The Recognition and Treatment of Nutritional Anaemia.
(A Review)

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The importance of food for the proper production of the blood has been recognised for many centuries. The Caraka Samhita (written between 13th and 16th century B.C.) says "Just as the fuel cooks rice and water in a pot and converts it into boiled rice, so the gastric fire cooks the ingested food to convert it to the nutrient fluid... From the nutrient fluid is formed the blood, then the flesh... ".

The three main nutrients necessary for red cell production are iron, vitamin B₁₂ and folic acid. The normal well nourished person has considerable reserves of these substances so that even if the dietary intake is completely stopped, anaemia will not develop until available body stores are depleted. The extent of the stores varies from person to person. In the case of vitamin B₁₂, body stores may be sufficient for up to 5 years, whereas in the case of folic acid they may only be sufficient for a few weeks. In a given individual, at any time, the level of body stores will depend on a number of factors such as the previous dietary intake, the level of absorption from the gut, the demands of the organism and the extent of the losses from the body. When body stores are depleted anaemia will develop, but this is usually a late manifestation of nutritional deficiency.

An awareness, on the part of the clinician, of the various conditions likely to lead to, or be associated with, iron, vitamin B₁₂ or folate deficiency is the first step in the recognition of the deficiency.

AETIOLOGY OF DEFICIENCY STATES

Deficient foetal stores

The developing foetus in utero acquires from its mother stores of iron, vitamin B₁₂ and folic acid, which increase in amount with increasing period of gestation. In cases of premature delivery, the total amount of such stores will be correspondingly reduced, and therefore render the infant more susceptible to the development of deficiency anaemia. There appears to be a preferential transfer of these substances across the placenta, so that even in cases of maternal deficiency, levels in the foetal blood are higher than in the maternal blood. Nevertheless deficiency of vitamin B₁₂ in the mother will lead to reduction of B₁₂ stores in the new born. Whether or not this is also true of folic acid and iron is not known.

Deficient dietary intake

After birth individuals are solely dependent on dietary sources for the supply of nutrients. The daily iron requirement of children is in the region of 0.4 to 1.0 mgm., and of adults 0.6 to 1.0 mgm. in males and 1 to 2 mgm. per day in normal non-pregnant females.

Iron is widely distributed in various foodstuffs, cereals, pulses, meat, vegetables etc. but both breast milk and cows milk have a low iron content. Therefore children fed purely on milk for periods longer than six months are very liable to develop iron deficiency unless given iron supplements. In marasmus and kwashiorkor iron deficiency anaemia is very common, being present in up to 80% of cases. The mean daily intake of iron by Indian adults, as estimated by dietary analysis, varies between 15-30 mgm. per day. Nevertheless iron deficiency and iron deficiency anaemia is extremely common.

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even where there is no evidence of excess iron loss.

It is clear that not only is the total amount of iron in the diet important, but also the chemical form in which it is present. For instance it has been demonstrated that food iron in greens, may only be about one twentieth as available as an equivalent amount of ferrous sulphate. The specific forms and availability of iron in Indian diets has yet to be studied. Dietary iron absorption is also depressed by phytates and phosphates which are high in most Indian diets.

The daily vitamin B12, and folate requirement of infants and children has not been extensively studied. Infants with vitamin B12 deficiency anaemia will respond well to a daily oral dose of 0.1 µg of vitamin B12, by mouth and infants with folate acid deficiency anaemia associated with kwashiorkor will respond to a daily oral dose of 25 µg of folate acid. The daily requirements of both vitamins are therefore presumably less than these amounts. In adults the daily requirement for vitamin B12 is probably in the region of 0.5 µg and for folate in the region of 50 µg.

Vitamin B12 is present in many animal products such as liver, meat, fish, eggs and milk. It has been suggested that liver bound vitamin B12 is absorbed better than pure cyanocobalamin but this has not been confirmed.

Folate is present in liver, green vegetables, fruits and nuts and to a smaller extent in milk. However, folate in the diet is fairly heat labile, and excessive cooking may destroy much of the original activity present in the uncooked food. There is no data regarding the availability of the folate in different food stuffs.

Coasts' milk, boiled cows' milk and unsupplemented processed milks have a low folate content; and infants fed on these, or on breast milk from mothers who are folate deficient, may develop folate deficiency. In children with protein—calorie malnutrition megaloblastic anaemia due to folate acid deficiency is very common. Infants born to, and suckled by vitamin B12 deficient mothers may develop a pure vitamin B12 deficiency anaemia.

In older children and adults, ignorance, poverty, vegetarianism and food faddism may lead to insufficient intake of vitamin B12 or folate.

Diseases of the stomach

For normal vitamin B12 absorption, intrinsic factor, produced by the parietal cells of the stomach, is necessary. In rare cases histologically normal parietal cells fail to produce intrinsic factor. Usually reduction of intrinsic factor secretion, sufficient to interfere with vitamin B12 absorption, is associated with atrophic gastritis, gastric atrophy or gastric resection.

Gastric atrophy occurs classically in pernicious anaemia which may be defined as a vitamin B12 deficiency anaemia caused by a lack of secretion of intrinsic factor, due to a genetically determined gastric atrophy and associated with a high incidence of antibodies to intrinsic factor and parietal cells, in the serum. The incidence of pernicious anaemia in Indians is very low. Gastric atrophy may also occur in chronic gastritis, diverticulosis, fish tapeworm infestation, non-tropical sprue and tropical sprue. These diseases may produce a syndrome closely resembling classical pernicious anaemia.

After total gastrectomy, vitamin B12 deficiency will invariably supervene, provided the patient lives long enough. The time necessary for the development of frank vitamin B12 deficiency will vary according to the level of the body stores at the time of the operation. With normal stores this may be from three to five years. Partial gastrectomy, depending on its extent, may produce varying degrees of intrinsic factor deficiency. In the Polyta type of operation, and in patients with gastroenterostomy, vitamin B12 absorption may also be interfered with because of the "blind loop" formed by the gastrojejunostomy. The incidence of vitamin B12 deficiency after partial gastrectomy in a Western community may be as high as 15%, and in areas of poor nutrition is almost certainly higher.

Diseases of the stomach per se do not appear to interfere with folate acid absorption, but by causing anorexia they may decrease the dietary intake of folate.

After partial gastronomy iron deficiency anaemia is common even in a Western population. Different series give figures ranging from 10 to 50 per cent. In India the in-
cidence of postgastrectomy iron deficiency is probably greater, because of the high incidence of iron deficiency after partial gastrectomy are not fully understood, but it has been shown that absorption of iron is more affected than the absorption of ferrous iron salts. The effect of achlorhydria and gastritis on iron absorption has often been disputed, but with the use of modern isotopic techniques it has definitely been shown that absorption is reduced in the presence of achlorhydria — the reduction being more marked in the case of inorganic iron than organic iron.

Disorders of the small intestine

From the public health view point, hookworm infestation is undoubtedly the single most important small intestinal disease in the causation of nutritional anemia. It was estimated in 1947 that 650 million people in the world were infected. The number now is probably considerably more as the population at risk is larger. The anemia of hookworm infestation is an iron deficiency anemia, due to increased blood loss. The amount of blood lost depends on the number and type of worms, A. duodenale causing greater losses than N. americanus. In heavy infestations with the former, losses of up to 400 ml of blood per day have been recorded. The amount of iron lost to the body depends on the hookworm load, the hemoglobin level and the per cent of iron reabsorbed as the blood passes down the small intestine. The development of anemia can be prevented by providing an adequate intake of absorbable iron to compensate for the excess losses. Non-tropical sprue and tropical sprue are frequently associated with iron deficiency, and iron deficiency anemia, presumably due to defective iron absorption. The importance of iron absorption has been little studied.

Disorders of the small intestine frequently interfere with vitamin B12 absorption. Fish tapeworm infestation produces vitamin B12 deficiency, at least partly by competitive uptake of vitamin B12 by the worm. Most cases of megaloblastic anemia associated with worm infestation have been reported from Scandinavian countries. Its presence has not been so far been reported in India. Anatomical lesions of the small intestine such as nodal resec-

tions, diverticulosis, strictures, short circuits and blind loops frequently interfere with vitamin B12 absorption, either by removal of the region where vitamin B12 is normally absorbed, or by bacterial contamination of the gut producing interference with absorption.

Patients with coeliac disease, or non-tropical sprue, often develop megaloblastic anemia. Most commonly this is due to folic acid deficiency, but vitamin B12 deficiency may also occur due to malabsorption of vitamin B12.

In tropical sprue megaloblastosis occurs in a high proportion of cases. The reported incidence varies from 60-100% in Africa and Asia. The megaloblastosis is most often associated with a major deficiency of folic acid, and deficiency of folate malabsorption is rare. Similar results have been obtained using a double lumen technique. In preliminary studies excessive faecal losses of plasma folate have been found in association with diarrhoea and this may be an added factor in producing folate depletion. Vitamin B12 deficiency occurs in 1/3 to 1/2 of Indian patients with tropical sprue and is probably related to the lowered stores of the population at risk, together with defective vitamin B12 absorption. This absorptive defect is not usually corrected by intrinsic factor administration, but in some cases may be corrected by antibiotics.

Isolated defective intestinal transport of vitamin B12 which is not influenced by intrinsic factor, may be seen in the rare syndrome of familial relapsing megaloblastic anaemia and proteinuria.

Increased demands

The increased nutritional demands imposed by the foetus make pregnant women particularly susceptible to the development of deficiency states. The incidence and type of deficiency in pregnancy vary in different regions, presumably depending on differences in the basic diet. In most parts of the world the iron de-
Folic acid deficiency is the most common nutritional disorder in pregnancy. In a recent study in South India, 95% of women in the middle and lower social economic groups were found to be greatly iron deficient131.

Folate deficiency is also common in pregnancy. In South India, 45% of women have a serum folate level of 4 μg/mL and 59% have megaloblastic changes in the bone marrow131. Serum B12 levels fall during pregnancy132,134, but frank vitamin B12 deficiency is comparatively rare.

Chronic haemolytic anaemias, and other conditions associated with prolonged over-production of cells such as leukaemias, lymphomas, etc., may lead to a relative folate deficiency and frank megaloblastic change in the developing red cells135,136,147.

Increased demand for haematinics will also occur when there is excessive loss from the body. This is particularly well documented in the case of iron. Chronic blood loss from any cause is well known to predispose to iron deficiency. Iron may also be lost in the sweat. On the basis of chemical studies it has been suggested that excessive iron losses may occur in the sweat in tropical climates6,8,10,12. However isotopic studies have failed to confirm this finding65. The reasons for the discrepancy between the two techniques is not clear. The final answer to the role of dermal losses in the production of iron deficiency anaemia must await further study.

Infections, rheumatoid arthritis, renal disorders and various other diseases, interfere with iron metabolism and may produce an iron deficiency type of anaemia even in the presence of adequate total body iron stores.

Infections of various types may also precipitate folate deficiency. This is particularly so in children135 in whom gastroenteritis and respiratory infections are the ones most commonly associated with folate deficiency146. Patients with cirrhosis of the liver, especially when associated with alcoholism67,97,103 and patients with rheumatoid arthritis66 also appear to be prone to develop folate deficiency. In patients with thyroid disease folate deficiency69 and vitamin B12 deficiency172 have both been described.

**Drug administration.**

Megaloblastic anaemia occasionally occurs in patients receiving anticonvulsant drugs—especially diphenylhydantoin, primidone and phenobarbitone. This anaemia is usually associated with high serum levels and responds to folinic acid162. The antimalarial drug pyrimethamine may also produce a folate deficiency megaloblastic anaemia154.

Folic acid when given by mouth has also been shown to reduce the incidence of megaloblastic changes in the developing red cells155. Folic acid when given by mouth has also been shown to reduce the incidence of megaloblastic changes in the developing red cells155. Further administration of folic acid has been shown to improve anaemia in those with megaloblastic changes155. Folic acid when given by mouth has also been shown to reduce the incidence of megaloblastic changes in the developing red cells155.

**SYMPTOMS AND SIGNS OF DEFICIENT STATES**

The most commonly recognised symptoms and signs of iron, vitamin B12 and folate deficiency states are those directly associated with anaemia. If the anaemia is severe there may be symptoms of splenomegaly and in cases of megaloblastic anaemia there may also be cold icterus.

**The tongue**

Glossitis may be seen in iron deficiency, but is usually more severe, and more common, in vitamin B12 and folate deficiency. The precise incidence varies widely in different series and in the same series with different observers. In Indians, patchy hyperpigmentation of the tongue may be seen in some cases of vitamin B12 and folate deficiency156. It is most commonly seen on the dorsal surface of the tongue but may also be seen on the ventral surface, around the gum margins and in the buccal mucosa. The hyperpigmentation can be observed to disappear with treatment. Similar hyperpigmentation may also occur as a congenital anomaly and in other conditions associated with generalised hyperpigmentation, such as Addison’s disease of the suprarenals.

**The skin**

Hyperpigmentation of the skin may be seen in cases of megaloblastic anaemia in Indians and Africans107 and may be a presenting symptom of this disorder131. It is often associated with vitamin B12 deficiency135 but can also occur in pure folate deficiency12 and need not necessarily be associated with anaemia. The hyperpigmentation is most marked on the exposed parts and those subjected to pressure. It is usually maximal on the dorsum of the hands, over the terminal phalanges and the interphalangeal and metacarpophalangeal
from a mild degree of impairment of the sense of vibration to the fully developed classical picture of subacute combined degeneration of the cord. Involvement of the cerebrum may produce slowing of mental processes, depression, hallucinations, psychosis and finally severe dementia. Retro-bulbar neuritis and optic atrophy may also occur. It is important to emphasize that subacute combined degeneration of the cord, and all the other neurological manifestations are not confined to cases of classical pernicious anaemia but may occur in patients with vitamin B$_{12}$ deficiency arising from any cause.

**Hematological Diagnosis**

**Morphology**

The presence of obvious anaemia is a relatively late sign of deficiency. Examination of peripheral blood and bone marrow smears may suggest the presence of a deficiency state even in the absence of marked anaemia.

The cardinal morphological sign of iron deficiency is hypochromia of the circulating red cells, together with a decrease in their size. This hypochromia and microcytosis is also reflected in the red cell indices. Examination of the bone marrow shows a lack of haemoglobinisation of the developing normoblasts, which also have a ragged cytoplasmic outline. In a person with normal iron stores, stainable iron can be demonstrated both intr- and extracellularly, but in iron deficiency there is little or no stainable iron present. This absence of stainable iron is the first morphological evidence of iron deficiency.

The earliest morphological sign of folate and vitamin B$_{12}$ deficiency in the peripheral blood is probably hypersegmentation of the polymorphs. Subsequently leucopenia and thrombocytopenia may occur, and the red cells develop macrocytosis and pocksiform cytosis. The changes in the marrow vary according to the severity and duration of the deficiency. The classical morphological hallmarks of these deficiencies are the changes in the developing red cells. In the severest forms the marrow will be markedly hypercellular and will contain many large primitive megaloblasts. In lesser degrees of deficiency, the abnormalities will be less marked, and in mild deficiency states cells which are only just distinguishable from normal may be seen. The red cells ab-
normalities may be graded according to the degree of morphological change—grade I being the least abnormal and grade IV being the grossly abnormal. The interpretation of morphology is a subjective matter, and there may therefore be considerable differences in interpreting the minor degrees of change represented by grades I and II. In such cases, the ultimate test of abnormality is to observe a change towards normality in the morphology of the nucleated red cells following specific treatment. The changes of megaloblastosis may be masked by severe iron deficiency and by defects of haemoglobin synthesis.

The presence of megaloblasts in the bone marrow is not absolutely diagnostic of vitamin B₁₂ or folate deficiency. They may also be present in DiGiuglielm's disease and in some cases of leukaemia, where serum vitamin B₁₂ and folate levels are normal and where there is no response to these agents. Megaloblastosis has also been reported in scurvy, but this may be related to concomitant folate deficiency. Megaloblastosis responding to vitamin E therapy has also been reported in cases of marasmus and kwashiorkor, but the precise role if any, of vitamin E in erythropoesis is not yet clear.

The changes in the white cells in the marrow in vitamin B₁₂ and folate deficiency are increase in size of the cells, characteristic giant metamyelocytes, giant band or "stab" cells and large hypersegmented polymorphs or "macro-polyocytes". In some cases of milder deficiency these changes in the developing white cells may be more obvious than those in the red cell precursors.

**Measurement of iron vitamin B₁₂ and folate**

Direct measurements of serum and/or tissue levels of iron, vitamin B₁₂ and folate provide quantitative information regarding these substances not available by other techniques, and may detect deficiency states long before they produce any change in morphology. Good chemical methods are available for the measurement of serum iron levels. The results in normal subjects vary somewhat depending on the technique employed and the population under study. Levels below 50 μg% may be taken to indicate the presence of definite iron deficiency. The iron binding protein of the plasma (transferrin) may also be measured.

The level of transferrin rises in iron deficiency, and the percentage saturation of transferrin falls. A level of 16% saturation or less indicates marked iron deficiency.

In South India, 96% of pregnant women in the last trimester were found to have a serum iron of less than 50 μg% (mean 31 μg%) and a percent saturation of transferrin less than 16% (mean 7,2%) 18. These findings indicate the widespread prevalence of iron deficiency in this part of India.

Tissue levels of iron may also be measured in liver biopsy specimens. This is a useful research tool in delineating iron stores in a population, but is scarcely applicable to routine practice.

A number of microbiochemical assay methods are available for the estimation of vitamin B₁₂ levels in the serum. These include *Escherichia coli* 19, 20, *Pseudomonas aeruginosa* 21, *Lactobacillus leichmannii* 22, 23, *Escherichia coli* 24, 25, and *Ochromonas malhamensis* 26. Of these E. coli is the most rapid but least specific. *L. Leichmannii* and *Escherichia coli* are probably the most widely used organisms, but *Ochromonas* is the most specific in its growth requirements. In addition to microbiological assay methods for vitamin B₁₂, radioactive labelled vitamin B₁₂ of high specific activity has made possible the introduction of saturation analysis techniques for measuring serum levels. This is still not widely employed but may ultimately displace microbiological methods.

For the measurement of serum folate levels microbiological assay with the organisms *Lactobacillus casei* is used. This organism responds to a number of folate forms including a 5-nitro-5-methyl-tetrahydrofolate which is the chief folate form in serum.

In the application of microbiological assay procedures it is important to delineate the normal range for the population under study by the particular laboratory. The normal range reported from different laboratories varies widely. A review of 17 reported series of folate assays showed variations in the mean normal value from 4.6 to 15.8 μg/ml.

The interpretation of the results of serum assays is not always straightforward. When the folate level in the plasma is lowered, it is probably always indicative of folate deficiency, but normal folate levels do not always
rule out folate deficiency. For example in cases of kwashiorkor, even in the absence of obvious infection, the serum folate level may be normal or high and yet the child have a megaloblastic anaemia which responds to folate administration. In vitamin B12 deficiency, the serum folate levels may rise due to the accumulation of N5-methyl-tetrahydrofolate in the plasma, while the overall body stores of folate are depleted.

Interpretation of serum vitamin B12 levels may be even more difficult. A low serum vitamin B12 level in the presence of a normal to high folate level is almost certainly indicative of vitamin B12 deficiency. However, with a low folate level in the blood, a low serum vitamin B12 level may also be found which rises on treatment with folic acid. In cases of liver disease there may be very high levels of vitamin B12 in the plasma, yet total body stores may be reduced. In all these instances the results of serum assays do not accurately reflect the position of the body stores.

Microbiological assays may also be used for studying tissue levels of vitamin B12 and folate. Red cell folate levels have been studied by a number of investigators. They are reduced not only in cases of folate deficiency, but also in vitamin B12 deficiency. Red cell folate levels are therefore difficult to interpret in cases where there may be combined deficiencies present. In developing folate deficiency the serum level falls before the red cell level, but the red cell levels probably give a better indication of tissue folate stores, and therefore of total body folate, than do the serum levels.

The content of vitamin B12 and folate may also be measured in liver biopsy specimens. The problem associated with liver biopsy makes it unlikely that the assay of liver tissue will ever become a routine investigation in the diagnosis of deficiency states. It is however a useful research method for obtaining an indication of body stores of these materials.

Changes in intermediary metabolism

In folate deficiency the conversion of folic acid (folic) to glutamic acid is impaired, and when a loading dose of folic acid is given, uracil acid and folic are excreted in excess in the urine. However, the test is also abnormal in some cases of vitamin B12 deficiency and therefore is of very limited value in distinguishing the two deficiencies. It has been claimed that by modifying the test it can be made more specific, but this awaits confirmation. The folic test becomes positive only a number of weeks after the fall in serum folate levels and after the appearance of morphological changes in the peripheral blood. The test is therefore of little value in the diagnosis of early folate deficiency, or in distinguishing vitamin B12 deficiency from folate deficiency.

The excretion of aminoimidazole carboxamide in the urine is raised in cases of vitamin B12 deficiency and this has been suggested as a test for B12 deficiency. However, a similar finding has been reported in folate deficiency so the test cannot distinguish between deficiencies of the two substances.

Urinary methylmalonic and propionic acid excretion are increased in subjects with vitamin B12 deficiency but not in subjects with folic acid deficiency. Most of the methods for estimating methylmalonic acid are not suitable for routine use, however two simpler methods have been introduced which may make the test more applicable to routine studies. If the usefulness of these methods is confirmed the test may become important in the investigation and differentiation of vitamin B12 and folate deficiency states.

Haematological responses

The final proof of the presence of a deficiency state of sufficient severity to cause a recognisable abnormality, is its reversion to normal following specific therapy. This is most easily followed in those cases where there is a significant degree of anaemia, but the method can also be applied to the clinical, biochemical and metabolic manifestations of deficiency states. In anaemic subjects, studies of the haematological response to iron, vitamin B12 or folic acid may provide the best indication of the nature of the deficiency. In megaloblastic anaemia it is important to use small or “physiological” doses of vitamin B12 or folic acid as with large doses the responses may not be specific. In cases of pure vitamin B12 deficiency the parenteral administration of 200 micrograms of folic acid daily will pro-
dace no haematological response, whereas 1 μg of vitamin B₁₂ will produce a prompt response. Conversely, in cases of pure folate deficiency, there will be no haematological response to the daily parenteral administration of 1 μg of vitamin B₁₂, but an adequate response following the administration of 100-200 μg of folic acid. In some cases of mixed deficiency there may be a response to physiological amounts of both vitamin B₁₂ and folate when they are given one after the other. In other cases of mixed deficiency, it appears as though a severe deficiency of the second therapeutic agent may prevent any haematological response to the first, until the second agent is also administered—in such cases, a study of therapeutic responses alone, may fail to give a true indication of the nature of the deficiencies present.

Other investigations
The cause of a deficiency may be obvious, but at times other special investigations may be necessary to establish the precise etiology. Some of the more important of these investigations are listed in the table.

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TREATMENT

Once the diagnosis is established treatment of the deficiency is relatively simple. The appropriate haematologic should be administered in adequate dosage, for sufficient period of time, to cure the deficiency and replenish body stores. The duration of therapy will vary according to the aetiology of the deficiency state. Thus a patient with a total gastrectomy will need lifelong supplementation with vitamin B\textsubscript{12}, whereas someone with folate deficiency megaloblastic anaemia of pregnancy will not need further therapy, once stores are repleted and the periconception is passed.

Iron therapy should usually be given orally, since even in cases of tropical sprue therapeutic amounts of iron are adequately absorbed. The standard treatment of 180 mgm. of ferrous sulphate given two or three times daily provides more than adequate iron for the treatment of iron deficiency. This dose has been found adequate even in cases of iron deficiency anaemia in tropical sprue. Various authors have suggested using other iron salts but there is no good evidence that these are superior in any way.

The practise of using parenteral iron therapy in place or oral iron is increasing. It has been shown that response to parenteral iron therapy is no greater and no more rapid than the response to oral therapy. The risk of complications from parenteral iron is by no means negligible, and the cost is considerably greater. The indications for parenteral therapy are therefore very few and consist mainly of the rare cases who fail to tolerate even small amounts of oral iron or those who cannot absorb it.

Prophylactic iron therapy, to prevent the occurrence of iron deficiency anaemia, should be given at least to those sections of the population most at risk, namely infants and pregnant women. It has been demonstrated that as little as 6.6 mgm. of elemental iron, given as ferrous sulphate will cause a significant increase in haemoglobin in an iron deficient population. The best dose and best method of supplementation for prophylactic therapy in India, on a public health scale, has yet to be worked out.

Since malabsorption of therapeutic folic acid is very rare, the treatment of folic acid deficiency is simple and can be adequately carried out by oral administration. One tablet of 5 mgm. of folic acid daily for more than is necessary to cure the severe folic acid deficiency megaloblastic anaemias, all of which will respond to iron in the region of 200 mg per day. The prophylactic use of folic acid supplements in pregnancy will significantly reduce the incidence of megaloblastic anaemia in pregnancy. The minimal effective prophylactic dose in an Indian population has yet to be determined.

When vitamin B\textsubscript{12} deficiency is present, treatment should be by parenteral administration of vitamin B\textsubscript{12}, unless it can be clearly demonstrated that absorption of the vitamin is normal. An injection of 1 mg per day is enough to cure B\textsubscript{12} deficiency anaemia, but it is easier to give 50-100 mg per week. In those patients requiring prolonged or lifelong therapy injections of 200 to 1,000 mg once a month are adequate. Hydroxocobalamin is better retained in the body than cyanocobalamin but its superiority in therapy is only marginal.

When facilities are not available for differentiating between vitamin B\textsubscript{12} and folate deficiency, it is probably safer to treat the patient empirically with both vitamin B\textsubscript{12} and folic acid. The danger of treating a B\textsubscript{12} deficient subject with folic acid, and precipitating a severe neurological disorder, has perhaps been overstressed. Nevertheless, if the risk is a real one it is safer to avoid it by giving both drugs whenever there is any doubt.

Where modern investigative facilities are not available to determine the precise aetiology of a deficiency state, it may not be possible to determine whether or not the patient needs prolonged therapy. In such cases initial therapy should be given for three months, and then further therapy withheld, and the patient kept under observation for the next 18 to 24 months. If no relapse occurs during that time, it is probable that further therapy will be unnecessary.

SUMMARY AND CONCLUSION

The recognition of iron, vitamin B\textsubscript{12} and folate deficiency depends on an awareness of the conditions likely to lead to deficiency states, a knowledge of their clinical manifestations and adequate haematological study.
The severity and precise nature of the deficiency can usually be determined by measurement of the iron, vitamin B_{12} and folate in the blood and tissues, by a study of the excretion of abnormal metabolites and of therapeutic responses.

Other investigations may be necessary to elucidate the precise etiology of the deficiency. Treatment of individual cases is usually straightforward but further study is needed to determine the best approaches to mass prophylaxis in different areas.

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