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# Editorial

The first paper in this issue of *Nutrition Research Reviews* (Ingenbleek & Young, 2004) is a signal, but sad, honour for the editor; it is the last paper written by Vernon Young, who died in April this year, shortly after it was submitted for publication. Young's prolific output (more than 600 publications) has established much of our understanding of protein and amino acid requirements, and while his work has sometimes been controversial, it has always been challenging. This last paper is no exception; the authors propose that the essentiality of sulphur is closely related to nitrogen (and hence protein) metabolism. Since the role of homocysteine as an independent risk factor for atherosclerosis and CVD was suggested by Boers (1997) and D'Angelo & Selhub (1997) there has been great interest in ways in which plasma homocysteine can be lowered by increased intakes of folate, and perhaps also vitamins $B_2$, $B_6$ and $B_{12}$, as a result of increased remethylation to methionine, or increased activity of the trans-sulphuration pathway to form cysteine. The sulphur amino acids are limiting in most diets, and Ingenbleek & Young (2004) suggest that accumulation of homocysteine is an adaptive response to conserve sulphur, by restriction of trans-sulphuration (which leads ultimately to oxidation and loss from the body) and retain it for remethylation to methionine – an example of an evolutionary adaptation that was valuable when protein intake was low, but is superfluous, and possibly hazardous, when protein intakes are more than adequate.

Wild & Byrne (2004) continue the theme of evolutionary adaptation that was beneficial when food was scarce, but is hazardous when it is plentiful, with a discussion of the evidence for fetal programming of adult obesity and the metabolic syndrome. Low birth weight (at the lower end of the normal range, which is not considered to be clinically significant) is associated with the development of central obesity and the metabolic syndrome in later life, if food is abundantly available. The hypothesis is that marginal undernutrition *in utero* alters the regulation of metabolic pathways towards greater conservation of energy, and this fetal adaptation is maintained throughout life. We are beginning to see the effects of this in rapidly developing countries, where there is still widespread undernutrition, but obesity and the metabolic syndrome are increasingly prevalent. It was estimated this summer that there are now as many obese people worldwide as there are undernourished – the 'demographic time bomb' is beginning to explode.

Duncan & Scott (2004) note that early hunter gatherers were evolutionarily adapted to an omnivorous diet that was well balanced compared with the cereal-based diet that resulted from the Neolithic revolution some 12,000 years ago (a short time in evolutionary terms). They suggest that it was the development of agriculture that was responsible for periodic food shortages super-imposed on seasonal variation of food availability – precisely the conditions that would be expected to result in metabolic (and perhaps also genetic) adaptation in favour of increased conservation of energy. Their review provides evidence for the hypothesis proposed by Malthus in his *Essay on the Principles of Population*, published in 1798, which postulated that any temporary or local improvement in living conditions will increase population faster than the food supply, and that disasters such as war and pestilence, which check population growth, are inescapable features of human society.

On a more optimistic note, Baracos and coworkers (Baracos *et al*. 2004) review the evidence that diets rich in *n*-3 polyunsaturated fatty acids are protective against cancer, acting to reduce initiation, promotion, progression and neoplastic transformation, providing yet another argument in favour of consuming oily fish. They also suggest that fish oil supplements enhance the efficacy of chemotherapy, reduce its toxic side-effects and attenuate the wasting (cachexia) associated with some cancers.

Vissers and coworkers (Vissers *et al*. 2004) also discuss nutritional supplementation in disease, this time with the amino acid arginine, as the precursor of nitric oxide, and its possibly beneficial effects in sepsis, trauma and wound repair. Arginine is depleted in sepsis because of the increased utilisation for the formation of nitric oxide, but *de novo* arginine synthesis is not increased; they suggest that supplements are needed to maintain arginine homeostasis, and hence nitrogen balance. Similarly, cancer is associated with arginine depletion, both as a result of increased nitric oxide formation and also the activity of arginase in tumour cells. The results of trials of supplementation have not been encouraging, but the authors note that there have been few trials of monotherapy – supplementation with arginine alone; most have used arginine together with other supplements, and there may be interactions between arginine and other nutritional supplements. They argue for more trials of arginine alone.

Thurnham (2004) explores the many interactions between different micronutrients, between micronutrients and drugs, and between micronutrients and such life-style factors as smoking and drinking tea or alcohol. Prescribed medication may have widespread nutritional effects, ranging from the reduced food intake resulting from the nausea that is a side effect of many drugs, or the drug-induced alterations of the senses of taste and smell that render foods unpalatable or aversive, to more specific effects on the absorption, metabolism and utilisation of individual nutrients. In some cases (e.g. the folate antagonists used in cancer chemotherapy) the anti-vitamin anti-metabolic action is the basis of the beneficial action of the drug; in other cases it is simply an undesirable side-effect. Conversely, moderately high intakes of micronutrients may impair the efficacy of medication – folate in excess of about 2000 μg/d reduces the action of many anticonvulsants used to treat epilepsy, and high intakes of vitamin K will antagonise anticoagulants that act as vitamin K anti-metabolites.

The pioneering work of DeLuca and coworkers in the USA and Kodicek and coworkers in the UK in the 1960s and 1970s led to our current understanding of the role of the kidney in forming the active metabolite of vitamin D (calcitriol or 1,25-dihydroxy-vitamin D), which acts like a steroid hormone, binding to nuclear receptors and modulating gene expression to control calcium homeostasis. Fleet *et al*. (2004) note that there has long been evidence of rapid responses to vitamin D, not associated with changes in gene expression. They discuss the evidence that in addition to its nuclear actions, calcitriol acts via cell surface receptors, leading to the formation of a second messenger and initiating a kinase cascade. Not all of these actions are concerned with calcium homeostasis; vitamin D regulates cell proliferation (and hence immune responses and cancer development) by both nuclear and cell surface receptor mediated pathways. They also suggest that plasma calcidiol (25-hydroxyvitamin D, formed in the liver) is not simply a reserve of the precursor for synthesis of calcitriol, but is important in its own right, with formation of calcitriol in extra-renal cells.

Returning to the differences between prehistoric and modern diets discussed by Duncan and Scott (2004), Demigné *et al*. (2004) discuss the problem that modern diets provide more sodium, and less potassium, than the diet of hunter-gatherers. They note that in animal foods much of the potassium is present as phosphate, while in plant foods there is a variety of potassium salts of organic anions such as citrate and malate. Metabolism of these organic anions results in the formation of potassium bicarbonate, which is critically important in the renal regulation of acid–base balance. While Ingenbleek & Young (2004) discussed sulphur metabolism in terms of the evolutionary need to conserve methionine, modern diets provide more than enough methionine, and Demigné *et al*. (2004) propose that this leads to a low grade metabolic acidosis caused by the sulphate formed by oxidation of excess organic sulphur. They suggest this may be a factor in the development of osteoporosis and sarcopenia (muscle wasting associated with ageing). This provides further evidence for the beneficial effects of consuming fruits and vegetables, and a high vegetable consumption may protect against sarcopenia in a manner quite distinct from the role of protein and energy intake discussed by Fujita & Volpi (2004).

The term prebiotics was introduced a decade ago by Gibson & Roberfroid (1995) for non-digestible components of food that confer a health benefit by stimulating the growth of beneficial intestinal bacteria, and in the last issue van Loo (2004) discussed the specificity of β(1–2)fructans of differing chain length for stimulation of different bacteria. Gibson *et al*. (2004) broaden the discussion to consider three sets of factors that are important in considering prebiotics: how they are handled in the human gastro-intestinal tract; their fermentation by intestinal microflora; and their selective promotion of bacteria associated with health and well-being. They conclude that three groups of compounds are currently promising for fortification of a range of foods: fructo- and galacto-oligosaccharides and lactulose, although other dietary carbohydrates may also prove to be useful. They conclude with the hope that new molecular microbiological techniques will permit more precise studies of the way in which different prebiotics affect individual species of intestinal bacteria; some species of bifidobacteria and lactobacillus may be more desirable than others.

Rafter (2004) considers the effects of probiotics (the micro-organisms that are stimulated by prebiotics) on the development of colon cancer. Although there is epidemiological evidence that dairy products containing lactic acid bacteria (species of *Lactobacillus*, *Bifidobacterium* and *Streptococcus)* are associated with lower incidence of colo-rectal cancer, and there is much laboratory evidence, to date there is no direct experimental evidence that probiotic cultures suppress colorectal cancer in human beings. The way in which probiotics may act is not known, but there are a number of possible mechanisms, including changed metabolism of potential or actual carcinogens and promoters in the colon, production of anti-mutagenic compounds, stimulation of host immune responses and the fact that the SCFA produced by fermentation are a significant energy source for colonic enterocytes. Although functional foods containing probiotic cultures are increasingly popular, it remains to establish their efficacy, and, if they are effective, how they act.

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