TODAY'S DRUGS

With the help of expert contributors we print in this section notes on drugs in current use.

Folic Acid and Combined Iron and Folic Acid Preparations

Folate deficiency occurs in a wide variety of clinical conditions (Table I), and though severe megaloblastic anaemia is relatively uncommon in Britain, except perhaps during pregnancy, less severe degrees of folate deficiency are more common than is usually suspected. Such patients may have little or no anaemia, but a careful examination of the blood film and bone-marrow often reveals early megaloblastic changes. Even in the absence of haematological changes early folate deficiency may produce symptoms such as anorexia, malaise, and irritability which can be relieved by treatment with folic acid. Frequently it is a manifestation of an unsuspected malabsorption syndrome, and recent observations suggest that early folate deficiency, or perhaps abnormal folate metabolism, may be responsible for some obstetric complications, such as recurrent abortion, foetal abnormalities, antepartum haemorrhage, and abruptio placentae.

TABLE I.—*Folate-deficiency Syndromes*

INADEQUATE DIETARY INTAKE*
- Nutritional megaloblastic anaemia (including scurvy)

INTESTINAL MALABSORPTION (due to lesions of proximal small intestine)
- Idiopathic steatorrhoea and coeliac disease
- Tropical sprue

INCREASED REQUIREMENT (conditions associated with increased cellular turnover)

Physiological
- Pregnancy
- Prematurity
- Lactation
- Infancy

Pathological
- Haemolytic anaemia
- Myeloproliferative disorders
- Leukaemias and lymphomas
- Ineffective erythropoiesis (e.g. sideroblastic anaemia)
- Chronic iron deficiency
- Malignancy
- Chronic inflammatory conditions
  - e.g. rheumatoid arthritis
    - Crohn's disease
    - tuberculosis
- Skin diseases
  - e.g. psoriasis

INCREASED LOSS (e.g. renal dialysis)

INTERFERENCE WITH METABOLISM
- Folic acid antagonists
- Anticonvulsants and barbiturates
- Alcohol (especially in alcoholic cirrhosis)
- Pyrimethamine
- Nitrofurantoin

* Inadequate dietary intake is a common feature of all folate deficiency syndromes.

The detection of mild folate deficiency is therefore a matter of practical importance, and the new methods of studying folate metabolism have made it possible to diagnose deficiency at a very early stage. Diagnosis is based on the microbiological assay of serum and red cell folate with *Lactobacillus casei* and the urinary excretion of formiminoglutamic acid (Figlu) after a loading dose of histidine. The serum concentration of folate is the earliest and most sensitive index of deficiency, while the red-cell folate concentration and urinary Figlu excretion are indices of more severe deficiency. Megaloblastic anaemia is the end result. The red-cell folate concentration and Figlu excretion are particularly useful in assessing the severity of folate deficiency in a patient without megaloblastic anaemia who nevertheless has a subnormal serum folate concentration.

† Such small doses of folic acid are generally not available, but can easily be prepared for particular cases by diluting the standard folic acid for injection—for example, 1 ml. (15 mg.) of Folvite in 149 ml. of sterile water gives 100 μg. per ml. This should be assayed microbiologically to confirm its folic acid concentration. Obviously it would be more convenient if this dose were generally available in tablet form.

Folate Requirements

The normal adult folate requirement is approximately 50–75 μg. of folic acid daily. The average British diet contains 150–200 μg. per day of "free" *L. casei*-active folate after cooking. Although this figure may not necessarily represent the available folate in the diet, there is probably not much surplus folate after cooking.

In conditions associated with increased cellular proliferation (Table I) the folate requirement is increased. Of these, pregnancy is perhaps the most extensively studied in terms of supply and demand for folate. In normal pregnancy the average folate requirement appears to be increased at least three times,[1] and similar observations have been made in relation to the folate requirements of patients with haemolytic anaemia[2 3] and myelofibrosis.[4] There is also some evidence that iron deficiency may aggravate folate deficiency and precipitate the onset of megaloblastic anaemia, especially in conditions associated with increased folate requirement, as in pregnancy.[5]

Therapeutic Use

The only established therapeutic application of folic acid is in the treatment of folate deficiency. Folic acid (pteroylglutamic acid) is available as 5 mg. tablets and as a solution (15 mg./ml.) for injection.

The pharmacological dose of folic acid is 5 to 15 mg. daily, which is usually given orally. However, it may be given by injection, especially if malabsorption is suspected, but at these dosage levels adequate amounts of folic acid will usually diffuse across the intestinal mucosa even in the malabsorption syndrome.

The physiological dose of folic acid, on the other hand, is of the order of 100 μg. per day.† This dose should be used for therapeutic trials in patients with megaloblastic anaemia, since it will produce haematological responses only in patients with folate deficiency, and thereby avoid cross-reactions in patients with B_{12} deficiency as produced by the usual pharmacological doses of folic acid. The procedure of therapeutic trial is time-consuming and requires careful supervision. The patient should be anaemic enough to detect a significant haematological response, which usually means a haemoglobin of less than 10 g./100 ml., but obviously not too ill to run any risk from possible delay in the institution of specific therapy. Furthermore, the patient should not be suffering from complications likely to block the haematological response (e.g., infection, chronic renal failure, malignancy, alcoholism, and active inflammatory conditions, such as rheumatoid arthritis and active Crohn's disease). The diet should be controlled and low in folate and vitamin B_{12}. In particular, the patient should receive no liver or kidney. The trials should not be started for 7 to 10 days after admission to hospital to exclude a spontaneous haematological remission associated with a better diet or withdrawal of drugs (including alcohol). The patient should then be given folic acid (100 μg. daily) and the haematological response carefully followed. If there is no response after 14 days, small doses of vitamin B_{12} (1–2 μg. per day) should then be tried.

While 100 μg. daily of folic acid will produce a satisfactory haematological response in uncomplicated folate deficiency, larger doses (up to 1 mg.) are recommended in patients suffering from conditions likely to suppress haemopoiesis (see above) or increase folate requirements (Table I). However, it should be pointed out that the usual pharmacological dose of 5–15 mg. is greatly in excess of requirements.

An absolute contraindication to the use of folic acid is severe B_{12} deficiency, as occurs in Addisonian pernicious anaemia, and

in some patients with total or partial gastrectomy, ileal resection, intestinal blind loop syndrome, or chronic tropical sprue. While pharmacological doses of folic acid will usually produce a haematological response in such patients, this is potentially dangerous in that it permits severe neurological damage to develop in some cases. Even physiological doses of folic acid may prevent the onset of anaemia and thereby delay diagnosis in some patients with pernicious anaemia until the onset of neurological damage. For this reason multivitamin preparations containing small physiological doses of folic acid should not be used indiscriminately.

Combined Folic Acid and Iron Preparations

Prophylactic iron is routinely given during pregnancy, and there is now a good case for giving folic acid supplements as well. In practice one should aim at giving a single tablet per day containing enough iron and folic acid to meet the increased requirements of normal pregnancy. The purpose of what follows is to guide the general practitioner in selecting a suitable prophylactic tablet from the many proprietary preparations now available (Table II).

TABLE II.—*Combined Folic Acid and Iron Preparations*

Proprietary Name	Folic Acid	Iron
Ferfolic M	100 μg.	Fe gluconate (30 mg. Fe)
Ferromyn "S" with folic acid	100 μg.	Fe succinate (37 mg. Fe)
Pregamal	100 μg.	Fe fumarate (65 mg. Fe)
Kelfolate	150 μg.	Fe glycine sulphate (40 mg. Fe)
Plesmet F. A.	150 μg.	Fe aminoacetosulphate (50 mg. Fe)
Ferrograd folic	350 μg.	Fe sulphate (105 mg. Fe)
Folex-350	350 μg.	Fe gluconate (35 mg. Fe)
Fefol Spansule	500 μg.	Fe sulphate (45 mg. Fe)
Pregfol	500 μg.	Fe sulphate (60 mg. Fe)
Plastules with folic acid	1 mg.	Fe sulphate (59 mg. Fe)
Folvron	1·7 mg.	Fe sulphate (61 mg. Fe)
Folicin	2·5 mg.	Fe sulphate (51 mg. Fe)
Feravol—F	3 mg.	Fe gluconate (36 mg. Fe)
Feravol (forte)	5 mg.	Fe gluconate (36 mg. Fe)
Cyfol	5 mg.	Fe gluconate (36 mg. Fe)
Ferfolic	5 mg.	Fe gluconate (30 mg. Fe)
Ferfolic SV	5 mg.	Fe gluconate (30 mg. Fe)
Folex	5 mg.	Fe gluconate (35 mg. Fe)

Very few controlled clinical trials have been carried out to determine the optimal amounts of iron and folic acid required for prophylactic administration during pregnancy, and this is still a controversial topic. In a recent study de Leeuw and co-workers[6] found that a daily supplement of 39 mg. of elemental iron was insufficient, but that 78 mg. was adequate to produce an optimal haemoglobin mass and to maintain bone-marrow iron stores during normal pregnancy. With regard to folic acid, Chanarin and co-workers[7] have suggested a supplement of 100 μg. daily starting at the 20th week of pregnancy, and in a similar study Willoughby and Jewell[8] recommended 300 μg. daily during the last trimester, when the folate requirements are greatest. A larger folate supplement would be required if the patient's diet was inadequate, in twin or multiple pregnancies, and in the presence of iron deficiency or intercurrent urinary tract infection. Under these circumstances the precise requirements would have to be assessed for the individual patient.

The risk of prophylactic folic acid masking an underlying severe B_{12} deficiency during pregnancy is remote. Severe B_{12} deficiency due to Addisonian pernicious anaemia is incompatible with a successful pregnancy[9]; even early pernicious anaemia often leads to infertility and is unlikely to cause the severe degrees of B_{12} deficiency associated with neurological damage. However, immigrant women from India with a background of tropical sprue may have significant B_{12} deficiency during pregnancy,[10] and such patients may run the risk of developing mild neurological symptoms during folic acid prophylaxis.

Finally, it should be stressed that in spite of prophylaxis routine haematological examination in late pregnancy is still an essential part of antenatal care. There will always be the defaulters and the occasional patient with latent idiopathic steatorrhoea who may develop severe iron deficiency or megaloblastic anaemia.

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ANY QUESTIONS?

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

Sensitivity to Bee Stings

Q.—*What precautions could be taken by people who know they are hypersensitive to bee or wasp stings to avert anaphylaxis should they be stung again? What remedy could they carry for immediate application?*

A.—If there is a serious risk of further stings—for example, from a nearby apiary—desensitization should be considered. Since the antigen is not confined to the venom but is present throughout the body of the insect and is not species specific, mixed extracts of whole insects are used. Messrs. C. L. Bencard Ltd. will give full details of doses and boosters.

A worker-bee, unlike a wasp, leaves its sting behind. Since the muscles of the poison sac continue to inject venom, very prompt removal of the sting by scraping it out with the finger nail is the best immediate local treatment. If it is in an inaccessible place the sting should be wiped out with a handkerchief. An antihistamine cream rubbed in at once may mitigate the effects. The old treatment by vinegar for wasp stings and bluebag (that is, alkali) for bee stings has no scientific basis, since the effects of the venom are not due to acidity or alkalinity but to complex polypeptides.

When there is a strong possibility of being stung—for example, when visiting a friend's garden—ephedrine 15 mg. by mouth beforehand may lessen any reaction, and some bee-keepers who know they react badly use this. It would be wise to take a trial tablet first lest unpleasant side-effects contraindicate its use.

If a sting occurs a 10-mg. tablet of isoprenaline should be placed under the tongue at once and the patient should keep a supply at hand. Alternatively, 0.5 ml. adrenaline hydrochloride *B.P.* (1 in 1,000) could be injected subcutaneously. But this is less easy for a victim to carry out when suffering intense pain. Isoprenaline and adrenaline are alternatives. They must not be used together. A doctor should be called, and he may in addition give cortisone acetate intramuscularly or other steroid preparation. A soothing calamine lotion, preferably of the spray type, may help.

Glyceryl Trinitrate and Glaucoma

Q.—*Is it safe to use sublingual glyceryl trinitrate and sustained-action glyceryl trinitrate in the presence of glaucoma?*

A.—It is said[1] that glyceryl trinitrate should be used with caution in patients with