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NUTRITION IN THE 21ST CENTURY : UPDATES AND CHALLENGES

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ABSTRACT

By the next century, Nutrition Science and its application to human health will be radically different. This will be for general reasons.

The human biology of the non-nutrients in food will be much more completely understood and their potential ready for exploitation (eg flavonoids on immune function, phytoestrogens on cardiovascular physiology and bone density, salicylates on cell proliferation). There will be a more integrated analysis of the human diet by way of mathematical models so that dietary patterns and complete episodes of eating will be taken into account, not simply nutrients or other food components. Agricultural production of food will be revolutionised by genetic engineering with plants and animals for food producing a new range of products. Food technology will allow the design of numerous foods to modulate gene expression and physiological processes. Gene therapy will overcome increasing numbers of inherited metabolic disorders, like that of familial hypercholesterolaemia with auto transplantation of genetically transfected hepatocytes. Other important reasons for nutritionally-related health advances in the next century will include a definition of 'nutritional reserve capacity' - which will define the probably wide limits of variation in the human diet; and there will be increasing manipulation of human physiology and pathophysiology with a high degree of specificity, particularly in the areas of ageing, immune function, bone turnover, arterial wall biology, myocardial function, cell differentiation, cognitive function and energy balance. These changes will be both propitious for human health and requiring of discipline in food law and nutritional surveillance. The challenges will be to create a new and relevant food toxicology, engaging clinical trials and kinetic studies of food components more like what is familiar to pharmacologists, and develop a nexus between food and drug law, eg. food that is seen to be more therapeutic and medication that is seen to be more like food. Consumer food and nutrition literacy requirements will be greater than ever before to cope with the new complexities and food choice requirements. Close working arrangements will be required between agribusiness, food industry, the education and the health care professions. An appropriate ethical framework for these developments and a sustainable ecosystem for food production and healthy ways of living will be amongst the paramount challenges.

PREAMBLE

Changes in the food and health sciences as in so many other areas of human knowledge, is now faster than at in any other time in human history. But this is particularly because of the multi-and-inter disciplinatory nature of the food, nutrition and health sciences; their change is catalysed by the major progress in informatics, molecular biology, the social sciences and is proceeding in a number of areas.

HUMAN BIOLOGY AND THE NON-NUTRIENT COMPONENTS OF FOOD

Throughout the 20th century food and nutrition science has been characterised by the study of nutrients in relation to human health, mainly micronutrients, the 13 vitamins (four fat soluble and nine water soluble) and the several elements, major and minor, regarded as essential for human health; and in the latter part of the 20th century, the macronutrients namely protein, fat, carbohydrate, alcohol and dietary fibre have been regarded as central to the manifestation of protein energy malnutrition (PEM) on the one hand and non-communicable diseases, regarded as ones of excess intake, on the other. But that all nutritionally-related disease could be explained in these nutrient terms has been increasingly in dispute. One reason for a conceptual review has been the evident transition between subsistence agriculture and industrialised economies where the conjoint problems of so-called under-nutrition and over-nutrition began to be experienced. The addition of dietary fibre to the list of macronutrients was unsetting to nutrition scientists because this group of chemicals was not previouslyregarded as essential to human health and yet was increasingly shown to optimize human health. The definition of 'essentiality' seemed to have more to do with the timeframe over which the non-ingestion of a food component operated than whether or not it was consumed at all; or, perhaps, there were trade-offs between the ingestion of food compounds so that it was possible to manage with more or less depending on the intake of another - the interplay between anti-oxidant nutrients like selenium, Vitamin E and Vitamin C was an example of this. The increasing sophistication of analytic food chemistry also changed the view of food and developed an understanding that food was an extraordinarily complex set of chemicals, many of which had the potential to influence human biology, at least as powerfully, if not more so, than the so-called nutrients (Wahlqvist,1993; 1994). Isoforms of traditional nutrients like those of vitamin E (tocopherols and tocotrienols) and carotenoids (other than beta-carotene, like lycopene) were being discovered and some of these had biological activity of a kind quite distinct from that usually attributed to such micronutrients. Conditioned nutrient essentiality was also becoming a more and more recognised clinical and public headed phenomenon, with glutamine, for example, being recognised as an essential amino acid in the stressed individual (Furst 1994; Lin et al. 1992). For reasons that will be discussed elsewhere in this paper, a redefinition of food-health relationships was emerging to take account of the non nutrient components of food and their role in human health.

The corollary to these new insights has been an inevitable stimulus to the development of novel and designer foods sometimes referred to as functional foods. This is still in its infancy although it is a more comfortable development in oriental food technology, given the traditional linkage between food and medicine in eastern cultures (Wahlqvist 1988). The rational and ethical management of this explosion in food technology requires a close coalition between food technologists and health scientists.

APPRECIATION OF NUTRITIONAL MODULATION OF GENE EXPRESSION

Whereas environment, including food environment, and genetic make-up were once regarded as distinct and separate entities, there is a new appreciation that nutritional factors can modulate gene expression (Rucker, 1994). This provides us with a much more integrated view of the human organism and one whose biology requires a more ecological perspective. It also provides human biologists with the opportunity to consider how human performance may be optimised through nutritional means for a given genetic makeup.

There is a growing number of interesting examples of nutritional modulation of gene expression. It includes genes that regulate the production of transport proteins for elements like iron and zinc (Rucker 1994; Wahlqvist 1990; Morley et al. 1988) and of enzymes for the turnover of the LDL (low density lipoprotein) receptor, the apo proteins of lipoproteins, as well as enzymes that influence their turnover (Rudel et al. 1994). There is evidence that genetic expression may be determined by early childhood rearing practices where HDL cholesterol concentrations have been used as a paradigm in combined twin and adoptive register studies in Sweden (Heller et al. 1993), it is remarkable that this determination of genetic expression should last into later life, and it raises possibilities not only for family practices and genetic expression but, on a wider scale, group and community practices which may not be easily dissected by conventional studies of environmental and genetic factors with an over-attribution to genetic factors alone. Like studies also address the long term effects of early childhood growth on long term cardiovascular health (Margetts and Jackson 1993; Osmond et al. 1993; Barker et al. 1993). Yet another example of an alteration in genetic expression early in life is the work of Wilcken on LP(a) isoforms where the phenotype has been shown to change in childhood, for a lipoprotein whose concentration is dependent on phenotype and thought to be strongly genetically determined (Wang et al. 1992).

We need to understand what is changeable about genetic expression by nutritional and other environmental means, since there will be increasing interest in gene therapy of an interventionist kind to set aside the need for nutritional therapy to all appearances. There will always tend to be a somewhat simplistic view that single food or nutrient intake adjustments (Rudel et al. 1994) can deal with metabolic risk factors or disease endpoints. A good example of the imminent use of gene therapy is in hypercholesterolaemia which is known to be autosomal dominant. The majority of affected individuals develop premature coronary heart disease, yet there are some individuals in families, sometimes women, who appear to be remarkably protected against this outcome. The gene therapy in question ex vivo is the autologous transection of a portion of the liver, followed by a hepatocyte culture to genetically correct the LDL receptor defect with a recombinant retrovirus, and a reinfusion of hepatic cells into the partal circulation (Rudel et al. 1994).

NUTRITIONAL RESERVE CAPACITY

One of the biological strengths of the human species is that it is omnivorous which has allowed it to roam and feed itself across the planet Earth. When one examines the difference in human food cultures across the planet, they are remarkably diverse with more or less emphasis on plant derived or animal derived foods and, within this broad classification of food types there may be many different emphasis towards root vegetables, cereal crops, leguminous vegetables, fish or land animals of various kinds. The question is, "how different can the human diet be for comparably good levels of health?". This is a somewhat different proposition to that which has obtained in the formulation of national nutrition policies around staples of limited kind, like rice or potatoes, and dietary guidelines which emphasise a particular preferred way of eating. Low fat intakes are encouraged in most contemporary guidelines, yet long living populations from the Mediterranean to Japan and to Scandinavia may have fat intakes contributory to energy intake ranging from 25 to 40 percent, albeit of differing fat quality. Ultimately, commonalities in the human diet are to be sought for optimal health like, for example, the value of regular fish intake from the Mediterranean to Japan to Scandinavia; even here it is apparently possible for populations to be vegan, consume no fish and yet to be equally well in terms of morbidity and mortality. The International Union of Nutrition Sciences (IUNS) cross cultural study of "Food Habits in Later Life" has addressed the question of possible variation in the food intake patterns of elderly people, who have exceeded an age of 70 and found a good deal of resilience (Wahlqvist et al. 1993). The ability to describe "nutritional reserve capacity" will require an analytic capacity as for that in other areas of human physiology like that pertaining to cardio-respiratory physiology where cardiac and lung functional reserve is well understood and predict which might happen to an individual if further demands are made on cardio respiratory function with exercise, change in attitude, or illness. It can only be safe to "push" the human diet in one or other direction if this reserve capacity is understood. One of the prerequisites for the analysis of nutritional reserve capacity will be the more effective mathematical modelling of the human diet to take account not only of food components and particular foods, but episodes of eating and patterns of eating.

MANIPULATION OF NUTRITIONAL PHYSIOLOGY AND PATHOPHYSIOLOGY WITH HIGH SPECIFICITY

Advances in pharmacotherapy have taken advantage of the detailed knowledge of drug binding sites in different tissues and cells, minimising side effects and enhancing benefit. This progress has required a much more precise understanding of structure - function relationships and mechanisms of action. It is increasingly possible to achieve such precision in food component action by nutritional means. The caveat for manipulation of physiology and pathophysiology is that ultimately the human organism must work in a coordinated way in relation to its diet, with thousands of food factors operating on many thousands discreet biological mechanisms. Imbalances in the entire human diet can occur even with single factor change for a single mechanism and, therefore, it is imperative that risk-benefit analysis may be applied as we move into this mode of nutritional thinking and so that we be encouraged to take food intake in its entirety into account, in relation to overall health profiles. In the years ahead, we will need to move on from reductionist approaches to develop the new nutrition science as an integrative science requiring modelling and appreciation of chaos theory.

Ageing

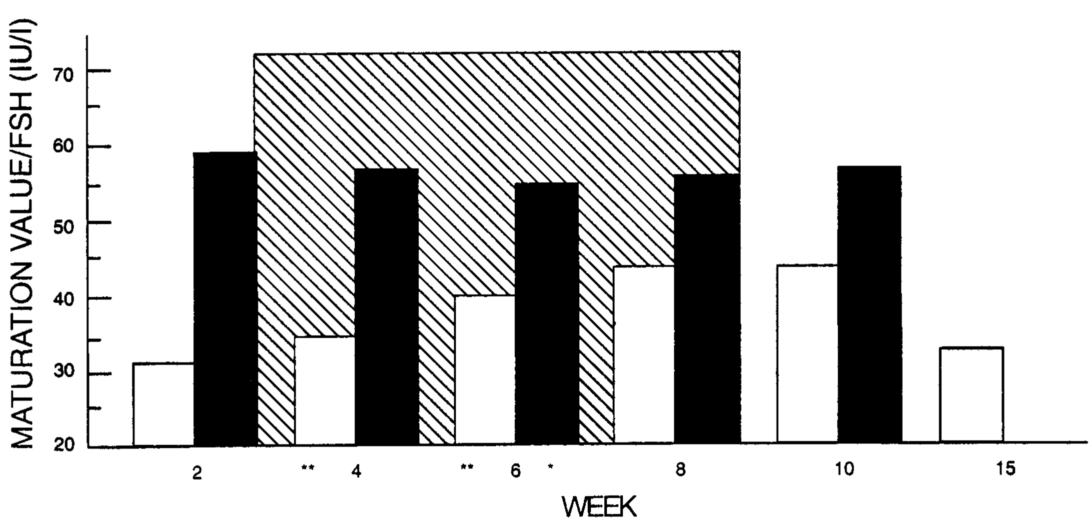
Ageing remains a poorly understood concept. Mostly what people talk about is age-related physiological impairment or age-related disease. Ageing, however, connotes some form of inexorable decline in biological function with age, as though set by a biological closk, possibly with different slopes for decline against time. There is presumably a maximal human lifespan and with it a maximal duration of certain biological functions. If this is the case, there are many age related biological phenomena which have the potential to be prevented, slowed, or reversed. Much confused thinking has shrouded the analysis of nutritional determination of age-related phenomena. This particularly applies in relation to energy balance which reflects the relationship between energy intake and energy expenditure. A case has been made by a number of investigators on the basis of animal experiments usually in rodents, that restricted energy intake is favourable for life expectancy. The problems here are several. Firstly, the plane of energy nutrition has not always been considered so that, dependent principally on the level of physical activity, it will be possible to be in positive, negative or zero energy balance at the time of energy restriction. Energy balance is likely to be more important than energy conditions to be at a higher that a lower level. This is more likely to be the case if one can eat food of higher nutritional quality, measured as nutrient density, in kilojoule per mass of food. Then one might obtain biologically useful compounds to a greater extent that if a restricted energy intake at a low energy throughput obtained. It is also possible, if one eats more, to ingest more noxious compounds as well, but this does not have to be the case. There is a high degree of consistency in prospective human studies in the findings that, with a higher energy intake people live longer (Kromhaut et al. 1982) or, at least, have lower coronary mortality rates (Lapidus et al. 1986; Kushi et al. 1985; Larsson et al. 1984; Morris et al. 1977) and, that those who engage in higher levels of physical activity live longer (Pekkanen et al.1987; Paffenbarger et al. 1986). Moreover, there is a remarkable agreement between the prospective energy intake and expenditure studies which indicates that something like an increment of 300 calories a day of energy throughput over the customary levels in an industralised community allow these mortality benefits to obtain. It seems likely that for the energy restriction studies in animals to be extrapolated to humans they would have to begin early in life with excess and ethically unacceptably, childhood mortality. Energy restriction in childhood is not a safe option.

Once people reach advanced years over the age of 70, in the IUNS studies, of "Food Habits in Later Life" there are certain features which appear to characterise the healthy:

- A high degree of food variety
- Social activity including that around food
- Regular physical activity

One area of considerable interest in relation to age, is ovarian failure which is known as the "menopause" in women. The symptoms and adverse health outcomes of the menopause seem to relate to oestrogen deficiency where there are no oocytes. However, there is now renewed interest in exogenous or food-derived oestrogens which may partially replace endogenous oestrogen activity. These compounds were first recognised in the late 1940s by the Australian agricultural scientist, Eric Underwood as contributing to disorders of fertility in sheep grazing on clover (Bennetts et al. 1946). Our group showed, in 1990, that adding plant foods, namely soya flour, clover sprouts or linseed as ingredients to the background diet of oestrogen deficient women, allowed (using in cross over design) improvement in oestrogenic indicators, vaginal cytological maturation values and reduced sexcretion of the gonadotrophin FSH (follicle stimulating hormone) in as short a time as 2 to 8 weeks. Responses were similar although not as great as those with hormone replacement therapy in post menopausal women. Moreover, they were seen in women whose background was Anglo-Celtic and where, during the study, the energy intake occupied by oestrogenic compounds was less that 5% of the total energy intake. The contrast in Asian diets is that up to 50% of the energy intake of men and women is accompanied by such compounds. The compounds are weakly oestrogenic, in contrast to hormone replacement therapy (Figure1).

There is growing evidence that such compounds, derived from soya products, lik e bean curd (tofu) may be protective against breast cancer (Lee 1992; Lee et al. 1991) and be comparable to Tamoxifen which is used in the treatment of breast cancer and which also oestrogenises the vaginal epithelium. It is an equally intriguing possibility that such compounds protect against prostatic cancer in men. It may well be that the changing intakes of phytoestrogen containing foods (Wilcox et al. 1990) account for changing incidences of breast and prostatic cancer in Asian populations, for what are basically hormone dependent and age-related tumours.



Vaginal Cytological
Maturation value FSH (IU/1)

*p < .05
**p < .01

Source: Wilcox et al.1990

Figure 1. Mean values for astrogenic indicators in postmenopausal women consuming phytooestrogens

Immune function

Some of the most important physiological changes with age are the decline in immune function. Remarkably, for all of the investment in immunology research, there has been little in the way of immuno epidemiology, let alone that combined with studies of food intake and other aspects of nutritional status. In representative samples of the Melbourne population, Lukito and Wahlqvist have confirmed the view that immune function declines with age using indices like CD4:CD8, lymphocyte subset ratios and that it may in later life affect up to 30% of the population depending on the variable used and on cut off points. It has also been shown by Chandra, in Newfoundland, that nutrient supplementation of the aged can reverse aspects of immuno deficiency and reduce the incidence of respiratory infections. Thus, some of the decline in immune function with age is probably nutritionally dependent and nutritionally reversible.

There are other circumstances in which immuno deficiency is seen and these include the treatment of disease or the management of organ transplantation with immuno suppresive agents like steroids, azithioprine and cyclosporin A. There is growing interest in the extent to which the immuno deficiency in these situations may be minimised by nutritional support. Again, disease state may be characterised by immuno deficiency as is seen with wasting states in neo plastic disease, cardio respiratory disease, cachexia, peri operative states, malnutrition and HIV (human immuno deficiency virus) positivity. In each of these situations there is a growing body of evidence that there are opportunities to improve indices of immune function through nutritional means (Lustig 1993). Micronutrients can play a role in immuno modulation as shown in Figure 2 below.

Of particular interest is the amino acid glutamine which becomes essential in the stressed individual, principally because of the requirements for it by rapidly turning over proliferating cells, like those lining the gut, and lymphocytes (van Loverem and Vos 1989). Not only glutamine, but also the non nutrient components of food like gluathione (Jones 1992) and flavonoids (Middleton and Kandaswami 1992) can play an important role. Glutathione in reduced other forms can be absorbed from ingested food and is present in relatively high concentrations in freshly prepared meats, with moderate amounts in fruit and vegetables and low amount in dairy products, cereals and breads. However, some foods are good sources of cysteine, one of the three amino acids in the tripeptide glutathione or alternatively, can produce significant amounts of the dipeptide glutamyl cysteine which can stimulate the endogenous synthesis of glutathione and, thereby, increase tissue concentrations in sites like the spleen. Whey proteins are a good example of a food low in gluthathione but capable of stimulating endogenous glutathione production (Regester 1993).

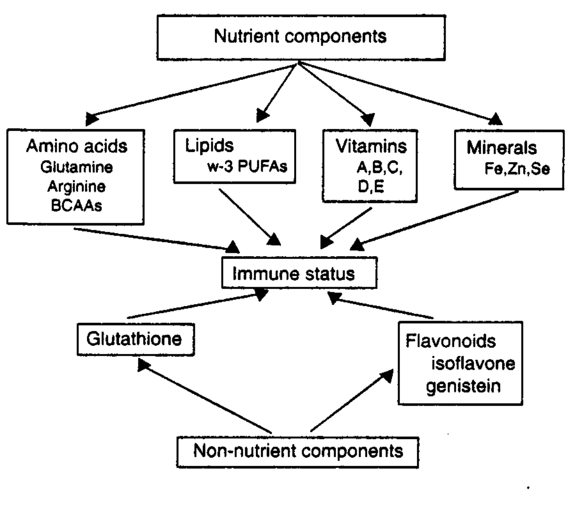


Figure 2. Food factors affecting immune status

An area of current interest is the extent to which pesticide residues may adversely affect immune function. This food safety issue is beginning to be addressed by International Agencies like the International Union of Nutrition Sciences Taskforce, Nutrition and Pollution and through the International Atomic Agency (IEA)(Thomas et al. 1990). In the event that this is a biologically significant issue, it will be of interest as to the extent to which different food patterns will protect against the immuno suppressant effects of residues. A food pattern analysis is likely to be more helpful than a single food factor analysis because of the sheer complexity of factors which may modulate immune function. A resolution of this issue like so many others, will require a modelling of the human diet.

Bone turnover

A simple view of nutrition and bone health has been that intakes of calcium will be protective against osteoporosis and the optimal Vitamin D status will protect against osteomalacia and rickets. Recently it has become clear that a number of food factors may influence calcium balance and bone density and these include sodium (which can increase calcium loss) Shklar et al. 1993; Hernandez-Avila et al. 1991; Garret et al. 1990; Anon.1988; Goulding et al.1985), caffeine and boron which has a favourable effect on calcium balance and also increases endogenous oestrogen levels. Boron at physiological intakes principally from fruits (Naghii and Samman 1993), Vitamin K dependent bone proteins like osteocalcin (Price 1988), ascorbic acid since osteopenia occurs in scurvy, copper deficiency (conceivably adversely affected with excessive zinc intakes although bone is the important storage site for zinc in the human organism (Bobilya et al. 1994; Togari et al. 1993) and even oestrogenic compounds in food are likely to be important factors in bone health.

The concept that weakly oestrogenic compounds from foods may play a role in maintenance of bone health is of particular interest since their effect may also be enhanced by the coingestion of calcium as is the case with combined hormone replacement therapy and calcium supplements in post - menopausal women (Almustafa et al. 1992). As has been already mentioned in relation to "ageing" and breast cancer, Tamoxifen is a pharmaceutical roughly equivalent in oestrogenic spectrum to food oestrogens. Studies on the effect of Tamoxifen on bone are relevant to this line of argument (Love et al. 1992). In studies over 24 months, comparing Tamoxifen with Placebo, there was a significant reduction in bone loss and even accretion in post-menopausal women. With this in mind, the view of an Asian diet rich in phytoestrogens from the point of view of age-related and post-menopausal bone loss and other health outcomes, changes rather drastically, particularly since such diets are often modest in their calcium content. A possible concern about phy- toestrogens is what they may do to see risk of endometrial cancer in women, but at the moment the incidence data for this cancer in high phytoestrogen intake groups are reassuring, although more work is required (Tkeshelashsvili et al. 1993, Wilcox et al. 1990).

Arterial wall biology

It is worth considering arterial wall biology and myocardial function separately, as far as the nutritional pathogenesis of coronary heart disease is concerned and moreover, arterial wall biology as relevance for end organ disease in the territories supplied by the cerebro vasculature, the peripheral vasculature, (supplying lower and upper limbs) the mesenteric vasculature (supplying the gut) and the renal vasculature (supplying the kidneys) Table 1.

Table 1. Nutrition - Arterial Wall Biology

1. Endothelial function (Arginine and NO)
2. Platelet aggregation (w-3 fatty acids, salicylates)
3. Vascular toxicity (B-6, folacin, B-12 deficiency and homocysteine)
4. Oxidation of lipoproteins carotenoids, phenolic compounds, phytoestrogens)
5. Serum lipoprotein concentrations (especially LDL cholesterol, HDL, I DL, LLDL triglyceride, Lp(a), apoE, CETP)

Most of the nutritional focus on atherogenesis (atherosclerosis) has been on circulating cholesterol concentrations, pricipally in low density lipoproteins (LDL). Increasingly, there has also been interest in a relatively protective form of cholesterol, the high density lipoprotein cholesterol (HDL). Also of interest are other lipoproteins or their protein components, the intermediate particles between very low and low density lipoprotein, the intermediate density lipoprotein (VLDL) and the LDL variant, LP(a), along with apoprotein E, both t otal and phenotype, and the protein that transfers cholesterol ester between lipoprotein particles, the cholesterol ester transfer protein (CETP), whose increased activity moves chol esterol fron HDL to the more atherogenic lipoprotein fractions (Table 1).

Altogether new ways of thinking about nutrition and arterial biology are now promised. Endothelial function is important in so far as the development of the atherosclerotic plaque and as far as vascular contractility are concerned. For example, the gaso dilator agent, nitric oxide is produced by endothelium, and an important precursor for it is the amino acid arginine. Interestingly, the richest source of arginine amongst food proteins is nuts. Just exactly what a higher intake of nuts, for example amongst those who may have more in the way of peanuts in their diet or sesame seeds, does for arterial function requires investigation (Sabate 1993; Fraser et al. 1992). But there are studies now indicating that people who have a higher intake of nuts are relatively more protected against coronary heart disease (Singh et al. 1992). Of course not all of the putative protection of nuts may reside in the amino acid composition of their proteins since nuts have a fatty acid profile which is either dominantly mono unsaturated or sometimes polyunsaturated (like the omega 6 richness of walnuts), and they may also be reasonable sources of phytoestrogens. That platelet aggregation can be decreased by higher intakes of omega 3 fatty acids, for example, from fish or from lean meat or from sea plants or from some land plants like rape seed and linseed, is now well known. This probably accounts for the lower coronary mortality rates amongst fish eaters (Wahlqvist et al. 1989a), and the more favourable arterial wall characteristics seen in apparently healthy people and also in people with diabetes who have a regular intake of fish (Wahlqvist et al. 1989b). However, not all the beneficial effects of fish may reside in the omega 3 fatty acid content. Acetylsalicylic acid (Aspirin) is a well known inhibitor of prostaglandin synthesis and this is generally regarded as the mechanism by which aspirin reduced platelet aggregation (Weissmann 1991). To a lesser extent, salicylates themselves can contribute to the same mechanism, whichi is of particular interest, since foods, whilst not a source of aspirin, are a source of salicylates, the most important sources being fruits (Swain et al. 1982)(Table 2).

Table 2. Salicylate Content of Food (mg/100g)

Where there are significant amounts

Vegetables	- gherkins (6.0), mushrooms (1.2), capsicum (1.2), zucchini (1.0), eggplant (0.9), green bean (0.7), tomatoes (0.3- 0.6).
Fruits	- sultanas (7.8), raisins (6.6), dates (4.5), cherries (2.8), pineapple (2.1), orange (1.7), rockmelon (1.5), apricots (1.4), strawberries (1.4), apples (1.1), grapefruit (0.7), peaches (0.7), avocado (0.6).
Drinks	- *Benedictine* (9.0), port (4.2), tea (2g leaves/100 ml water)(2.0-6.4), *Drambuie* (1.6), *Cointreau* (0.7), herbal teas (up to 1.1).
Condiments	- thyme (183), oregano (66), cinnamon (15), mint (9.4).

Source: Swain et al. (1982)

Vascular toxicity occurs with homocysteine, although the mechanisms for this are unclear. The work of Wilckens and co-workers in Sydney has shown that a significant proportion of the population has elevated homocysteine levels (Murphy-Chutorian and Alderman 1994; Lindenbaum et al. 1994). In the prospective Framingham study of risk factors for coronary heart disease, it has also now become clear that homocysteine is a risk factor for this disease. In apparently healthy populations, lower blook levels of pyridoxine (B-6) folacin and vitamin B12 are associated with higher concentrations of homocysteine. This has implications for the intake of foods which are good sources of pyridoxine like bananas, fish, nuts and liver; folacin like citrus foods, green leafy vegetables, nuts, liver and cereals; and B12 from animal derived foods.

Oxidation of lipoproteins

A great deal of interest is presently being shown in the oxidisability of lipoproteins and protection against this since, unless LDL cholesterol is oxidised, it is unlikely to be incorporated into the atherosclerotic plaque. Thus, it may be possible to tolerate a higher LDL cholesterol concentration if the molecule co-transports a spectrum of antioxidants. A spectrum is required since upon an oxidative stimulus, there are various lag times to oxidation in which individual antioxidants can act - any one alone will not fully protect the LDL molecule. So, for example, beta carotene alone is not enough to protect LDL cholesterol but a range of carotenoids including alpha carotene, lycopene, lutein and cryptoxanthin is to be preferred. The additional contribution to protection against oxidation may be conferred by various phenolic compounds and even by oestrogenic compounds (Esterbauer et al. 1989; Timmins et al. 1993; Wilcox et al. 1990). Thus it is increasingly attractive to talk about an arterial wall protective way of eating which extends well beyong a consideration of saturated fat and cholesterol intakes and how they affect circulating LDL cholesterol concentrations.

Myocardial functions

The myocardium may be more or less vulnerable to an ischaemic epidose depending on certain nutritionally determined states (Table 3).

Table 3. Myocardial Function

1. Substrate
    - Lipid
      .FFA and TG
    - Carbohydrate
      .glucose, glycogen

2. Cardiac membrane function
    - Electrical stability
    - Insulin receptor

For the sustained work in which the myocardium must engage, lipid as a fuel is to be desired for its efficiency of presentation. This may be either exogenous to the heart, to arriving from the circulation as free fatty acid bound to albumin or triglyceride as part of Chylomicra or very low density lipoprotein triglyceride (Wahlqvist et al. 1973; Boberg et al. 1972; Wahlqvist et al. 1972; Lassers et al. 1971).

Endogenous triglyceride within myocardial muscle also serves as a fuel, but must usually be in a steady state, except during exercise when these stores tend to be decreased (Wahlqvist et al. 1974). The healthy myocardium is characterised not only by driving most of its energy from lipid, but also by being a net user of lactate as a fuel, produced elsewhere in the body as a product of glucose or glycogen utilization. On the other hand, the ischaemic heart is a producer of lactate, which under these circumstances cannot enter the tricarboxyllic acid (TCA) cycle because of the myocardial redox state and how it influences the activity of pyruvate dehydrogenase. Energy demands in these circumstances, are met through glycolysis with glucose as a substrate, or through the utilization of myocardial stores of glycogen (Lustig 1993; Regester 1993; Rucker 1994; Wahlqvist et al. 1973; Kaijser et al. 1972; Lassers et al. 1971).

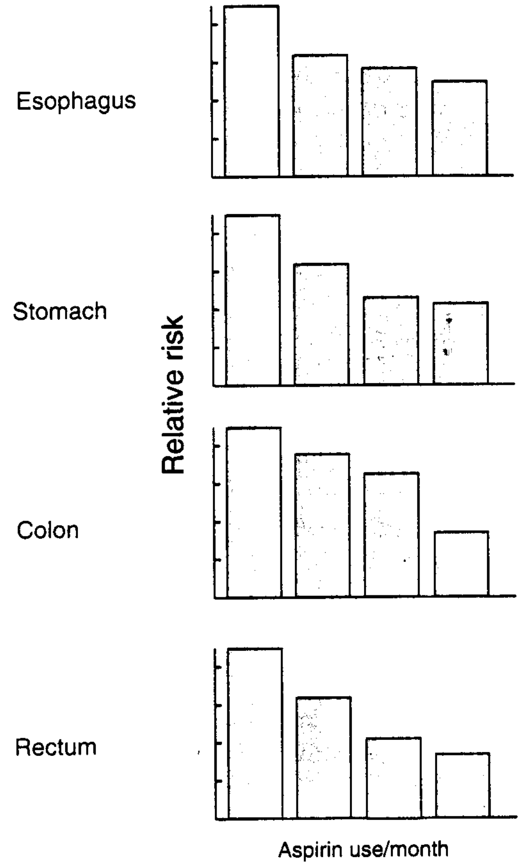
This background knowledge of human myocardium metabolism, is of interest in that, by increasing the relative energy intake from carbohydrate, the angina threshold increases and the heart tends to produce less lactate (Wahlqvist 1985). Thus, at a time of critical blood flow, the human heart may depend for its viability on the dietary pattern of the individual affected. The availability of glucose for uptake by the human heart is also influenced by abdominal obseity (Wahlqvist et al. 1994). Whatever determines the deposition of omental fat, including positive energy balance and other factors, will be additional mechanisms contributing to myocardial damage.

Cardiac membrane function can also be determined by diet, notably the essential fatty acid profile of the diet. Charnock and MacLennan in the CSIRO Division of Human Nutrition in Adelaide have shown that the hierarchy of protection against electrical instability of the heart ranks, from the highest protection to the least, omega 3 polyunsaturated acids, omega 6 polyunsaturated acids, omega 9 monounsaturated fatty acids and saturated fatty acids. The dietary profile of these fatty acids can influence the fatty acid composition of the cardiac membrane and, in turn, its electrical stability. It is this phenomenon which is likely to account for the impressive reduction in total mortality seen in the Dart Study in Wales where three meals of fatty fish a week reduced total mortality by 30% at 2 years in comparison with those who did not eat fish (a secondary prevention study in those who had already sustained a myocardial infarction).

There is also evidence now that the sensitivity of the insulin receptor to insulin is determined by its fatty acid composition and that it is most sensitivie when composed of relatively more omega 3 fatty acid. Although the determination of glucose uptake by the human myocardium is only partly dependent on insulin, also being dependent particularly on free fatty acids (Wahlqvist et al. 1973), it is likely that myocardiac insulin receptor composition will also play a role in the well being of the human myocardium when threatened with ischaemic injury.

Studies on the reduction in total mortality or cardiac deaths within months of dietary change encourage the view that nutritional pathways, other than those through lipoprotein and the arterial wall, are important. Yet another study along these lines is that of De Logeril (De Logeril et al. 1994), which studied the Mediterranean diet, characterised by relatively more fish, plant food and monounsaturated, as well as omega 3 alpha linolenic acid. The survival curves of experimental and control groups diverged markedly over the 5 years after randomisation, for total mortality and cardiac deaths.

There are yet other pathways connecting food patterns to myocardial events and these operate through



Source: Thun et al. (1993)

Figure 3. Relative risk of oesophogeal, stomach, colon and rectal cancers

nutritional determinants of blood pressure (sodium/potassium ratios, alcohol, fatty acid composition, plant food orientation of the diet) and, as has been mentioned, abdominal obesity.

Cell Differentiation and Turnover

The regulation of cell differentiation and turnover is of increasing interest. Firstly, butyrate is a powerful cell differentiator. This effect has been shown for different cell types, including the coloncytes lining the large intestine and also for breast cancer cells. In the former, the production of butyrate through fermentation of resistant starch in the large intestine is of particular interest. Resistant starch from foods like noodles and rice, eaten warm at the table, where the starch is gelatinised during cooking and then assumes a crystalline structure during cooling is greater than produced from soluble dietary fibre. This has provided a new way of thinking about otherwise low dietary fibre foods from the point of view of their potential protection to protect against colorectal cancer. It is possible that perturbation of circulating concentrations of butyrate may be relevant to, say, the development of breast cancer.

The finding that acetylsaslicylic acid (Aspirin) can protect against gastrointestinal tumors in the oesophagus, stomach, colon and rectum has particularly interesting applications for the value of foods as sources of salicylates (Thun et al. 1993)(Figure 3). An ability of aspirin or salicylate to alter cell membrane properties through interference with G-protein regulation of adhesion molecules in cell membranes, may be an attractive mechanism for these effects. It was thought that salicylates only mode of action was through the inhibition of prostaglandin synthesis.

The tripeptide glutathione can be absorbed from the gut and then have anti-oxidant immunomodulatory and anti-carcinogenic properties (Shklar et al. 1993; Regester 1993). In experimental animals oral cancer tumour burdens are reduced with supplementary glutathione (Shklar et al. 1993), and in experimental colon cancer, the stimulation of endogenous glutathione production by whey proteins reduces tumor burden (Regester 1993).

Cognitive function

The field of impaired cognitive function, with the ultimate development of dementia has been a vexed one from the nutritional point of view. A lot of attention has been paid to the accumulation of aluminium in the neuro fibrillary tangles in the brains of Alzheimer disease sufferers, but most workers feel that aluminium is not of primary pathogenetic significance (Strittmatter et al. 1993; Jeandel et al. 1989). However, there are at least three nutritional factors which now appear to be coming together as of pathogenetic importance. The first is that zinc can modulate the function of the beta A4 amyloid protein precursor of Alzheimer's disease in brain and in peripheral blood, and zinc can also induce acutely changes in cognitive function in susceptible individuals (Halliwell and Gutteridge 1985). The second is that the Apoprotein E4/E4 genotype confers on the apoE protein in the brain a great propensity for beta A4 peptide to accumulate in senile plaques in Alzheimer's disease. This seems to also relate to the increased density of LDL receptor related protein, (LDL RP) one of the two low density lipoprotein receptors, in astrocytes, in the brains of those with Alzheimer's disease. The third is that glutathione may play a role in achieving an adequate state of anti-oxidation in brain and may not do so as effectively in Alzheimer's disease (Regester 1993).

ENERGY BALANCE

The table below (Table 4) summarizes the various food factors which may influence energy balance.

Table 4. A Classification of Factors in Food of Potential Importance for Energy Balance and Fat Distribution in Humans

A. Physico-chemical factors
- Dietary fiber with effects on particle size and viscosity
- Extrusion technology to alter particle size and viscosity

B. Chemical factors

1. Macronutrient
- Carbohydrate
- Dietary fiber
- Protein
- Fat
- Amount
- Quality (degree of polyunsaturation, omega-3 or omega-6 fatty acid content)

2. Micronutrient
- Thiamin
- Zinc

3. Non-nutrient
- Caffeine
- Phytoestrogens
- Capsaicin

Thus, there are more options, by way of food, to influence energy under and over-nutrition than previously canvassed in regard to the proximate analysis of food for macronutrients and particular Atwater factors.

FOOD LAW

Progressive changes in food products for acceptability, transport, storage, safety and medical purposes, and in therapeutic goods in the direction of food, will alter the boundaries between food and medicine, much as they always have been blurred in the Orient. Advances in food and therapeutic Food Law will be needed to accommodate and direct these changes.

NUTRITIONAL SURVEILLANCE

The new Nutrition Sciences and the changes in ways of eating will require close nutritional surveillance lest unexpected problems emerge. More and more, clinical trials of food products will need to precede their introduction into the market place.

ECOSYSTEMS

New and increasing pressures will be placed on the earth's ecosystems as its population doubles in the first half of the 21st century; and as food production and processing changes. Nutrition-health sciences must strive to minimise the adverse ecological effects, and, hopefully improve ecosystems. For example, the case to eat more fish will grow, but it will not be possible to meet the demand from existing natural fisheries, but may be possible from fish farms developed in ecologically attractive ways.

CONSUMER FOOD AND NUTRITIONAL LITERACY

Whereas staying within one's traditional food culture simplified one's nutritional decision-making this will be less and less possible. Food labels are diversifying rapidly and the market place is replete and new products and the information that goes with them. Helpful advice will depend on being literate about food origins, processing and composition and about health messages and claims.

ETHICAL FRAMEWORK

A new imperative for a conjoint and cohesive ethical framework for agriculture, food industry, the education system and health care professionals alike, that has to do with food and health is with us.

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