Role of Folate in Preventive Medicine

Three micronutrients viz. iron, vitamin A, and iodine, have well-established roles in public health. Iron is added to wheat flour during milling by statutory requirement in several countries. Iodized salt is promoted in geographical regions which are endemic for goitre, and several trials are in progress adding vitamin A to the staple food in countries where vitamin A deficiency is a public health problem. Folic acid is now being considered as the next candidate for food fortification by a number of national authorities.

The term folate is used to describe members of a family of compounds in which pteroyl polyglutamic acid (2, 4, 6-substituted pteridine ring bound to para-amino benzoic acid) is bound to one or more molecules of L-glutamate. Folic acid is a pteroyl monoglutamic acid. It is a synthetic folate which is used as a supplement and for food fortification. Folate is found in a large variety of foods, including green leafy vegetables, nuts, and whole grain products. Orange juice is an important source of folate except liver which is a particularly rich source. Three-quarters of dietary folate occurs as polyglutamates and one-quarter in monoglutamate form. For absorption polyglutamates must first be hydrolysed to monoglutamyl forms for transport across the intestinal mucosa. Losses during cooking, particularly prolonged boiling, and the presence of naturally occurring folate hydrolase affect the bioavailability of folates in food. For practical purposes about 50 per cent of daily intake is available. Transport in blood is mainly in the form of 5-methyl-tetrahydro (5-methyl-H4) folate.

Folate acts as a co-enzyme in many essential cellular reactions including the transfer of single carbon units in reactions essential to several amino acids, and to nucleic acid synthesis. Rapidly dividing cells such as those in the haemopoietic system are most susceptible to irregularities in DNA production. Folate deficiency as a cause of macrocytic anaemia has been well established in several studies.

A central process in foetal development is widespread and sustained cell division. Because of its role in nucleic acid synthesis the need for folate increases during times of rapid tissue growth, for example, during pregnancy not only for foetal growth but also for increase of red cell mass, enlargement of the uterus, and growth of the placenta.

A nimal studies have indicated the possible protective role of vitamins including folic acid against neural tube defects (NTD's), and this had led to small scale intervention studies in pregnant women. In 1991 the results of a clinical trial sponsored by the British Medical Research Council provided evidence that the risk of recurrent NTD was significantly lower among women who took 400 µg of folic acid daily (without other supplemental vitamins) than among those who did not. More recently a population-based intervention study in China has reported on the effectiveness of 400 µg of folic acid in preventing NTD in northern China which suffers a high incidence of the defect.

It has been proposed that closure of the neural tube occurs at several sites and that the clinical types of NTD differ depending on the site at which closure fails. Variations in the cellular mechanisms of closure at various sites might also contribute to clinical variations in NTD. It has also been suggested that a closed tube may reopen in some cases. All these studies indicate that folic acid is just one of the factors influencing closure of the neural tube, and explain why supplementation brings about only 70 per cent reduction in the occurrence of NTD.

Marked geographic and temporal variability in the rates of occurrence of NTD suggest that environmental and genetic factors have a joint role. Geographical variations between and within countries have been reported for decades. Similarly temporal trends both by season and over the long term are known to occur. In various studies the vitamin concentration in the blood of mothers with NTD affected foetuses have been compared with those of control mothers who have borne healthy infants, and were found to be similar. A possible explanation of these observations could be problems in the transfer of folate from the mother to the foetus; and disorders in folate metabolism which are partly compensated for by supplementation. Moreover, the development and closure of the neural tube are normally completed within 28 days after conception, before many women are aware that they are pregnant.

Recent studies suggest that a reduced activity of the enzyme 5-10-methylene-THF reductase (MTHR) and methionine synthase due to genetic defect may play a role in the pathogenesis of NTD. The reduced activity in one of these two enzymes would lead to increased homocysteine levels in plasma which could be cytotoxic to the developing foetus. An approximate doubling of the risk of spina bifida has been associated with homozygosity for a mutation in the gene that codes for MTHR resulting in an enzyme...
with reduced activity. Hence the current practice is to advise women of childbearing age to consume 0.4 mg folic acid per day commencing before and continuing into early pregnancy in addition to a diet rich in folate. The dose should be increased to 4–5 mg for women with prior NTD-affected pregnancy.

Raised levels of homocysteine are also regarded as a risk factor for vascular disease with an adverse influence comparable to that of hypercholesterolaemia. Homocysteine concentration in plasma can be lowered by an improved intake of vitamins involved in homocysteine metabolism viz. folic acid, B12 and B6. A combination of these vitamins has a more pronounced effect than folic acid alone. The role of folate in health has come to be better understood public health authorities in several countries are taking steps to improve the intake of folate in the general population. In the USA all grain products like flours and pasta are now fortified with 140 µg of folic acid per 100 g of grain. National health services in several countries recommend that at the diagnosis of pregnancy women should be prescribed a daily dose of 400 µg of folic acid to be continued during the early months of pregnancy. The evolving knowledge about the role of folate in health should lead to a global health policy response in the form of education of the general public, supplementation for the vulnerable groups, and fortification of staple foods.

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References
Tuberculous granulomas and meningitis

What is the role of intracranial tuberculous granulomas in childhood tuberculous meningitis? Dr Ravenscroft and colleagues at Tygerberg Hospital and University of Stellenbosch (South Africa) describe the clinical course and serial CT scans in 202 children admitted with the diagnosis of tuberculous meningitis. More than half of meningeal granulomas were not present at admission, and would have been missed without repeat scans as routine. Parenchymal granulomas commonly occurred in association with miliary tuberculosis. Ependymal granulomas behave like the meningeal group, but were of particular significance when the inflammatory process resulted in obstruction in the path of the cerebrospinal fluid.

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Heredity and childhood asthma

Environmental triggers as well as heredity contribute to the aetiology of asthma. Communities with a high rate of consanguinity provide an opportunity for teasing out the genetic factors predisposing to a disease. Drs Hijazi and Haider from the University of Kuwait have investigated an association between severe asthma and homozygous variant of an IgE receptor with an equal maternal and paternal contribution.

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Low birthweight in developing countries

How much of low birthweight (LBW) in developing countries is preventable through health interventions alone? Dr Peters and colleagues in Papua New Guinea (LBW prevalence rate of 23 per cent) report in a case-control study (75 LBW infants: 224 controls) that maternal age (OR 1.92), birth interval <2 years (OR 3.56), lack of or inadequate antenatal care (OR 2.89), pregnancy complications (OR 19.89), and maternal smoking (OR 2.86) were the main risk factors.

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H. influenzae (Hib) vaccine given jointly with diphtheria, tetanus and pertussis (DTP) vaccination

Can Hib vaccine be included in a national expanded programme of immunization? Dr Lolekha and colleagues (Mahidol University and other institutions in Thailand) used Hib vaccine (PRP-T) either reconstituted jointly with DTP and administered intramuscularly at one site, or DTP and Hib vaccines injected at separate sites to study the safety and immunogenicity of the procedures. No significant differences were noticed with regard to side effects. Ninety-eight per cent of the vaccinees in both groups showed satisfactory immune response.

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Perinatal outcome in Mozambique

Carefully monitored cohort studies of perinatal outcome in countries of sub-Saharan Africa are rare. Here is a large (n = 908) prospectively enrolled cohort study by Dr Osman (Eduardo Mondlane University, Maputo), and collaborators from the Karolinska and other institutions in Sweden. The rates of low birthweight and preterm births were 16.2 and 15.4 per cent respectively. Perinatal deaths occurred in 4.7 per cent. The authors describe and discuss risk factors associated with each of these outcomes.

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Vitamin E for reversal of neurological deficits in protein-energy malnutrition

In 1998 Dr Kalra and colleagues from the All India Institute of Medical Sciences (New Delhi, India) drew attention to specific forms of neurologic deficits in children suffering from malnutrition (J Trop Ped 1998; 44: 291–95). They have now carried their work forward in the form of a blinded controlled trial of vitamin E in 100 subjects suffering from moderate malnutrition. Oral administration of vitamin E (100 mg/kg/day) for 6 weeks resulted in improvement in clinical signs as well as in biochemical and electrophysiological parameters.

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