

a viral cause of some tumours of man continues. It is particularly worth while because the history of medicine in recent times has repeatedly shown that the identification of a micro-organism as the cause of a disease opens the way to the conquest of the disease.

Folic-acid Balance

Folic acid plays an important part in the metabolism of nucleic acid and deficiencies of this vitamin affect especially tissues which have a high rate of turnover of their cells. Among these the tissues responsible for producing blood cells occupy the foremost place, and the earliest sign of deficiency of folic acid is often the development of macrocytic anaemia together with megaloblastic erythropoiesis. Non-Addisonian megaloblastic anaemia may be associated with sprue, idiopathic steatorrhoea, and other mechanical, inflammatory, or neoplastic lesions of the intestines, and defective absorption of folic acid in the gut contributes largely to the pathogenesis of this anaemia. But absorption serves merely as a bridge between supply in the diet and demand by the tissues, and it is now known that, even when absorption is normal, folic acid may be deficient in the diet or needed in unusual amounts in the body.

Nutritional deficiencies of folic acid are not confined to peoples with low standards of living in tropical and sub-tropical areas, but occur also among affluent societies and in temperate zones. K. R. Gough and his associates¹ reported seven cases recently from Bristol, where megaloblastic anaemia arose because the intake of folic acid in the diet fell considerably below the normal daily requirement of 50 μg . On the other hand deficiency may develop because the tissues need more; this is probably the cause of megaloblastic anaemia in pregnancy, since I. Chanarin and his colleagues² have shown that during the final weeks of pregnancy most women have a moderate deficiency of folic acid.²

Several observations now support the view that an increased rate of formation of blood cells may itself increase the requirement of folic acid. Patients with pernicious anaemia in relapse excrete a smaller proportion of a test dose of folic acid in the urine than normal subjects,³⁻⁵ and many examples of megaloblastic erythropoiesis responding to folic acid have been reported in patients with haemolytic anaemias. For example, J. Lindenbaum and F. A. Klipstein⁶ described a patient with sickle-cell anaemia who developed megaloblastic changes that failed to respond to treatment with 50 or 200 μg . of folic acid daily. A response was eventually obtained after giving 1,000 μg . daily, a dose which suggests an abnormally high requirement. Deficiency of folic acid may also occur in myelofibrosis, and at page 671 of this issue of the *B.M.J.* Dr. J. Forshaw and his colleagues report this complication in three patients with the disease.

¹ Gough, K. R., Read, A. E., McCarthy, C. F., and Waters, A. H., *Quart. J. Med.*, 1963, 32, 243.

² Chanarin, I., MacGibbon, B. M., O'Sullivan, W. J., and Mollin, D. L., *Lancet*, 1959, 2, 634.

³ Spray, G. H., and Witts, L. J., *Clin. Sci.*, 1952, 11, 273.

⁴ Girdwood, R. H., *Lancet*, 1953, 2, 53.

⁵ Cox, E. V., Meynell, M. J., Cooke, W. T., and Gaddie, R., *Clin. Sci.*, 1958, 17, 693.

⁶ Lindenbaum, J., and Klipstein, F. A., *New Engl. J. Med.*, 1963, 269, 875.

⁷ Gough, K. R., McCarthy, C., Read, A. E., Mollin, D. L., and Waters, A. H., *Brit. med. J.*, 1964, 1, 212.

A combination of low intake in the diet and enhanced demand by the tissues probably explains the deficiency of folic acid which Gough and his colleagues found in a group of patients with rheumatoid arthritis.⁷ The finding of megaloblastic anaemia due to deficiency of folic acid in four patients with rheumatoid arthritis led them to study the folic-acid balance in a further 46 patients with the disease. Two were found to have a frank megaloblastic anaemia, and no fewer than 30 (65%) had subnormal levels of folate in the serum. Of these 30 patients, 22 excreted excessive amounts of formimino-glutamic acid (figlu) in the urine after a loading dose of histidine, a test which confirms the existence of folic-acid deficiency. The average daily intake of folic acid in all patients was between 30 and 100 μg ., which is lower than the national average (100 μg . daily). The amount of ascorbic acid in the patients' diet was also found to be considerably reduced.

None of the patients included in the survey was receiving phenylbutazone, barbiturates, or anticonvulsants, drugs which are known to conduce to folic-acid deficiency, but most were taking analgesics or steroids, which may have stimulated erythropoiesis and increased the metabolic rate. Salicylates may have led to loss of blood from the gut, with a consequent increase in demand on the bone-marrow. These factors, together with proliferation of the synovial membranes in the diseased joints, may have raised the demand for folic acid to a level above that provided by the borderline dietary intake and thus caused a state of deficiency.

Though any deficiency can readily be treated by the administration of 100-200 μg . of folic acid daily, patients with rheumatoid arthritis are apt to develop Addisonian pernicious anaemia, and because of the risk of subacute combined degeneration of the spinal cord folic acid should be given only under careful medical supervision or when absorption of vitamin B₁₂ has been shown to be normal.

Bladder Cancer and Smoking

Cancer of the bladder is one of the few major types of cancer which is believed to be increasing in incidence. Cancer registries show a small increase in the incidence of the disease among men in the U.S.A.¹ and a somewhat larger increase in Denmark.² In England and Wales the mortality data adjusted for age show a 16% increase in men and a 7% increase in women over the last twelve years.³ In America the incidence has increased very little among women, but some increase has been noted in Denmark. Since the diagnosis is not difficult, there seems no reason to suppose that these increases are due to a greater efficiency in case finding. The most reasonable assumption is that environmental factors causing the disease are more prevalent.

Recently E. L. Wynder, J. Onderdonk, and N. Mantel⁴ have made a detailed inquiry into the histories of 300 men and 70 women with bladder cancer in seven New York hospitals and compared them with the histories given by a similar number of control patients matched for sex and age in the same hospitals. Patients with bladder cancer were included only if the diagnosis was confirmed histologically and the growth was of the squamous or transitional type. Patients were excluded from the control series if they suffered from cancer of the respiratory system or the upper alimentary tract or from myocardial infarction. Detailed inquiries failed