to a patient who then developed tetanus could consider himself liable to a charge of negligence.² The incidence of reactions, mainly serum sickness, after horse antitoxin ranged from 5.3% to 7% and the risk of fatal anaphylaxis was between 1:50,000 and 1:200,000 injections.³ Any protection provided by a first dose of antitoxin did not persist for more than about seven days and after subsequent doses for more than about two days. It was not surprising therefore that some doctors considered themselves under pressure to use a product which they did not regard as particularly safe or effective and that "more antitoxin was given to protect the doctor than is given to protect the patient."²

Though procaine penicillin was shown in 1951 to be more effective than heterologous tetanus antitoxin in preventing tetanus in mice, firm recommendations that it should replace horse antitoxin in human tetanus prophylaxis were not made until 1960 in the United States and 1963 in Britain.⁴ Antibiotics offered a means of escape from pressure to use antitoxin and were consequently widely accepted. Smith however reported in 1964⁵ that although all 22 strains of *Clostridium tetani* tested were sensitive in vitro to 0.05 units/ml of penicillin, this level of antibiotic had to be maintained in the plasma of mice for about four days for effective tetanus prophylaxis. The antibiotic was ineffective against spores and had to be given earlier than antitoxin to be effective. So antibiotics are of limited value and even then only if adequate blood levels are maintained for at least five days.

The use of tetanus antitoxin of human source for tetanus prophylaxis was first suggested in 1954⁶ and by 1961-2 had been investigated at a number of centres.^{7,8} It does not have the disadvantages of horse antitoxin as it rarely produces any adverse effects or sensitization, and a first or subsequent dose of 250 units will usually give passive protection for about four weeks. This covers the incubation period of tetanus in most instances. In order to stimulate active immunity against tetanus and thus avoid the need of further injections of human tetanus immunoglobulin, tetanus vaccine should be administered concurrently but at another site. A second dose of tetanus vaccine should be given six weeks later.

¹ Parish, H. J., and Cannon, D. A. *Antisera, Toxoids, Vaccines and Tuberculin in Prophylaxis and Treatment*. 5th edn., chart opp. p. 60. E. & S. Livingstone, Ltd., Edinburgh and London, 1961.

² Reynard, W. A., *British Medical Journal*, 1957, 1, 818.

³ Laurent, L. J. M., and Parish, H. J., *British Medical Journal*, 1952, 1, 1294.

⁴ Cox, C. A., Knowelden, J., and Sharrard, W. J. W., *British Medical Journal*, 1963, 2, 1360.

⁵ Smith, J. W. G., *British Medical Journal*, 1964, 2, 1293.

⁶ Stafford, E. S., Turner, T. B., and Goldman, L., *Annals of Surgery*, 1954, 140, 563.

⁷ Ellis, M., *British Medical Journal*, 1963, 1, 1123.