BRITISH MEDICAL JOURNAL

LONDON SATURDAY 18 MAY 1968

Pointers

Cardiac Surgery: Possibilities of radical treatment make correct diagnosis and prognosis of paramount importance, and some controversial aspects of rheumatic heart disease are discussed in this light (p. 383); Four patients with advanced cardiac disease and hopeless prognosis successfully treated by valve replacement (p. 400); Leader at p. 379.

Pregnancy and Folate Status: Patients with low red cell folate at 15 weeks showed megaloblastic changes near term (p. 390); Significant correlation between folate intake and red cell folate shown, and normal dietary intake is inadequate in pregnancy (p. 394). Leader at p. 377.

Propranolol: Two groups of patients with acute myocardial infarction were compared, one treated with propranolol, the other without. No difference between the groups in incidence of mortality, heart failure, or other symptoms was found (p. 398).

Obstetric Analgesia: Paracervical block in labour gave effective pain relief in 35 out of 40 cases, with no foetal or maternal complications (p. 403).

Renal Transplantation: Out of 49 patients who received 54 transplanted kidneys, 51 from cadavers, 70% are still alive, and the longest period of survival is two and a half years (p. 404).

Drugs and Physique: Patients who volunteered side-effects while on imipramine were significantly taller than those who did not (p. 406).

Case Reports: Haemorrhagic fever (p. 408).

Sleep: Use of hypnotics (p. 409).

Ankylosing Spondylitis: Early case with fatal secondary amyloidosis discussed at clinicopathological conference (p. 412).

Surgical Tutors: Royal College of Surgeons appoints tutors in hospital regions (p. 416); leader at p. 379.

Records in General Practice: Proposed wallet for N.H.S. records devised by Scottish Council of Royal College of General Practitioners (p. 420).

Time off in Copenhagen: General practice relief scheme (p. 423).

Personal View: Mrs. Patricia Norton (p. 426).

Annual Clinical Meeting: Provisional programme of joint meeting with British Paediatric Association at Cheltenham (*Supplement*, p. 133).

Hospital Junior Staff: Group Council will ask Representative Body to press for more consultant posts and to reject medical assistant grade (*Supplement*, p. 136).

Teachers and Research Workers: Welcomed report of Royal Commission on Medical Education (*Supplement*, p. 138).

Nutritional Folate Deficiency

In underdeveloped tropical countries nutritional folate deficiency is common, and recent reports suggest that it is not so rare in Great Britain as was previously thought. The extent of the problem depends on the criteria used for defining this condition.

The end result of severe folate deficiency is megaloblastic anaemia. Likewise, nutritional megaloblastic anaemia is the haematological sign of inadequate dietary intake of folate—and less commonly of vitamin B_{12}. Severe nutritional megaloblastic anaemia due to folate deficiency is uncommon in Britain, except perhaps in pregnancy, but occasional well-documented cases have been reported.[1-5] Such cases are usually seen in old people, often incapacitated in some way, or in patients suffering from psychiatric problems, and some cases have been reported where a patient has developed severe megaloblastic anaemia while taking a restricted diet for therapeutic reasons.[6]

However, the disease is not uncommon in a mild form, especially in conditions associated with increased cellular proliferation. These may be either physiological, such as pregnancy, lactation, premature birth, and infancy, or pathological. In the latter category are such diseases as haemolytic anaemia, leukaemia and myeloproliferative disorders, ineffective erythropoiesis (e.g., sideroblastic anaemia), chronic iron deficiency, extensive psoriasis, and some inflammatory disorders—for instance, Crohn's disease,[7] rheumatoid arthritis, and tuberculosis. In these conditions it is assumed that the dietary intake of folate is inadequate to meet the increased requirement for the vitamin, because no other explanation can be found. The ingestion of certain drugs may also be associated with megaloblastic anaemia of this type—most frequently barbiturates and anticonvulsants, and also alcohol. The precise mode of action of these drugs is uncertain, but they probably only precipitate megaloblastic anaemia when the patient is already folate-deficient. It should be stressed that many of these patients, though folate-deficient, show no haematological signs of being so. Consequently the clinical significance of folate deficiency is often difficult to assess.

To establish a diagnosis of nutritional megaloblastic anaemia due to folate deficiency it must be shown that the patient has a megaloblastic anaemia resulting from inadequate dietary intake of the vitamin. The haematological diagnosis is thus the first step. The characteristic picture of severe megaloblastic anaemia is well recognized, but most patients seen in Britain are in an early stage, so that the morphological changes in the peripheral blood and bone marrow, often minimal, may be overlooked. In the blood film there may be no more than increased anisocytosis with occasional macrocytes or hypersegmented neutrophils in an otherwise normal film, while in the bone marrow some of the developing polychromatic erythroblasts show early megaloblastic changes (intermediate megaloblasts) and there are occasional giant metamyelocytes. These changes become more obvious with increasing anaemia.

The laboratory diagnosis of folate deficiency, which must come next, 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 concentration of folate and urinary Figlu excretion are indices of more severe deficiency. Megaloblastic anaemia is the end result.[8] The red-cell concentration of folate and Figlu excretion are particularly useful in assessing the severity of folate deficiency in a patient without megaloblastic anaemia who nevertheless has a subnormal concentration of serum folate. In this respect the red-cell concentration of folate is probably the best single index of folate deficiency when assessing its incidence in population surveys.

At the same time as establishing a diagnosis of folate deficiency, vitamin B_{12} deficiency should be excluded by measuring the serum concentration of B_{12}. This is usually within the normal range in patients with mild nutritional folate deficiency, but subnormal levels may be found in severe cases.[6] In these circumstances the procedure of therapeutic trial is invaluable. Such patients usually respond to treatment with physiological doses of folic acid (100 μg. daily by mouth), and on this treatment the serum concentration of B_{12} will increase, often to normal levels.[9] Furthermore, the urinary excretion of methylmalonic acid, which tends to parallel the severity of B_{12} deficiency, is normal in such patients,[10] and the liver B_{12} stores are not so low as in patients with pernicious anaemia of comparable severity.[11]

The next step in the diagnosis of nutritional megaloblastic anaemia depends on excluding malabsorption and showing that an inadequate dietary intake of folate is the cause of the deficiency. The usual studies of gastrointestinal structure and function[12] should be carried out to exclude a possible latent malabsorption syndrome. It should be pointed out, however, that tests for absorption of vitamin B_{12} and folate should be carried out after correction of the underlying deficiency, because there is increasing evidence that B_{12} and folate deficiency as such may interfere with the intestinal absorption of these vitamins and possibly of other substances.[6 13-16]

Assessment of the patient's diet is still partly a subjective process and consequently inaccurate, but some facts are emerging. Dietary folate is probably best estimated by microbiological assay with *Lactobacillus casei,* because its growth response to different folates closely parallels their clinical activity. Methylfolate, the naturally occurring folate in liver and probably in most other animal tissues, is readily destroyed during assay unless protected with ascorbic acid or other reducing agents. Unfortunately, the need for protection during the assay of food folate has only recently been appreciated,[17-18] and most published figures tend to underestimate the folate content of food. When estimating the dietary intake of folate, losses due to cooking and other processing should be considered, as they are often considerable and depend on the particular item of food and the method of preparation.[17-19] Food also contains polyglutamates (mainly heptaglutamates), which are not measured by *L. casei* assay unless the food is first treated with pancreatic conjugase. However, it is doubtful if heptaglutamates are absorbed in man, and V. Herbert[17] has suggested that the *L. casei* assay of "free" folate (i.e., without conjugase treatment) is the best indication of available folate in the diet. In the *B.M.J.* this week Dr. I. Chanarin and his colleagues report (page 390) that they have assayed the daily folate intake (after cooking) of normal healthy pregnant women and found a mean value of 160 μg. of free folate per day. Other workers using essentially the same technique, have reported mean values of 150–225 μg. per day for representative adult diets.[6 18 20] However, much remains to be done to determine the extent to which folates in food are absorbed. Nevertheless, if we equate activity of free folate in food as measured by *L. casei* with clinical activity, the average dietary intake of folate by healthy adults (150–225 μg.) is at least twice the estimated minimal requirement of 50–75 μg. of crystalline folic acid.[21]

Though dietary deficiency alone can produce megaloblastic anaemia, this is often associated with conditions which increase the requirement for folate. Of these pregnancy is probably the most extensively studied in terms of the supply and demand for folate. In another paper this week (page 394) Dr. Chanarin and his colleagues show that during normal pregnancy a dietary intake of 160 μg. of "free" *L. casei*-active folate is inadequate to maintain a normal concentration of folate in the red cells, but that this can be achieved by a daily supplement of 100 μg. of crystalline folic acid. H. Hansen and G. Rybo have recommended a similar level of supplementation.[22]. In healthy non-pregnant women Herbert[21] found a minimal folate requirement of about 50–75 μg. of crystalline folic acid per day. From these figures the folate requirement during normal pregnancy (160 μg of free dietary folate+100 μg. of folic acid) appears to be at least three times that of a non-pregnant woman. However, a larger folate supplement is required if the patient's diet is inadequate or if the pregnancy is multiple. It should be stressed that these folate requirements are valid only in the absence of iron deficiency, which also seems to increase folate requirement during pregnancy.[23] In practice, prophylactic iron is commonly given during pregnancy, and there is now a good case for giving folic acid supplements as well.[24] While the dose of folate is still a matter for debate, the present study by Dr. Chanarin and his colleagues suggests that the requirement during normal pregnancy can be met by a total intake of about 250–300 μg. daily.

Nutritional folate deficiency is thus more common in Britain than previously expected, and, though the extreme manifestation of florid megaloblastic anaemia is rare, lesser degrees of megaloblastic change with mild or moderate

1 Gough, K. R., Read, A. E., McCarthy, C. F., and Waters, A. H., *Quart. J. med.*, 1963, **32**, 243.
2 Forshaw, J., Moorhouse, E. H., and Harwood, L., *Lancet*, 1964, **1**, 1004.
3 Jackson, I. M. D., *Scot. med. J.*, 1965, **10**, 389.
4 Read, A. E., Gough, K. R., Pardoe, J. L., and Nicholas, A., *Brit. med. J.*, 1965, **2**, 843.
5 Hurdle, A. D. F., and Williams, T. C. P., *Brit. med. J.*, 1966, **2**, 202.
6 Mollin, D. L., and Waters, A. H., in *Swedish Nutrition Foundation Symposium*,.6. 1968. Stockholm. In press.
7 Hoffbrand, A. V., Stewart, J. S., Booth, C. C., and Mollin, D. L., *Brit. med. J.*, 1968, **2**, 71.
8 Mollin, D. L., and Hoffbrand, A. V., in *Vitamin B_{12} and Folic Acid* (*Scand. J. Haemat.*, Series Haematologica, 3), 1965, p. 1. Copenhagen.
9 Mollin, D. L., Waters, A. H., and Harriss, E., in *Vitamin B_{12} und Intrinsic Factor*, ed. H. C. Heinrich, Second European Symposium, Hamburg, 1961, 1962, p. 737. Stuttgart.
10 Brozovic, M., Hoffbrand, A. V., Dimitriadou, A., and Mollin, D. L., *Brit. J. Haemat.*, 1967, **13**, 1021.
11 Anderson, B. B., Ph.D. Thesis, University of London. 1965.
12 Dyer, N. H., and Dawson, A. M., *Brit. med. J.*, 1968, **2**, 161.
13 Schloesser, L. L., and Schilling, R. F., *Amer. J. clin. Nutr.*, 1963, **12**, 70.
14 O'Brien, W., and England, N. W. J., *Brit. med. J.*, 1966, **2**, 1157.
15 Carmel. R., and Herbert, V., *Ann. intern med.*, 1967, **67**, 1201.
16 Mattnews, D. M., *Brit. med. Bull.*, 1967, **23**, 258.
17 Herbert, V., *Amer. J. clin. Nutr.*, 1963, **12**, 17.
18 Hurdle, A. D. F., M.D Thesis, University of London. 1967.
19 McCance, R. A., and Widdowson, E. M., *Spec. Rep. Ser. med. Res. Coun.* (*Lond.*), No. 297, 1960.
20 Butterworth, C. E., Santini, R., and Frommeyer, W. B., *J. clin. Invest.*, 1963, **42**, 1929.
21 Herbert, V., *Arch. intern. Med.*, 1962, **110**, 649.
22 Hansen, H., and Rybo, G., *Acta obstet. gynec. scand.*, 1967, **46**, Suppl. 7, p. 107.
23 Chanarin, I., Rothman, D., and Berry, V., *Brit. med. J.*, 1965, **1**, 480.
24 *Brit. med. J.*, 1964, **2**, 1248.

anaemia are not uncommon, especially in pregnancy and in a wide variety of chronic illnesses. Even without haematological changes folate deficiency is common, and though the clinical significance of this is difficult to assess it may contribute to illness in elderly and mentally disturbed patients and those with chronic diseases. It certainly predisposes such patients to overt nutritional megaloblastic anaemia if they develop a severe infection, become pregnant, or suffer from conditions like myelofibrosis or haemolytic anaemia which increase folate requirement.

When to Replace Heart Valves

Replacement of damaged heart valves became a practical clinical procedure with the development of a ball-valve prosthesis by A. Starr in 1960.[1] It was made of steel and plastic substance (Silastic). Since then many other types of valves have been tried, but today most valve replacements are with artificial ball-valves and aortic valves taken from cadavers.[2-4]

Many difficulties attended the early operations for replacement of valves. They arose partly from deficiencies in design of the valves. But in addition the problems of operative and postoperative management of older patients with a poor myocardium and multiple valve disease were at first unfamiliar to cardiac teams used to operating primarily on patients with congenital heart disease. These complications are now well recognized and largely overcome, so that at last it is possible to draw valid conclusions about the effect of the patient's preoperative condition on the surgical results. In other words the operation is well established, and the indications and contraindications of valve replacement are now becoming standardized.

Among the indications for any cardiac operation are symptoms that prevent the patient from leading a normal life, or a prognosis for the disease that is worse than the risks of surgical treatment. The risks of surgery comprise those of the operative mortality and the postoperative morbidity, while the long-term results to be expected from the artificial valve that has been inserted must also be assessed.

The average patient referred for valve replacement to the cardiac surgeon is too breathless to live a normal life, and can expect a mortality associated with operation of about 10% for replacement of a single valve and 20–30% for replacement of more than one. There can be little hesitation in recommending surgery in these circumstances.

Difficulties arise when the question is whether the patient is too well or too ill for surgery. With the present relatively low surgical mortality, the main risk for the patient with few or no symptoms is the long-term prognosis of the artificial valve. Prosthetic valves and homografts have been inserted in any numbers for only about four years, but even this experience has shown that the complications associated with the artificial valve itself—thrombosis and fracture of prosthetic valves and calcification of homografts and heterografts—are by no means negligible. Most surgeons regard valve replacement as a palliative rather than a curative operation, and so they believe it should not be offered to a patient who has few or no symptoms unless the prognosis of the condition resulting from his cardiac lesion is estimated to be less than four years.

[1] Starr, A., and Edwards, M. L., *Ann. Surg.*, 1961, **154**, 726.
[2] Ross, D., *J. thorac. cardiovasc. Surg.*, 1964, **47**, 713.
[3] Barratt-Boyes, B. G., *Thorax*, 1964, **19**, 131.
[4] *Brit. med. J.*, 1968, **1**, 200.

The problem when considering the moribund patient is emphasized by Dr. Richard Emanuel in his account of four patients in this issue of the *B.M.J.* (page 400) and is simpler in being essentially one of operative mortality. It is in this field that cardiac surgery has recently been making real progress owing to improvement in the methods of maintaining the circulation during and after surgery while the heart readjusts itself to the better haemodynamic situation that follows operation. The dramatic success of Mr. Donald Ross and his team at the National Heart Hospital in returning these four desperately ill patients to a normal life shows that heart failure alone is no longer a contraindication to cardiac surgery, though lung disease, a markedly raised pulmonary vascular resistance, and renal and hepatic failure are still factors to be reckoned with.

A note of caution is nevertheless necessary. Dr. Emanuel does not discuss the overall mortality associated with surgery of the moribund patient at the National Heart Hospital—one of the world's outstanding centres—but it is still in the region of 80% in most centres. On this basis sixteen patients will die for every four that survive. The load that this lays on the operative and postoperative facilities of a small centre that cannot do 461 open heart operations in 22 months is immense. Moreover, there are ill-defined but none the less important considerations that do not enter into statistics. Among these is the effect on the morale of the patients, nurses, and particularly the referring physicians, who sometimes and very naturally are apt to become depressed by the high mortality and so may be reluctant to seek surgical relief for their patients until too late a stage. The ethical questions that arise when, owing to limited resources, the interests of the individual patient conflict with the interests of a larger group of patients pose difficult problems, but they are best left in the hands of the physicians and surgeons concerned with these cases to solve in accordance with traditions of the profession.

Surgical Tutors

One consequence of the growing complexity of medicine in recent years has been that provision for postgraduate education has had to be increased. Many hospitals formerly unconnected with teaching have therefore been drawn into an educational role together with the established teaching hospitals and institutions. At the same time postgraduate centres in many parts of the country have come into existence to provide libraries, seminars, and formal courses of instruction. Foremost in arranging for satisfactory postgraduate instruction has been the Royal College of Surgeons.

Four years ago the College started a pilot scheme of appointing surgical tutors to regional hospital boards to help co-ordinate training in the regions.[1] This week it announces a further stage, the setting up of a full scheme throughout England and Wales. Details are given at page 416 together with the names of the tutors so far appointed. They hold office for five years in the first instance, and their task includes establishing facilities for education, arranging time off for study, and encouraging research.

This scheme should make a helpful contribution to the education of aspiring surgeons and go some way to repairing "the present disorganized state of training"[2] that too often

[1] *Brit. med. J.*, 1964, **1**, 580.
[2] *Royal Commission on Medical Education, 1965-8: Report*, 1968, Cmnd. 3569, H.M.S.O.
[3] *Brit. med. J.*, 1968, **2**, 65.