

## Review Article

# Global nutrition problems and novel foods

Graeme A Clugston MB, BS, MSc, DCH, PhD, DLSHTM and Trudy E Smith MSc, RD, RPHNutr

*Department of Nutrition for Health and Development, World Health Organization, Geneva*

The world's demand for food is becoming greater than ever. The current world population of 6 billion will exceed 8 billion in 2025 and new innovations are needed to meet the growing challenges of the poor and hungry world. Novel foods produced through biotechnology may help alleviate the problems of poverty and food insecurity, but only if steered by continual policy development and actions at the regional, national and international levels. The great progress made with iodized salt in combatting iodine deficiency disorders, through global partnership, provides inspiration for future applications of nutritional science and food technology to public health problems in the developing world. The attributes of biotechnology-produced novel foods are complex. As outlined in the present paper, they may also provide the diets of people in developing countries with more energy, protein and micronutrients. This could thereby reduce the extent of suffering associated with public health problems such as vitamin A deficiency and iron deficiency and anaemia, which affect millions. However, more research and resources need to be focused on the problems and opportunities that face small farmers and poor consumers in developing countries. In particular, attention should be focused on the foods that feature most predominately in their diets such as bananas, cassava, sweet potatoes, rice, maize, wheat, millet and yams, and unless this exciting science is given a chance to prove itself in the developing world we will never know if it is in fact the so-called "biosolution". Paradoxically, overnutrition, obesity, and related diseases characteristic of the developed world, are becoming serious public health problems in countries with widespread food insecurity. Children suffering from undernutrition today could well be afflicted with chronic diseases of development as adults. The economic development that has led to improved food security and better health in some countries needs to be harnessed, while at the same time incentives to avert the adverse health effects of the nutrition transition need to be taken. The potential of novel foods to alleviate undernutrition is becoming more apparent. But they are unlikely to have a role in the prevention of diseases associated with overnutrition in developing countries, who use growing incomes to replace their traditional diets high in complex carbohydrates and fibre, with diets that include a greater proportion of fats (especially saturated) and sugars. More aggressive public health policies are needed to steer populations in nutrition transition towards a healthy lifestyle and diet rather than investing in particular novel foods. In developed countries the wide variety of macronutrient-modified foods available to consumers has enabled people to eat a more healthy diet, along the lines of the recommendations issued by many governments, and so reduce the risk of diseases such as obesity, cardiovascular disease and cancer. Novel foods containing macronutrient substitutes can be a useful adjunct to consumers if they are used to supplement an overall effort to reduce fat and calories as part of a balanced diet. On a population basis it is difficult to ascertain the impact of such foods on the prevention of obesity, not least because of the confusion surrounding the role of individual macronutrient components in its aetiology. Efforts to encourage individuals, especially children, to eat healthy diets and have an active lifestyle are more likely to help prevent the growth of this already epidemic problem. The discovery that the intake of certain foods and their associated components can exert profound physiological effects has been accompanied by research into the potential health-promoting effects of functional foods. Many of these foods and beverages are already consumed by large population groups worldwide, and have been for centuries. It is unlikely that such foods or drinks are going to result in any untoward effects in these population groups. But for many functional foods, more research needs to be conducted in humans to judge whether or not they provide a true health-promoting edge, as well as ensuring that they conform to rigorous safety requirements. The present paper points to a future in which specific foods help protect against diseases to which we are genetically susceptible. There is no doubt that important applications of all aspects of nutritional science, coupled with advances in genetics and the optimization of dietary intake, are on the horizon. But only a meticulous scientific approach eliciting highly significant results will ensure the success and acceptability of this new discipline. Nutrigenomics will lead to development of diets targeted to individuals, and as new information on diet–gene interactions becomes available and genotypic analyses are used to enhance the quality of medical care, there are enormous ethical, legal and psychosocial issues that will need to be addressed. Safety evaluation is vital for all novel, functional or formulated foods, whatever their disease-preventing potential. It is equally important that they are considered as and eaten as part of a healthy balanced diet, not in isolation. This will help to dispel the notion that there are good and bad foods, and instead promote the significance of good and bad diets. Only then are these foods likely to be an important part of the global agenda for combatting malnutrition.

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**Correspondence address:** Dr Graeme A Clugston, Director, Nutrition for Health and Development, World Health Organization, Geneva, Switzerland.  
Tel: + 41 22 791 3326; Fax: + 41 22 791 4156  
Email: clugstong@who.int

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## Introduction

### *The spectrum of malnutrition*

During the last 30 years major advances have occurred in food production, largely as a result of the adoption of 'green revolution' technology and the development of high-yielding varieties of cereals. As a result of this we live today in a world of abundance compared with the relatively recent past. The proportion of population in the developing world that is malnourished fell from 46.5% in the early 1960s to 26.7% in 2000. Despite these improvements, hunger and malnutrition continue to dominate the health of the world's poorest nations. In addition to the problem of insufficient protein and energy intake, deficiencies of micronutrients such as iron, iodine, and vitamin A affect millions of people in the developing world.<sup>1-3</sup>

Along with the existing level of malnutrition, an increasing world population will have a major impact on the strategies required to meet the future global food and nutrient needs. The United Nations (UN) estimates that the world's population will grow from 6 billion in 2001 to 8 billion in 2025 and to 9.4 billion in 2050. Most of this increase (93%) will take place in the developing world. Just as the food requirements of today's population of nearly 6 billion people could not have been met by the technologies of the 1940s, we cannot assume that current practices will feed the population of 8 billion expected by 2025. New approaches are needed in addition to existing improvements in agricultural practices and food processing.<sup>4,5</sup>

World economic development and the associated improvement and progressive globalization of the human diet is also taking its toll on public health. As the world economy grows, differences in the structure of diet between nations at different levels of income are becoming less marked. Diets once high in complex carbohydrates and fibre tend to give way to more varied diets with a higher proportion of fats, saturated fats and sugars. These changes in diet structure are accompanied by changes in patterns of disease, with a shift away from infectious and nutrient-deficiency diseases toward higher rates of coronary heart disease, diabetes, some types of cancer, and obesity. Obesity is now a massive global epidemic, especially in rapidly industrializing and industrialized countries, affecting more than half of the adult population in some cases. A major challenge facing health professionals and agencies for international development is how best to promote economic growth while preventing the undesirable health effects of this nutrition transition.<sup>2,6,7</sup>

### *Meeting the challenge using novel foods*

The food and agricultural industry's ability to produce safe, nutritious and affordable foods globally depends largely on new technologies. Novel foods produced by biotechnology, dubbed the 'biosolution', have the potential to increase food yields enough that future global food shortages could be

eliminated. These foods have greater disease resistance, insect tolerance, and resistance to herbicides used to control weeds. They also have the potential to last longer and, in the case of fruits and vegetables, be better tasting. Enhancing the nutritional content of staple foods by using conventional plant breeding and biotechnology may also improve micronutrient nutritional status and reduce the risk of disease. For example, research is under way to introduce crops containing beta carotene to help alleviate vitamin A deficiency (a public health problem in 118 countries).<sup>2,8</sup>

For decades governments and the food industry in developed countries have responded to the threat of widespread nutrient deficiencies by introducing measures such as adding iodine to salt and B vitamins to bread and cereals. These measures have played a major role in the virtual elimination of traditional deficiency diseases in the industrialized world. Today people in developed countries enjoy a greater variety and quantity of foods than ever before but are more likely to succumb to the effects of overnutrition. In this respect the food industry has also been highly responsive, and in recent years there has been an explosion in the number of 'sugar-free', 'fat-free' or 'high fibre' versions of traditional foods available on the market. Furthermore, food scientists are now exploring the health-promoting potential of physiologically active substances present naturally in foods known as phytochemicals, some of which may positively influence responses to diseases such as cancer and cardiovascular disease (CVD).<sup>9,10</sup>

The major forms of malnutrition and nutrition-related disease prioritized by the World Health Organization (WHO) include protein-energy malnutrition (PEM), iodine deficiency disorders (IDD), vitamin A deficiency (VAD) blindness, iron deficiency anaemia, obesity, diet-related cancer, CVD, and osteoporosis. The present paper examines the potential impact of novel and functional foods on the prevention and/or treatment of all these disorders. It also outlines some possible applications for these foods in the postgenomic era.

### **Protein-energy malnutrition**

The WHO estimates that currently 150 million children under 5 years of age (26.7% of the world's children in this age group) are malnourished when measured in terms of weight for age, and 182 million are stunted. This global burden of malnutrition is rooted in poverty, underdevelopment, and inequality. But in some areas rapid population growth is an important contributing factor. In Africa natural disasters, wars, population displacement and civil disturbances have also contributed to the continuous increase in the prevalence of malnutrition. However, geographically it is Asia (especially South Asia) that is home to more than two-thirds of the world's malnourished children compared with the 25.6% in Africa and 2.3% in Latin America.

Although food insecurity is expected to be reduced in East Asia and to a lesser extent in South Asia and Latin America, it could accelerate significantly in Sub-Saharan Africa, West Asia and North Africa. A 1997 report by the International Food Policy Research Institute predicted that by 2010, every third person in Sub-Saharan Africa is likely to be food-insecure compared with every ninth person in South Asia and every twentieth person in East Asia.<sup>11</sup> Pervasive poverty rather than food shortage is frequently the underlying cause of hunger, limiting an individual's access to food. Poverty also exacerbates access to education, health-care services and a clean living environment, while malnutrition coupled with a poor education often impairs employment and therefore earning prospects, and ultimately less and less money to buy food.

Genetically improved novel foods with a higher yield potential, higher yield stability (i.e. more resistant to diseases and insects) and greater production efficiency have the potential to alleviate food insecurity and malnutrition in the world's most underfed populations. In the developing world reductions in the prevalence of PEM have generally been accompanied by a rapidly increasing output of food staples. Furthermore, countries that industrialize almost always do so after successful staples yield growth.<sup>3,8</sup> Several approaches are useful in raising yield potential of staple crops such as conventional hybridization and selection, widening crop gene pools through hybridization to exploit and improve traits (such as yield) and modification of plant types to increase genetic yield potential (e.g. modern high-yielding rice). Several biotechnological approaches for increasing crop yield potential are being investigated; for example, the introduction of cloned novel genes through transformation. Starch levels in potato plants have been successfully enhanced in field conditions using genetic transformation of the gene encoding for the enzyme involved in starch biosynthesis.<sup>12</sup> Seeds with greater nutritional value have also been produced, by increasing the levels of essential amino acids, vitamins and bioavailable iron. Additional traits that are already available and could help food production if transferred into crops in poor countries include more nutritious oils and better fatty acid profiles, and delayed overripening of fruits and vegetables.

Novel foods genetically improved to withstand the attack of diseases and insects could also contribute to food security. Numerous varieties of cereals with multiple resistance have been developed, especially by the introduction of novel genes for pest resistance from unrelated plants, animals and microorganisms into crop plants (in particular genes from the bacterium *Bacillus thuringiensis* or Bt). High-level-resistance varieties of maize, rice, potato, and cotton have increased or maintained crop yields, with significantly reduced use of insecticides. Scientists in many different countries are developing disease-resistant crops that are specific to their regions and diets. For example the sweet potato is a staple food for many countries including Kenya and Uganda. Unfortunately a virus carried by aphids can ruin up to two-thirds of a harvest and many African farmers

cannot afford the insecticides needed to prevent the spread of aphid infestation. Production of a virus-resistant sweet potato plant would be an economic bonus to some areas in Africa suffering from food insecurity and malnutrition.<sup>3,5</sup> Stable varieties of soybean, potato, maize and canola are already in large-scale agricultural production.

It has been proved that biotechnology can greatly advance staples farming and, as outlined in the previous section, the production of novel foods is undoubtedly a ray of hope in the fight against malnutrition. However, there has been criticism of the biotech industry for investing more tools and resources in the production of animal feed on large farms for rich consumers, rather than increasing staples yields for poor farmers in developing countries. For example, in 1998 developing countries held only 15% of the area planted with transgenic crops.<sup>13</sup> The specific crop traits sought have focused more on ways to save labour and improve herbicide resistance rather than yield enhancement and land-saving. More resources and research need to be directed towards problems in developing countries where this powerful tool has the capacity to alleviate food security and malnutrition. There is theoretically enough food in the world now to feed all people. Therefore, it is equally essential to consider how genetically modified foods will be the biosolution to world hunger in the absence of global cooperation and a fundamental rethinking of the strategy between private sector companies, public activities, and government institutions in rich and poor countries. Otherwise the politics of food are more likely to lead to these novel foods being part of the problem, rather than part of the solution.<sup>14-16</sup>

### **Iodine deficiency disorders**

Iodine deficiency disorders affect more than 740 million people, 13% of the world's population, while 30% of the remainder are at risk. These disorders constitute the single greatest cause of preventable brain damage in the fetus and infant, and of retarded psychomotor development in young children. Preschool children and pregnant women in low-income countries are at greatest risk, posing serious public health problems in 130 developing countries.<sup>1</sup>

Although the strategy adopted to tackle IDD, the iodization of salt, has not involved novel foods as defined in the strictest terms, the extent of its success both in terms of effectiveness and 'minimal cost for maximum benefits' deserve discussion here. Salt was chosen for a number of reasons. For example, it is widely consumed by most people in a population and the costs of iodizing it are very low at around 5 cents US per person per year. Since the World Health Assembly took a pioneering step urging action by Member States to eliminate IDD as a public health problem in 1990, extraordinary progress has been made in increasing the number of people who consume iodized salt. In 1990 only 46 countries had salt iodization programmes; by 1998 the number had increased to 93, more than 80% of which have legislation on iodized salt. Furthermore, where salt iodization has been implemented for more than 5 years, improvement in iodine status has been dramatic.<sup>1</sup>

The level of political commitment shown by so many countries nationally has been a major contributing factor towards the goal of eliminating IDD through the iodization of salt. From the perspective of a national government, the elimination of IDD can offer numerous positive outcomes for the promotion of national health and development. For example, increased child survival, increased child learning, greater economic productivity, and better quality of life. The great progress made through global partnerships between people, government, agencies, industry and the multidisciplinary non-governmental organization, the International Council for the Control of Iodine Deficiency Disorders, provides a model for other similar translations from nutritional or food science to international public health.<sup>1,17</sup>

### **Vitamin A deficiency**

Pregnant women and preschool children in low-income countries are also most vulnerable to VAD. Africa has the highest prevalence of clinical VAD, while the highest number of clinically affected are in South-East Asia. In children, VAD is the primary cause of preventable severe visual impairment and blindness. The WHO estimates that between 250 000 and 500 000 VAD children become blind every year, and approximately half of them die within a year. Vitamin A deficiency also reduces resistances to infections so that the risk of severe illness and death from common childhood infections, particularly diarrhoeal diseases and measles, significantly increases.<sup>2</sup>

Breast-feeding plays an essential role in providing an adequate vitamin A intake in infants and young children. In older children and the rest of the population, the challenge is to make vitamin A-rich foods accessible and affordable. Novel foods, such as 'Golden Rice' genetically modified to contain vitamin A, may have a future role to play in helping to solve this problem. The International Rice Research Institute has started a project using genetic transformation and conventional hybridization techniques to produce a beta carotene-containing rice available for large-scale cultivation during the next 3–4 years. The entire daily vitamin A requirement may be provided by eating as little as 300 g of the cooked rice per day. The introduction of crops containing beta carotene through breeding programmes is also possible. For example, carotenoid pigmentation was present in older varieties of bread wheat, but this century has seen these varieties phased out due to market demand for breeding to be focused on the production of wheat for white flour. Similarly, it is possible to obtain high-carotene types of maize that are also high yielding, but consumer demand for white maize lacking carotenoid content has been higher in recent years.<sup>1,2,18–21</sup>

In developed countries fortification of margarine with vitamin A has been in place for years. Food fortification programmes are also being implemented by an increasing number of developed countries. The addition of vitamin A to sugar in Guatemala has demonstrated the importance of creating consumer demand, coupled with accommodating producers and policy makers, to sustain a fortification pro-

gramme and tackle an important public health issue and humanitarian concern.

However, dietary improvement is likely to be more sustainable than supplementation or food fortification. Strategies that aim to improve dietary intake by introducing novel varieties of traditionally eaten foods (in this case containing beta carotene) are likely to be more acceptable to vulnerable populations than increasing the production of, or facilitating access to, foods rich in vitamin A that are not traditionally eaten. Supplying micronutrients to vulnerable populations in developing countries by using conventional plant breeding and biotechnology is also low cost and sustainable. Foods such as Golden Rice may therefore help to alleviate VAD without changing crop patterns, eating habits, implementing expensive logistic interventions, or imposing recurring costs that accompany supplementation and fortification programmes.

### **Iron deficiency and anaemia**

Iron deficiency is the world's most widespread nutritional disorder, affecting both developing and developed countries. In developing countries the risk of anaemia is increased because iron deficiency is so often accompanied by other micronutrient deficiencies, parasitic infections and chronic infections such as HIV. In the poorest populations the usual diet lacks variety and is based on cereals that are low in iron and contain high levels of iron absorption-inhibiting substances. The WHO estimates that nearly 2000 million people worldwide, or approximately one-third of the world's population are anaemic, and iron deficiency may affect more than twice as many. Iron deficiency and anaemia (IDA) affects all age groups, and their impact presents a major hurdle to national development.<sup>1</sup>

Strategies to control IDA to date have been based on a combination of iron supplementation, dietary approaches, food fortification, and other general public health measures to address other causes of anaemia. Dietary improvement strategies have not been particularly successful because increasing the amount of bioavailable iron in the diet implies ensuring access to foods that are unaffordable and frequently unavailable to at-risk populations. However, more and more countries are introducing fortification programmes.<sup>2</sup> Novel foods have the potential to make a huge contribution to the battle against IDA. Not least because few active programmes in both developed and developing countries have succeeded in reducing iron deficiency and anaemia. Contributing factors include a failure to recognize the causes of iron deficiency and anaemia, lack of political commitment to control it, and inadequate planning of control programmes. A programme utilizing genetically modified high-iron foods to combat IDA will also have to address ways to overcome these barriers.<sup>2,18</sup>

Since 1992 the International Rice Research Institute has also been working to develop improved rice varieties with high iron and zinc contents. The problem is that rice varieties with high iron and zinc contents are tall, traditional and low-yielding. As a result efforts are underway to develop

improved breeding lines with elevated levels of iron and zinc. Any improved rice varieties produced are then subjected to human feeding trials to determine the bioavailability of the iron.<sup>5,18,21</sup> Efforts are also under way to increase the micronutrient content of other cereals through genetic engineering. In 1999 Goto *et al.* published a paper describing how they transferred the ferritin gene in soybean to rice. The iron content of the transgenic seeds was up to threefold greater than that of the untransformed controls.<sup>22</sup> Genetic engineering has also been used to increase the bioavailability of iron in rice diets by eliminating phytate. A Swiss team has introduced a fungal gene for the enzyme phytase which breaks down phytate, thereby improving the bioavailability of iron in rice diets.<sup>21</sup>

Fortification of food with iron is common in the industrialized world. Wheat flour fortified with iron contributes approximately 40% of the dietary intake in Sweden, 20% in the USA, and 10% in the UK.<sup>23</sup> There are several functional foods available on the market to people in developed countries that have been modified to contain higher/high levels of micronutrients, including iron. Many breakfast cereals for example contain at least 25% of the recommended daily intake of iron and in the USA some contain 100%. Iron fortification of infant formulas and cereals has been shown to be effective in combatting iron deficiency in this target group. There are also many types of biscuits and fruit juices manufactured for babies and infants that have been fortified with iron.

Efforts to control IDA, as with all micronutrient deficiencies in the developing world, require holistic planning and systematic implementation that integrate into short- and long-term strategies adapted to local conditions and resources. Partnerships at all levels are essential, including community participation. These concepts apply whether the programme focuses on the introduction of iron-enhanced modified rice or otherwise. In industrialized countries the regular consumption of some iron-enriched functional foods, as part of a balanced diet, can make a significant contribution to the overall dietary iron intake and help prevent iron deficiency.

### **Overweight and obesity**

At the other end of the malnutrition scale, obesity threatens to become the leading cause of chronic disease in the world. Paradoxically coexisting with undernutrition, evidence suggests that overweight and obesity have reached epidemic proportions globally. That is, both developed and developing countries are seriously affected. Furthermore, because the problem is increasing rapidly in children as well as adults, the true health consequences may become fully realized only later. In 1995 there were an estimated 200 million obese adults worldwide, and 18 million children under 5 years of age were classified as overweight. In 2000 the number of obese adults was over 300 million. In many developed countries more than 50% of the population is overweight.<sup>1,2,24</sup>

The health consequences of obesity are well-known. It is a complex condition with serious social, health, metabolic

and psychological dimensions that affects virtually all age and socioeconomic groups. In many developing countries, such as India and China, obesity coexists with undernutrition. In Africa and Asia, obesity is still relatively uncommon, and it is more prevalent in urban than rural populations, but in economically advanced areas prevalence rates may be as high as industrialized countries. The WHO estimates that more than 115 million people suffer from obesity-related problems in developing countries.<sup>1,6,25</sup>

As a result of this epidemic, policy makers and health planners around the world have been collecting information, formulating strategies and allocating resources to combat overweight and obesity in their respective countries. However, public health experts face a quandary: describing patterns of obesity can help to identify and target high-risk groups but there is little evidence that intervention strategies prevent obesity in these groups or the general population.<sup>24</sup> In this respect it is difficult to see how novel foods can make an impact on the enormity of this problem, especially considering the complexity of its aetiology.

Dietary guidelines advising a reduced fat intake to no more than approximately 30% of total calories have been issued by most governments in developed countries for more than a decade. These followed research demonstrating that high-fat diets (particularly saturated fat) increased the risk of CVD, obesity and some types of cancer. This triggered a proliferation of food products targeted at consumers seeking a more healthy diet. Novel foods containing fat replacers such as olestra, and artificially sweetened foods and drinks containing products such as aspartame, are now widely available. Achieving long-term dietary change is difficult, and sensory preference for fats and sweetness is a characteristic human trait.<sup>6,26</sup> So while these novel foods are no substitute for long-established dietary principles of variety, balance and moderation, they do provide additional good-tasting food choices (of those foods that people have most trouble resisting) that can help people reduce fat and/or calorie intake in an overall effort to reduce fat and calories in their diets. This is assuming that they are substituted for their full-fat counterpart and not eaten in excess on the premise of being calorie free, which they are not.<sup>27</sup>

The role that these foods have to play on a population basis is far less clear. For example, epidemiological analysis of nutrient intake and obesity provide modest, but inconclusive, evidence that high-fat (low-carbohydrate) diets favour the development of obesity. In terms of prospective studies, there are still too few from which to draw conclusions about the role of dietary fat in the development of obesity.<sup>28</sup> In addition, although total fat consumption as a percentage of calories has declined slightly on a population basis in many countries, total caloric intake has risen, along with the prevalence of obesity.<sup>25,29</sup> So while an excessive intake of fat on an individual basis certainly contributes to the high prevalence of obesity, an increased consumption of novel foods that are fat free or fat modified cannot be excluded as a possible cause of excess calorie intake and weight gain. This is because it is not clear that the percentage of fat in the

diet is an independent risk factor for the development of obesity, and the role of fat-modified novel foods (and to an even greater extent other macronutrient substituted foods) in the development or treatment of obesity is unsubstantiated. Furthermore, although dietary treatment is fundamental to the management of obesity, the increased prevalence seen globally results from a series of fundamental changes in the world's social structure, which make any potential role for novel foods at this stage seem relatively insignificant. This is demonstrated better by looking at developing countries in nutrition transition.

An increasing availability of food, urbanization, and a reduction in physical activity have all contributed to the high prevalence of obesity seen today. Rapid urbanization has a major influence in accelerating the nutrition transition. This is especially apparent in Asian countries, so that developed and developing nations can be found in the same geographical region. Such regions once shared a similar diet structure and a typical Asian diet was consistently described as being low in fat and high in carbohydrates. But nutrition transition involves a shift from a limited number of high-carbohydrate staples to a more diverse diet that becomes increasingly available to more people, and there is evidence that the globalization of the human diet has resulted from an increased availability and intake of cheap vegetable fats, and to a lesser extent sugars, coupled with a preference for these foods. Parallel with these changes in diet are equally dramatic shifts in activity and body composition patterns in all age groups. Now societies that had virtually no reported obesity a decade ago have a growing public health problem affecting adults and children.<sup>2,6,7,30</sup> Novel or functional foods for the prevention or treatment of obesity do not have a significant role to play in the public health agenda for these nations in transition. Appropriate nutrition policies and programmes for education and intervention that can avert the adverse health effects of the nutrition transition, but at the same time preserve dietary diversity, need to be developed. Novel foods have perhaps greater potential to influence the diseases for which obesity is a risk factor.

### Diet and cancer

There are 10.3 million cases of cancer per year.<sup>2</sup> The World Cancer Research Fund and the American Institute for Cancer Research estimate that: (i) between 30 and 40% (3–4 million cases) of all cancers are preventable by appropriate diets, physical activity and maintenance of appropriate body-weight; and (ii) diets containing substantial and varied amounts of vegetables and fruits will prevent 20% or more of all cases of cancer.

One of the most consistent findings in recent years is that a sufficient consumption of fruits and vegetables reduces the risk of developing chronic diseases such as cancer. Although the nutrients they contain such as dietary fibre, vitamin C and E and beta-carotene, are considered to be protective against some types of cancer, there are a number of other physiologically active food components that may also provide protective effects. Food components that have been

shown to inhibit the development of some types of cancer in laboratory studies include phenols, flavones, indoles, protease inhibitors, isothiocyanates and allyl sulphides.<sup>31,32</sup> These exciting discoveries have led to research on the development of functional foods incorporated with some of these natural components or phytochemicals to serve specific physiological or pathological health benefits. Furthermore, many have physiological effects at levels found naturally in foods. A few examples with specific reference to cancer are discussed.

Apart from provitamin A activity, carotenoids possess important anti-oxidant, immunoenhancement, anticarcinogenesis, and antimutagenesis characteristics. Because carotenoids such as beta-carotene and lycopene have anti-oxidant actions as well as the ability to interact with free radicals and reduce oxidative stress, they may also help protect against heart disease. Much attention in the 1990s focused on beta-carotene supplementation and lung cancer. But several trials have been completed with none confirming a protective effect, and some studies showed that higher intakes of beta-carotene actually increased the incidence of lung cancer in a large subsection of the population-smokers. High-dose supplements of vitamin A/beta-carotene may be harmful and should therefore be avoided.<sup>33,34</sup> But dietary levels of carotenoids have not shown adverse effects and their cancer-preventing potential deserves attention. In the future we could be eating functional eggs from chickens fed higher levels of dietary carotenoids that are incorporated into the egg yolk.<sup>32</sup>

Tea is the second most frequently consumed beverage in the world. The medicinal uses of tea were first reported by Chinese scholars as far back as AD 221, but the physiological effects of tea and its components are probably only just being realized. Green tea is an excellent source of natural polyphenol anti-oxidants called catechins. These compounds have shown a broad spectrum of anticarcinogenic activity and can inhibit every stage of the carcinogenic process in animal models, including the development of tumours at different sites and in different organs. Importantly, these experiments consistently indicate that the concentrations of these phenolic compounds are the same as those usually consumed by humans. Consumption of tea on a regular basis has been associated with reduced risk of several forms of cancer in human populations, with the strongest evidence linking green tea use to reduction in cancer risk in parts of Asia.<sup>32,35,36</sup> There have also been reports of beneficial effects of tea in relation to blood pressure, serum cholesterol and other lipids. Packets of 'Tetley' tea are already carrying the statement 'rich in anti-oxidants'.

Phytoestrogens such as isoflavones and lignans are present in many traditional human diets in substantial amounts, particularly from soybeans and soy food, lentils and chickpeas. There is some evidence that the reduced rates of CVD and cancer seen in Asian communities who habitually consume large amounts of soy products in their diet might be due to phytoestrogens.<sup>37</sup> These compounds have structural similarities to natural oestrogens and anti-oestrogens.

The anti-oestrogenic activity of soya isoflavones has been linked to a reduced risk of breast cancer.<sup>38</sup> Genistein, the most abundant phytoestrogen, increases the activities of several anti-oxidant enzymes and, along with other phytochemicals, may provide cellular defence against free radicals and oxidative damage. Genistein also inhibits the growth of various human cancer cells and has been shown to inhibit endothelial cell proliferation *in vitro*.<sup>32,39</sup> There are several functional food products containing soy on the market, including soy crackers, bread, cheese and yoghurt. In addition, products such as tofu are prepared by calcium coagulation of the protein, thereby providing the food products with a ready source of calcium and a functional food claim for osteoporosis as well.

Although the data that increased soy consumption may reduce the risk of cancer and heart disease are quite compelling, other studies suggest harmful effects. These include an increased risk of tumour proliferation in some individuals consuming large amounts of soy.<sup>40</sup> Researchers have also highlighted the need for risk assessment when changes in food consumption patterns lead to sudden increases in the level of exposure, to large sectors of the population, to a food constituent not traditionally consumed. In this case, Asian communities who have traditionally consumed large quantities of phytoestrogens from soy products may have genetically adapted to the metabolism of these compounds over time. Such adaptations may be missing in other populations.<sup>39</sup>

Evidence continues to emerge showing that the intake of certain foods and their constituents can have profound physiological effects, including the potential to prevent or delay the onset of chronic diseases such as cancer. However, more research is needed from studies on humans. As with all novel foods, they must be subject to rigorous checks for safety and be considered as part of a healthy and balanced diet, not in isolation. The nutritional recommendations for cancer prevention such as to eat plenty of fruits and vegetables (at least five servings per day), and maintain a healthy bodyweight through regular physical activity, remain the priority.

### Cardiovascular disease

Although many CVD can be treated or prevented, WHO estimates that 17 million people die of CVD each year, with one heart attack every 4 s and one stroke every 5 s in 2001.<sup>41</sup>

In the last decade or so there has been a proliferation of low-fat, fat-reduced and fat-free food products available to help consumers eat a more healthy diet and reduce their risk of chronic conditions such as CVD. Following these, some of the most exciting developments in functional food science, based on a growing body of evidence, are those foods that have the potential to influence risk factors for CVD. One of the first types of novel foods approved for use in many developed countries and based on solid evidence was margarines with added sterols or stanol esters (e.g. Benecol; Johnson and Johnson), which have been shown to reduce low-density lipoprotein (LDL) cholesterol effectively in

some people.<sup>42,43</sup> Promoters of these products argue that margarine is a good way to reduce serum cholesterol levels in children and adults with genetic hypercholesterolaemia because it has no perceptible side-effects and there is likely to be good compliance. Again, the key is to use these products as a substitute for other fat, not in addition, and as part of a total cholesterol-lowering diet.

Omega 3 fatty acids derived from algae and fish have been promoted for many properties in the prevention of coronary heart disease. These include a reduction of total and LDL serum cholesterol, increase in serum high-density lipoprotein (HDL) cholesterol, and inhibition of arachidonic acid-derived products such as leukotrienes and prostaglandins resulting in reduced thrombotic risk. Originally these fatty acids were sold as supplements containing oil from fish liver, but the same positive effects have been shown from eating two–three portions of fish weekly (especially oily fish).<sup>44,45</sup> Functional foods such as eggs containing omega 3 fatty acids due to their addition in chicken feed are available, as well as omega-3 fatty acid-containing margarines. Plant species are also being developed through breeding and biotechnology programmes that will contain omega 3 fatty acids for use in a number of products.

Reductions of total plasma cholesterol, LDL cholesterol and triglycerides have also been demonstrated by eating isoflavones from soya; and patients with higher initial cholesterol levels demonstrate larger reductions in LDL cholesterol.<sup>46</sup> The hypocholesterolaemic effect of soya may be due to an increase in the number of LDL receptors. The amount of soya protein that must be consumed to obtain these effects is approximately 25 g daily, and drinking two glasses of soya milk provides approximately 20 g of soya protein. But the potential for soya to influence the risk of CVD is also based on a range of other attributes. For example, genistein increases the activity of anti-oxidant enzymes such as glutathione peroxidase and superoxide dismutase, and there is evidence from human studies that consumption of soya has a significant anti-oxidant effect.<sup>47</sup> Soya also has a favourable fatty acid content, being rich in polyunsaturated fatty acids such as linolenic acid, which reduce platelet aggregation and possibly the risk of thrombosis.

A lot of attention has recently been given to the potential role of folic acid in the prevention of CVD. Raised plasma homocysteine levels are independently associated with the risk of occlusive vascular disease and possibly with the prevalence of certain neuropsychiatric disorders. Furthermore, there is an inverse graded relationship between folate status and circulating levels of homocysteine. But there is still no evidence from randomized controlled trials that improving folate status and thereby reducing homocysteine levels will reduce the risk of CVD in populations.<sup>48</sup> Nevertheless, efforts to increase the intake of folic acid among women of child-bearing age for the prevention of neural tube defects, may prove additionally beneficial for those populations with raised homocysteine levels.

Folic acid provides an excellent example of the importance of determining the overall balance of advantage and

disadvantage from a population-wide exposure to increased levels of a micronutrient for the prevention of a condition specific to one population group, but which is potentially hazardous to another. That is, in the prevention of up to 70% of neural tube defects among women of child-bearing age there will be a small potential increase in neurological disorders in people (especially in the 50+ age group) with undiagnosed deficiency of vitamin B12. Means for continual risk surveillance should be implemented in countries with folic acid supplementation or mandatory fortification policies. There is also some concern that folic acid supplementation or increased intake through fortification could be associated with higher risk of fetal death from spontaneous abortions. The reason given for this is an effect of folic acid in allowing the survival of non-viable embryos to a stage where their loss is recognized as an abortion.<sup>48-50</sup>

Along with the nutritional guidelines issued by various authoritative bodies worldwide for the prevention and treatment of CVD, some functional foods available to consumers may have beneficial effects on their risk profiles as part of a balanced diet. However, for foods such as eggs and margarines it is imperative that these products are used in place of their original counterparts and not in addition.

### **Osteoporosis**

With the increasing size of the older population worldwide, osteoporosis is a growing public health problem. The WHO estimates that 2 million hip/spine fractures occur each year, 80% of these in women. Osteoporosis is the result of a complex series of events in which the relative importance of some nutrients, particularly calcium, is unclear. In some countries relatively low calcium intakes do not result in substantial increases in the incidence of osteoporosis. Other factors such as exercise and hormone levels may be more important. Yet with the growing size of older populations worldwide and the high prevalence of fractures due to osteoporosis, especially in postmenopausal women, calcium supplementation on a worldwide basis has been proposed. In the meantime several foods have been, or are in the process of being, developed with the aim of increasing dietary calcium intakes or enhancing calcium absorption among specific population groups in developed countries.<sup>2</sup>

Many ready-to-eat breakfast cereals, breakfast bars, and fruit juices have been fortified with calcium for years now, and a number of these are marketed towards women or 'people on the run'. Partial hydrolysis of casein can yield phosphorylated peptides that enhance calcium absorption. These peptides have been added to drinks as natural products that enhance calcium absorption. Prebiotics may also have a role in the achievement of peak bone mass. For example, oligosaccharides, such as oligofructose supplied in orange juice, may enhance calcium absorption in humans.<sup>51</sup>

Along with all their other potential attributes, soya isoflavones may have a role in the prevention of osteoporosis. It has been suggested that the high consumption of soya products in Asiatic countries is one of the reasons for

the low level of osteoporosis found in these countries. Genistein has been shown to enhance calcium retention in rats by inhibiting bone resorption and stimulating bone mineralization. The protective effects are observed in osteoporotic patients as well, but more research needs to be conducted on humans.<sup>32,39</sup> There is also evidence that calcium consumed with soya protein results in significantly less urinary calcium excretion than the same amount of calcium taken with animal protein. Furthermore, functional foods such as soya milk are enriched with calcium in order to provide as much as cow's milk.

There is some evidence that osteoporosis could be an adverse consequence of high intakes of vitamin A. In animals the most common adverse effect of toxic doses of retinol is spontaneous fracture. Scandinavian countries, especially Sweden and Norway, have the highest rate of hip fracture in Northern Europe. They also have high dietary intakes of vitamin A (up to sixfold higher than the rest of Europe), possibly from high consumption of cod liver oil and milk and dairy products fortified with vitamin A. In Sweden, a dietary retinol intake of greater than 1.5 mg/day was associated (dose-dependent) with reduced bone mineral density and increased risk of hip fracture. This example provides yet another incentive for caution when assessing risks and benefits from population-wide exposure to high levels of nutrients from fortified foods or otherwise.<sup>52</sup>

Osteoporosis is an important and expensive public health problem. It causes pain and morbidity among elderly people, especially women. The best way to avoid osteoporosis in later life is to achieve optimal genetic bone mass, and then retain this as long as possible. A lifelong sufficient calcium intake is an essential part of obtaining these goals and some functional foods may aid individuals in doing this, especially if they do not like dairy products. Other preventative measures such as participating in regular weight-bearing exercise, not smoking or drinking excessive amounts of alcohol, and maintaining optimal oestrogen status are equally important. In some countries the role of these other factors may be more important than dietary calcium intake alone.

### **Novel horizons for novel foods**

Nutrition, along with all sciences, is beginning to enter the postgenome era. It has long been recognized that not everyone exposed to the same environmental risk factors develop the associated disease; and advances in genetics have led to a greater understanding of the impact of genetic variation and susceptibility to the aetiology and pathogenesis of chronic diseases. How diets and their individual nutrient or non-nutrient constituents interact with genes to coparticipate in the same causal mechanism for disease development is likely to dominate our science for the foreseeable future. Ultimately this could lead to individualized risk profiling and the provision of information on how to modify the results of genetic predisposition, better known as personalized medicine. A few of the many examples are outlined here.

### **Nutrigenomics**

The term 'nutrigenomics' has been proposed to describe the dynamic era of scientific investigation based on understanding the effects of nutrients at the molecular level, as well as the variable effects that nutrients and non-nutrients have on each of us as individuals. However, the importance of genetic variation and the response to diet is not a new concept. An example of a well-known diet-gene interaction is that which results in in-born errors of metabolism, such as phenylketonuria (PKU). If a child with this genotype eats a diet containing normal levels of phenylalanine the result is mental retardation. With this type of interaction neither the genotype nor the dietary environmental exposure alone is enough to cause mental retardation. This is a genetic disorder (in fact hundreds of genetic mutations result in PKU) that is treated exclusively by environmental, in this case dietary, modification. Another example is how diet and genes interact to influence lipoprotein metabolism. For more than 20 years it has been known that there is great individual variability in the degree to which LDL-cholesterol responds to changes in dietary intake of saturated fat and cholesterol. Several genetic polymorphisms have been proposed as contributing to the variation in lipoprotein metabolism in the general population, for example APOE4. This APOE polymorphism has been reported to result in greater LDL-cholesterol reductions for people on a low-fat diet than people without this particular polymorphism. As a result of this it can be argued that low-fat diets are not beneficial to everyone with hyperlipidaemia.<sup>53,54</sup>

Altered nutritional status as a result of genetic variation is also quite common and relevant to many clinical conditions. For example, there is genetic variation in folate metabolism with people homozygous for the enzyme 5,10-methylenetetrahydrofolate reductase (MTHFR), who exhibit lower red cell folate levels compared with the normal population. Special consideration of this specific population may therefore be necessary when establishing nutritional requirements and recommendations for folate, and when strategies to reduce homocysteine by supplementation or fortification with folic acid are being devised. Furthermore, if genetic variants that cause altered nutritional status are more widespread, there may be no such thing as a 'normal' population regarding nutrient requirements, as was assumed when dietary reference values were established.<sup>54</sup>

Development in fetal and early life is one of the most promising targets for functional foods. Both the mother's and the infant's diet can influence this development, as known from research on folic acid in the diet of pregnant women, and the role of long-chain polyunsaturated fatty acids in early brain development. An example of current research in this area involves the two principal biologically plausible hypotheses for the impact of folate insufficiency on embryonic development. Both of these have a micronutrient and genetic component. One involves impaired embryonic folate transport, and the other involves hyperhomocysteinaemia leading to abnormal development of the human fetus, and they are each an independent risk factor. Researchers are

now designing experiments that will test the separate and joint effects of these conditions on gene expression, including folate-receptor genes and genes that regulate methionine-homocysteine metabolism.<sup>55</sup>

A recent review by Dauncey *et al.* describes the interactions between nutrition, genes and hormone receptors and their implications for development and disease.<sup>56</sup> Nutritional status can profoundly alter the phenotypic expression of a given genotype, especially during fetal and postnatal development. Hormone receptors have a key role in mediating the effects of nutrition on many genes involved in differentiation, growth and metabolism. Nutrition can also influence hormone synthesis, metabolism and hormone receptors with regulation mediated by either specific nutrients or energy status. Recent research on receptors for glucocorticoids and thyroid hormones (which directly regulate DNA transcription) have suggested that nutritional status can influence normal development and modify nutrient utilization, thermogenesis, peripheral sensitivity to insulin and optimal cardiac function. The authors predict that in the next decade there will be significant advances in understanding the precise mechanisms by which nutrition modulates hormone receptor function throughout the human life cycle. In addition, more insight into the relative contributions of nutrition (specific nutrients, energy status and overall intake) and genotype to optimal development should be gained. Ultimately this will lead to improvements in preventative and treatment strategies from the nutritional to the molecular level.<sup>56</sup>

### **Immunoenhancement**

Xenobiotic metabolism and its modulation by non-nutritive dietary compounds (e.g. phytochemicals) is another promising area for the development of functional foods with the goal of improving immunity or immunoenhancement. These modulations may have important implications for the control of toxicity or carcinogenicity caused by chemical toxins encountered in food or the environment. The process by which chemicals in the environment undergo changes as they enter the body is known as biotransformation, and it occurs mainly in the liver. A lot of research on diet-gene interactions has involved the biotransformation enzymes whose function is to stabilize xenobiotics so that they can be excreted more readily. For example, cytochrome P450 genes are responsible for the metabolism of a wide range of substrates, and nutrients involved as cofactors include B vitamins and flavanoids.

There are also many variant forms of these biotransformation genes, and the polymorphisms often result in differences in activity of the enzymes and ultimately the extent of detoxification of xenobiotics. So a variant of an enzyme responsible for the detoxification of a potentially carcinogenic chemical, which is a poor metabolizer phenotype, may be associated with an increased risk of cancer. However there are phenotypes that may also be protective. In fact genes encoding enzymes involved in the metabolism of dietary compounds, alcohol, tobacco and other chemical toxins and carcinogens

may vary considerably across the population (polymorphisms for these enzymes range from less than 1% to 50%), including variability by race. There is research suggesting that there are many interactions between biotransformation genes and dietary intake. Heterocyclic aromatic amines (HAA) produced from frying meat at high temperatures are known to be carcinogenic, possibly increasing the risk of colon cancer. But the degree of risk is likely to be dependent on the extent to which HAA are activated by phase 1 biotransformation enzymes, because the variability in activity level of these enzymes is partially due to genetics and partially because of environmental factors, such as nutrition. The activity of phase 2 detoxification biotransformation enzymes can also be induced by foods containing phytochemicals such as cruciferous vegetables, onions, and garlic.<sup>57,58</sup>

There are many other current and potential therapeutic applications of specific nutrients for immune defence. Omega 3 fatty acids are of interest as anti-inflammatory agents, acting at least partly by influencing leukotriene and prostaglandin balance. Consuming several grams of fish oil daily over weeks and months has produced clinical improvements in patients with a variety of inflammatory conditions such as rheumatoid arthritis and ulcerative colitis. Nutritional immunoenhancement is also relevant to chronic infectious conditions, which are characterized by multiple nutrient deficiencies. For example, daily vitamin A supplementation (3–7 times the US recommended daily allowance) may hinder the development of AIDS in HIV patients who often exhibit low blood retinol levels.<sup>59</sup> Single-dose micronutrient supplementation (vitamins C, E, B6) and multivitamin/mineral preparations can stimulate adaptive and innate immune defences, reduce the frequency of infections, and increase responses to vaccination in the elderly. But research has not resolved whether these supplements are simply correcting subclinical nutrient deficiencies, or revealing that the current recommended intakes for a number of micronutrients are insufficient for optimizing immunocompetence in the elderly.

#### *Novel foods and ageing: The secret of a long life?*

There is a worldwide increase in the proportion of people in the older age groups. By 2020 it is predicted that in some countries such as Japan, people over 65 years will comprise nearly one-quarter of the population. With the help of micronutrients, anti-oxidants (nutritive and non-nutritive), probably other compounds yet to be identified, and functional foods it is hoped that people will live longer and be healthier for longer. Currently, the only nutritional manipulation that has been shown to increase lifespan is a drastic restriction of food intake in laboratory rats with no direct application to humans. Still, the attention focused on the potential role of anti-oxidant nutrients in protecting against several chronic diseases that increase in prevalence with age has resulted in some individuals consuming large quantities of anti-oxidant supplements in the hope of eternal youth. Redox activities and anti-oxidant protection are important for almost every cell and tissue, and their imbalance is

associated with a variety of pathologies. Although there are biologically plausible mechanisms by which dietary anti-oxidants may result in beneficial effects, demonstrating these, except when they are consumed as fruits and vegetables, remains difficult.<sup>57,60</sup>

The effect of food components on mood and behaviour or cognition is a promising target area for functional food research. Evidence exists concerning a role for diet and its influence on cognitive impairment and decline in older age, particularly through its impact on vascular disease. For example, cognitive impairment is associated with atherosclerosis, non-insulin-dependent diabetes and hypertension. Epidemiological and correlation studies have shown significant relationships between cognitive function and intakes of nutrients such as long-chain polyunsaturated fatty acids, anti-oxidant vitamins, and folate and vitamin B12, as well as overall nutritional status. There is also evidence that the intake of omega 3 fatty acids can affect mood and aggression (with lower intakes associated with greater depression and aggression). Each of these are discussed in detail in a recent review by Rogers.<sup>61</sup> Unfortunately the border between nutritional and pharmacological effects is difficult to establish in this case, and methodologies for studying such effects are inadequate to produce the reliable quantitative data needed for statistical analysis. Intervention studies are needed to substantiate these findings, not least because depression and poor cognitive function themselves can contribute to the consumption of a poor diet. Rogers suggests that this could be efficiently achieved by including assessments of mood and cognitive function as outcome measures in long-term studies designed primarily to investigate the impact of dietary interventions on markers of physical health.<sup>61</sup>

The relative contribution of diet and genotype to bone development is very relevant to an ageing population, as outlined in the section on osteoporosis. Variations in diet and other environmental factors contribute 30–40% of total phenotypic variance in bone mineral density. But no specific dietary factor has yet been identified as making a significant contribution to environmental variability in bone mineral density or bone loss. In addition, the influence of nutrition on bone health may depend on the genotype of the individual. Research indicates that 60–70% of the variability in bone mineral density can be accounted for by genetic variation. But because many more genes are involved in bone metabolism that control various endocrine and other metabolic pathways, more research investigating the function of these genes is needed before optimal dietary requirements are defined and specific dietary advice can be given. Because diet and other environmental factors make such a significant contribution to the variability in bone density, and these factors can be modified, then every effort should be made to define what is the optimal diet and lifestyle.

#### *Perspective*

The genetic age is upon us. In some ways this represents a natural progression of biotechnology and molecular biology;

on the other hand it is a revolution in how diet and nutrition are viewed. Individual genetic differences in response to specific dietary components have been known for years, but genomic information will be used in the future to understand the reasons for individual differences in response to specific nutrients and dietary patterns. It may help define specific subpopulations, thereby allowing dietary interventions to be more targeted, and assist diet development and health outcomes from dietary patterns. It is also possible that the way in which dietary recommendations on a population basis are formulated will need to be redefined. Furthermore, diseases that are presently clinically indistinguishable will be subdivided into more distinct entities, allowing the implementation of more effective treatment and prevention strategies.

Future generations could be provided with a personal genetic propensity profile for illness and disease soon after birth. Proponents of this predict cost savings by consumers, employers and government through retarding and preventing disease. However, there are many complex ethical, legal and social implications of this type of genetic screening. Not least the potential discrimination by insurance companies and employers. A genetic profile may enable an individual to adopt the habits most likely to reduce risk. But public health providers will also need to consider the case in which people who have protective genotypes for specific diseases may adopt unhealthy lifestyles, on the premise that they are not susceptible to these diseases, thereby actually increasing their risk overall.

The development of foods and beverages either as preventive agents or as treatments specific for those with a propensity for disease certainly seems possible. These would have potentially huge market opportunities. The rapid advances in knowledge and availability of information on nutrition and genetics, combined with market forces and media focus, will require health professionals to become very familiar with this new discipline and respond to its implications. Ultimately, after elucidating the genetic profile of a patient, a diet could be formulated that includes novel or functional foods tailored to the patients specific needs, from farm to fork, in order to prevent or retard disease progression.

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