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Genetic individuality, diet and disease

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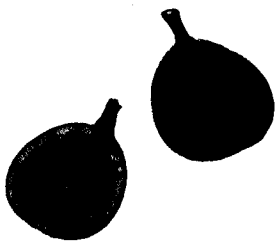

OBJECTIVES

- To highlight that humans today live in a nutritional environment that differs significantly from that for which our genetic constitution was selected in Paleolithic times.
- To clarify the interplay between genes and environment, including that part of the environment to which food intake contributes.
- To show how nutritional factors may modulate the expression of genes.
- To consider the implications of this knowledge for the optimisation of human health and related ethical matters.

GENETIC PROFILE OF OUR ANCESTORS AND MODERN-DAY DISEASES

Since the beginning of the Agricultural Revolution 10 000 years ago major changes have taken place in our diet. However, our genes have not changed very much over the past 10 000 years because the spontaneous mutation rate for nuclear DNA is estimated at 0.5% per million years (Simopoulos 1999). Our genes today are in fact very similar to the genes of our stone-age ancestors. During the paleolithic period 40 000 years ago our genetic profile was established, but humans today live in a nutritional environment that differs significantly from that for which our genetic constitution was selected. Human beings evolved on a diet in which there was a balance between omega-6 and omega-3 fatty acids, where energy intake matched energy expenditure, where saturated fat and sugar intakes were minimal and where intakes of complex carbohydrates and fibre were high. The rapid changes in our diet, particularly over the last 150 years, have contributed to the high prevalence of chronic diseases because the 'Western diet and lifestyle' is not consistent with the genetic programing of our paleolithic ancestors and may lead to maladaptation in genetically

predisposed individuals. Inappropriate food habits, sedentary lifestyles and exposure to noxious substances (for example, plutonium from nuclear plants) interact with genetically controlled biochemical processes that may lead to the development of chronic diseases.

GENETIC VARIATION AND HUMAN DIVERSITY

In the past, genetic makeup and lifestyle (which includes diet) were considered two competing forces—nature versus nurture—in influencing the development of the individual. Inherited genes were seen to be an unalterable blueprint when in fact they are merely a set of options, each more or less conditional, to be taken up according to what is being experienced in the environment, as well as what has been experienced. We now know that it is the interaction of nature and nuture that determine gene expression and phenotype of the individual (Simopoulos 1999).

Genetics deals with variation. Human populations represent storehouses of genetic variability. An appreciation of human diversity is a fundamental aspect of the genetic approach to disease. We should consider the nature and extent of a genetic variation, its origin and maintenance, its distribution in families and populations, its interaction with the environment, and its consequences for normal development and homeostasis (Simopoulos 1999).

Genetic individuality and human diversity is determined by:

1 genes (both major genes and modifiers);
2 constitutional factors (age, sex, developmental stage, parental factors);
3 environmental factors (time, geography, climate, socioeconomic status, occupation, education and diet).

Interactions among these three sources can result in significant human diversity.

Common alleles (variants at a single locus) or polymorphisms form the basis of human diversity. This includes the ability to handle environmental challenge and change. About 30% of loci have polymorphic variants (defined as two or more alleles with a frequency of at least 1% or more) in the population. Changes in nutritional environment will affect heritability of the variant phenotypes that are dependent to some extent on the nutrient environment for their expression.

Advances in genetic studies suggest considerable biochemical variability within and between human populations. Broadly defined, heritability is the proportion of the total variance that can be explained by genes. Studies have shown that 50% of the variance in plasma cholesterol concentration is genetically determined, 30–60% for blood pressure and 75% for bone density. However, heritability may vary between populations if they differ in the prevalence of the types of genes affecting the disease. For example, 15% of the variance in fibrinogen concentration (a risk factor for heart disease) in the United Kingdom is genetically determined compared with 51% in Hawaii. Since genetic variants are expressed in a specific environment, Simopoulos (1999) recommends that populations should not copy each other's dietary recommendations for the prevention of diseases. The effects of genetic variation on dietary response need to be considered (see below).

In the 1980s and 1990s, scientists have been studying the effects of genetic variation and gene-nutrient interactions in the management of chronic diseases. International data indicate that the incidence and prevalence of chronic diseases vary among individuals, families and countries. Genetic predisposition, environmental factors and quality of care all contribute to these variations. Susceptibility to most chronic diseases (such as obesity, heart disease and cancer) is to a great extent genetically determined; but, because of genetic variation, not everybody is susceptible to chronic diseases to the same degree (Simpoloulos 1999).

GENES AND THE ENVIRONMENT

It has been customary to think of health problems as having either a genetic or an environmental (including lifestyle) basis. In reality, both are usually operative. This is demonstrated, for example, in a characteristically genetically based disorder like phenylketonuria, where phenylalanine, an essential amino acid, cannot be converted to tyrosine—phenylketones accumulate, causing damage to the nervous system. The usual level of dietary phenylalanine (the 'normal environment') allows the disease to be manifest, but reduction of phenylalanine to a controlled minimum, and supple-

mentation with tyrosine (which will not have been formed in the usual way from phenylalanine because of impairment of the enzyme phenylalanine hydroxylase) disallows the expression of the disease. This is to say that the food or nutrient environment has determined health status in spite of genotype (Dice 1990; Goodridge 1994).

In contrast, for much of human history non-insulin dependent diabetes mellitus (NIDD) has scarcely been in evidence. When present it has a strong genetic basis, even 'autosomal dominant' (one gene from one parent) will suffice. But it is only with sedentary lifestyles and the consumption of fatty, refined food leading to the development of abdominal fatness as well that the disease is usually seen. Indeed, a reversion to more traditional lifestyles, as with some Aboriginal people, can allow corrections of the metabolic abnormalities in carbohydrate and lipid metabolism (O'Dea 1994). The gene frequency (or frequencies since there may be more than one) can apparently be high in a population, even though the gene has not been identified, since some ethnic groups like Pacific Islanders in Nauru and the Pima Indians in North America can have a prevalence of NIDD as high as 35% to 40% (Zimmet 1993). Thus a common gene, which may even have survival value in traditional environments, has required a new, now commonly encountered environment in which to manifest as a disease. It is, therefore, theoretically possible for a disease to be 100% genetic and 100% environmental. But what is sometimes considered by multivariate statistical analysis is how much of the variance of a biological phenomenon or disease can be accounted for by a genetic marker or an environmental factor. Here, the sum of the variances as percentages will add up to 100!

Phenotype and genotype

The measured metabolic or anatomic abnormality and the disease consequence of such abnormality is the *phenotype* for which the genetic abnormality(ies) is(are) the *genotype(s)*. The phenotype may be more or less severe and there may be several genetic abnormalities which lead to the same phenotype. For example, an inborn error of metabolism called homocystinuria can result due to abnormalities of one of two enzymes (cystathionine 10 beta-synthase or 5-methyl tetrahydrofolate homocysteine methyl transferase) which are responsible for the metabolism of homocysteine. As a result, homocysteine levels increase in blood where, in florid form, thromboses, osteoporosis, mental retardation, facial flushing and accelerated atherosclerosis can occur (see also Chapter 27). Much more commonly, with marginal states of water soluble vitamins, specifically pyridoxine (vitamin B-6), vitamin B-12 or folic acid, mild elevation of homocysteine in blood (homocysteinaemia) may also be seen, with the added risk of atherosclerosis because homocysteine can be a vascular toxin. This may not matter in a population where there is not also the expression of high blood cholesterol levels (hypercholesterolaemia or hyperLDLaemia).

Thus we may learn about genetic–environment interactions by studying rather rare and dramatic forms of the genetic abnormality. The public health implications of these observations can, however, be far-reaching and, in the example given, represent the interplay of both undernutrition (of water soluble vitamins) and overnutrition (with dietary fat) with genes.

NUTRITIONAL MODULATION OF GENE EXPRESSION

It is not known exactly when it was first identified that specific nutrients influence gene expression. It was clear by the 1950s that essential amino acids, when not available in essential amounts, limited the production of proteins. The classic experiments of Francois Jacob and Jacques Monod in 1961 demonstrated that regulatory genes under nutrient control influence genes needed for the synthesis of enzymes involved in the metabolism of that nutrient. In their study conducted on bacteria, lactose (the nutrient inducer) increased the expression of three structural genes (lac operon) coding for lactose metabolising enzymes. It is suspected that changes in nutrient and phytochemical intakes are likely to influence expression of many genes (Cousins 1999).

Gene expression can be defined as:

1 the exhibited phenotypes (which are manifestations of gene expression);
2 mechanics of gene transcription and messenger RNA (mRNA) translation that influence which proteins are produced.

Gene expression includes activation of the gene to a transcribable structure followed by transcription,

transcript processing and splicing, translocation to the cytoplasm and mRNA translation. For some proteins, post translational modification may also be affected by changes in gene expression (see Figure 25.1). The human genome contains about 30 000 genes, of which 10% may be transcriptionally active at any one time. Transcription rates of individual genes can be altered by various mechanisms and represent the major point of gene regulation. Factors influencing the binding of RNA polymerase to DNA, specifically the promotor region of the gene and other sequences in close proximity, control transcription.

Nutritional factors may determine the level of gene activity through effects on transcription from DNA to messenger RNA (mRNA) and on translation from mRNA to transfer RNA (tRNA) in polyribosomes to enzyme or other protein synthesis. From the viewpoint of nutritional influences on gene expression, processes are envisioned in which dietary conditions produce changes in transcription of specific genes to yield proteins, including mediators and enzymes, that define phenotypic expression. Specific nutrients and dietary conditions could interact *directly* with transcription factors or more commonly *indirectly* via hormones or signalling systems. Alternatively, nutrients can influence gene expression via control of mRNA translation that

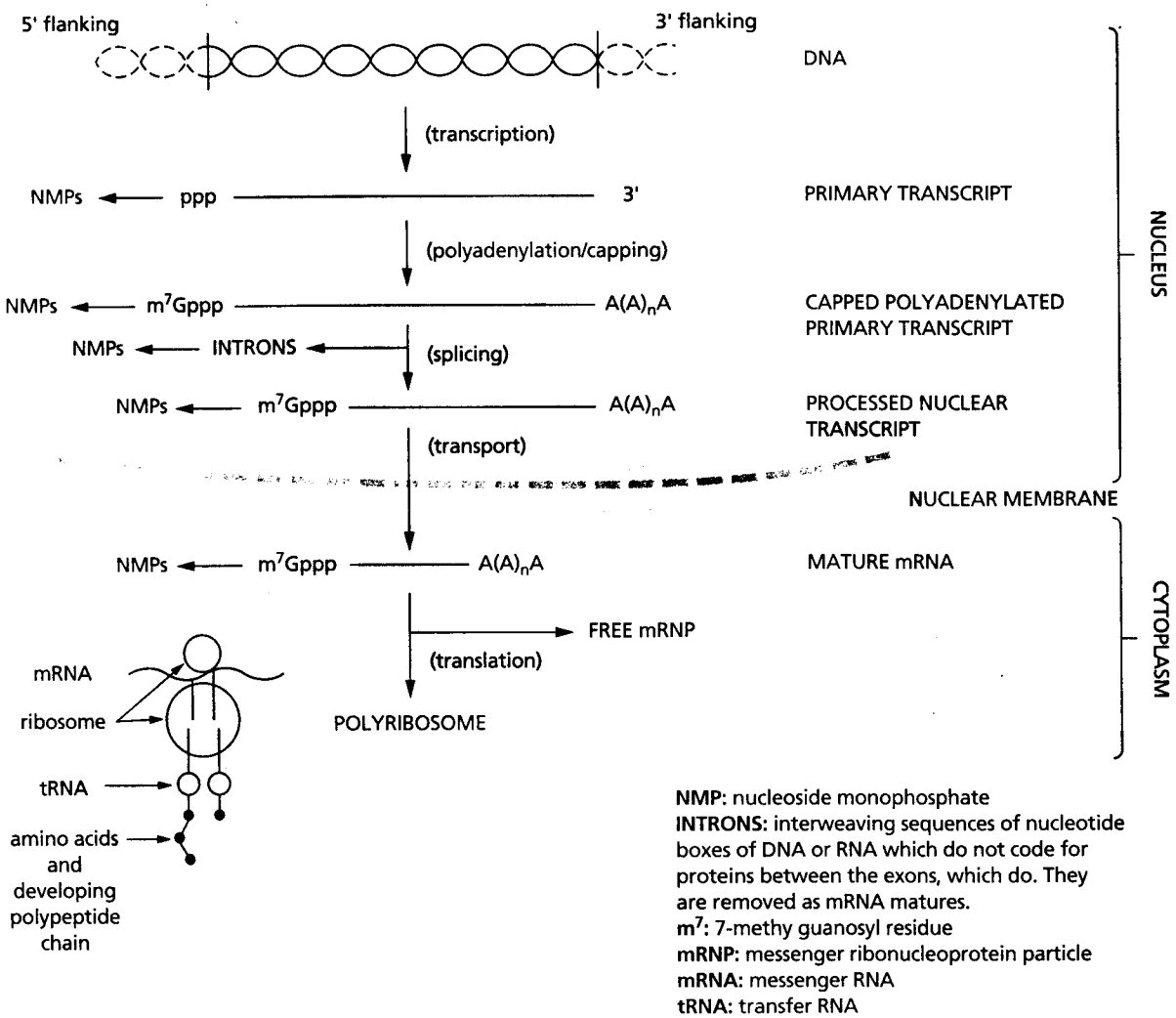

Figure 25.1 The pathway for gene expression: a generalised scheme for the transcription, processing, transport and degradation of intermediate and final products in the synthesis of mRNA (Goodridge 1987). The translation of mRNA through tRNA and protein in the ribosome is also shown

can also be mediated by direct or indirect means. Factors (which may be nutritional) influencing the turnover of mRNA will also be important (see Figure 25.1). Examples of genes which can be nutritionally modulated are shown in Table 25.1 (Dice 1990; Cousins 1999).

An indication of these effects is given by measuring the mRNA in relation to dietary change. This is most usually done by having the complementary DNA (cDNA) for the mRNA, allowing it to bind to the mRNA, and then assaying (for example, by autoradiography in an electrophoresis system like the 'northern' blot). Particularly interesting examples are:

1 the effects of carbohydrate feeding to stimulate production of the mRNA for lipogenic (fat synthesising) enzymes in liver (Goodridge 1987)—perhaps mediated, in part, via insulin;
2 the stimulation of LDL receptor mRNA formation by fat feeding with consequences for the ability of cells to remove cholesterol in LDL from the circulation, and to suppress their own formation of cholesterol (Rudel et al. 1994);
3 the ability of cells to alter the amount of mRNA for iron storage protein (ferritin protein) in cells in the face of iron deficiency (Rucker 1994).

Table 25.1 Examples of dietary modulation of gene expression

Refeeding of starved animal on carbohydrate-rich diet	
	Increases messenger RNA level of malic enzyme, L-type pyruvate kinase, fatty-acid synthase, glucose 6-phosphate dehydrogenase, 6-phosphogluconic dehydrogenase, acetyl-coenzyme A carboxylase, adenosine triphosphate-citrate lyase, and hepatic S_{14} and S_{11} proteins.
	Decreases phosphoenolpyruvate carboxykinase.
Protein depleted diet	
	Increases messenger RNA levels of albumin, prealbumin, transferrin, beta-chain of fibrinogen, apolipoprotein E.
	Casein diet increases ornithine decarboxylase messenger RNA.
	Cholesterol or a related metabolite decreases 3-hydroxy-3-methylglutaryl coenzyme A reductase messenger RNA.
Micronutrient effects	
	Zinc, cadmium, copper and mercury increase metallothionein messenger RNA.
	Iron deficiency increases transferrin messenger RNA.
	Vitamin D increases calcium-binding protein messenger RNA.
	Vitamin D deficiency decreases polyadenylated messenger RNA fraction.

These genetic responses to diet show considerable individual difference. This means that eventually it may be possible to tailor diets for individuals to optimise their health, but the costs and organisation of such 'genome profiling' and the relative benefits will require much examination. For example, one of the proteins which transports cholesterol is known as apo E and it has isoforms '2', '3' and '4'. Thus someone may be apo E 4/E4. It is now known that such individuals are more responsive to dietary fat, as far as their blood fats are concerned. What will be the costs, benefits and risks of such knowledge in an individual?

GENE THERAPY AND DIETARY RECOMMENDATIONS

The interaction of certain nutrients with genetically determined biochemical and metabolic factors such as familial hypercholesterolaemia suggests different requirements for individuals. Evolution has allowed humans to adapt to and survive on a variety of foods; however, genetic adaptations and limitations have occurred in relation to diet. Changes in the dietary patterns of genetically heterogenous populations will have a different impact to populations with similar genotypes (due to a similar evolutionary background). Therefore, to be successful, dietary interventions need to be based on knowing the frequency of genes whose effects we are attempting to control or modify with environmental factors.

For example, dietary guidelines promoting dairy products and cereals may not be appropriate for populations at low risk of osteoporosis or at high risk of coeliac disease, respectively. Fracture rates in Africans and Asians are considerably lower than in Caucasian populations despite low intakes of calcium. This has been related to the high frequency (80% versus 30%) of the b allele of the VDR gene that has been associated with bone mineral density and bone turnover. Of interest is the fact that the b allele frequency in African Americans is lower (43%) than Africans in Africa, providing further evidence that changes in the environment can ultimately influence genetic make-up and expression (Simopoulos 1999). Populations whose diet does not include wheat, barley, rye or oats manifest gluten sensitivity upon the introduction of those foods in their diet. The presence of gluten in the diet can trigger coeliac disease in genetically susceptible

individuals. Coeliac disease occurs in 1 in 3000 live births in Europeans and 1 in 200 live births in Ireland.

The effect of diet on plasma cholesterol concentrations provides another valuable example. The response of plasma cholesterol concentration to dietary intervention is heterogenous; the response to diet appears to be determined by the gene variant of apolipoprotein, as for example, in the case with apolipoprotein E (ApoE). ApoE4 is associated with hypercholesterolaemia. Northern European countries have higher frequencies of the Apo E4 allele (Finland 22.7%, Sweden 20.3%) than southern countries (Italy 9.4%). This suggests that ApoE4 may account, in part, for the differences in cardiovascular disease prevalence across Europe. The relationship between LDL cholesterol levels and Apo E genetic variation is influenced by environmental and ethnic factors. The association of the Apo E4 isoform with elevated serum cholesterol levels is greater in populations consuming diets rich in saturated fat and cholesterol. The higher LDL cholesterol levels observed in subjects carrying the ApoE4 isoform are observed when the diet is also high in saturated fat and cholesterol—in other words the response to diet differs among individuals with different Apo E phenotypes. Only people with Apo E3/3 phenotype (as opposed to Apo E 4/4, Apo E 4/3) will have a hypocholesterolaemic response to oatbran. Thus specific genetic information is needed to define the optimal diet for an individual. General dietary recommendations can lead to inconclusive studies or show lack of benefit.

It will be increasingly possible not only to define genetic differences between individuals, and how they might be responsive to dietary change, but also to correct perceived genetic abnormalities (Simopoulos 1993). For example, since the LDL receptor defect is most important in liver cells, where overproduction of cholesterol may occur, it is now possible to remove some liver tissue, correct the genetic abnormality, grow the liver cells in tissue culture and then re-implant them in the individual, so correcting (in part) the defect. With a lesser degree of this abnormality, a prudent lifestyle could probably deal with the problem, and provide other benefits.

At present the aim of dietary guidelines is to optimise health for the majority. We can expect a quest for individuals to optimise their health without regard to such guidelines (see Chapters 38 and 40). There are clearly societal and ethical, as well as economic, issues involved here.

Food and gene mutation

Food can alter gene mutation both adversely and favourably. Mutagenic components of food play a role in the development of certain cancers (see Chapter 32). However, the work of Beatrice Pool-Zobel and colleagues (1998), using bioinformatic techniques, indicates that over short time frames of several weeks, fruits and vegetables can decrease mutation rates in human cells. How these findings relate to disease expression remains to be determined, but the risk of certain cancers is likely to decrease when fruit and vegetable intakes increase.

SUMMARY

- Our genes today are very similar to the genes of our ancestors during the Paleolithic period 40 000 years ago.
- Humans today live in an environment (diet, lifestyle) that differs from that for which our genetic constitution was selected 40 000 years ago—this has contributed to current high prevalences of chronic diseases.
- It is usual for health outcomes to reflect both genetic and environmental factors.
- Gene activity can be modulated at transcription, translation and messenger RNA turnover by nutritional factors.
- Gene therapy and dietary individualisation will influence thinking on public health nutrition to a progressively greater extent.
- An individual's health status is the product of the interaction of his or her genetic endowment, age, nutrition and other aspects of physical and cultural environment. Family history (including demographic and ethnic aspects) is an important predictor of disease. In developing dietary guidelines genetic variants in the population should be taken into consideration. Since genetic variants are expressed in a specific environment, populations should not copy each other's dietary recommendations.
- Gene mutation can be adversely or favourably influenced by food.

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