33

Genetic individuality, diet and disease

Mark L. Wahlqvist

OBJECTIVES

- 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.

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. For example, in a characteristically genetically based disorder like phenylketonuria, the usual level of dietary phenylalanine (the 'normal environment') allows the disease to be manifest, but elimination of phenylalanine from the diet, and supplementation 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; Morley et al., 1988).

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! The estimates of relative genetic and nutritional contributions to certain disease states shown in Table 33.1 are, therefore, understandable.

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 β-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 24). Much more commonly, with marginal states of water soluble vitamins, specifically pyridoxine (vitamin B6), vitamin B12 or folic acid, mild elevation of homocysteine in blood (homocysteinaemia) may also be seen with this inborn error of metabolism, 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.

Table 33.1 Estimates of relative genetic and nutritional contributions to certain disease states

	Estimates of % variance accounted for by predictors	
Nutritionally related disease	**Genetic**	**Nutritional**
cancer	20–70	20–70
macrovascular disease	5–10	10–70
obesity	10–30	60–80
non-insulin dependent diabetes mellitus	10–20	60–70
Alzheimer's disease	20–30	?

NUTRITIONAL MODULATION OF GENE EXPRESSION

So far we have discussed how, with a given level of gene activity, phenotype status may be different for environmental reasons. Nutritional factors may also 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. Factors, which may be nutritional,

Table 33.2 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.

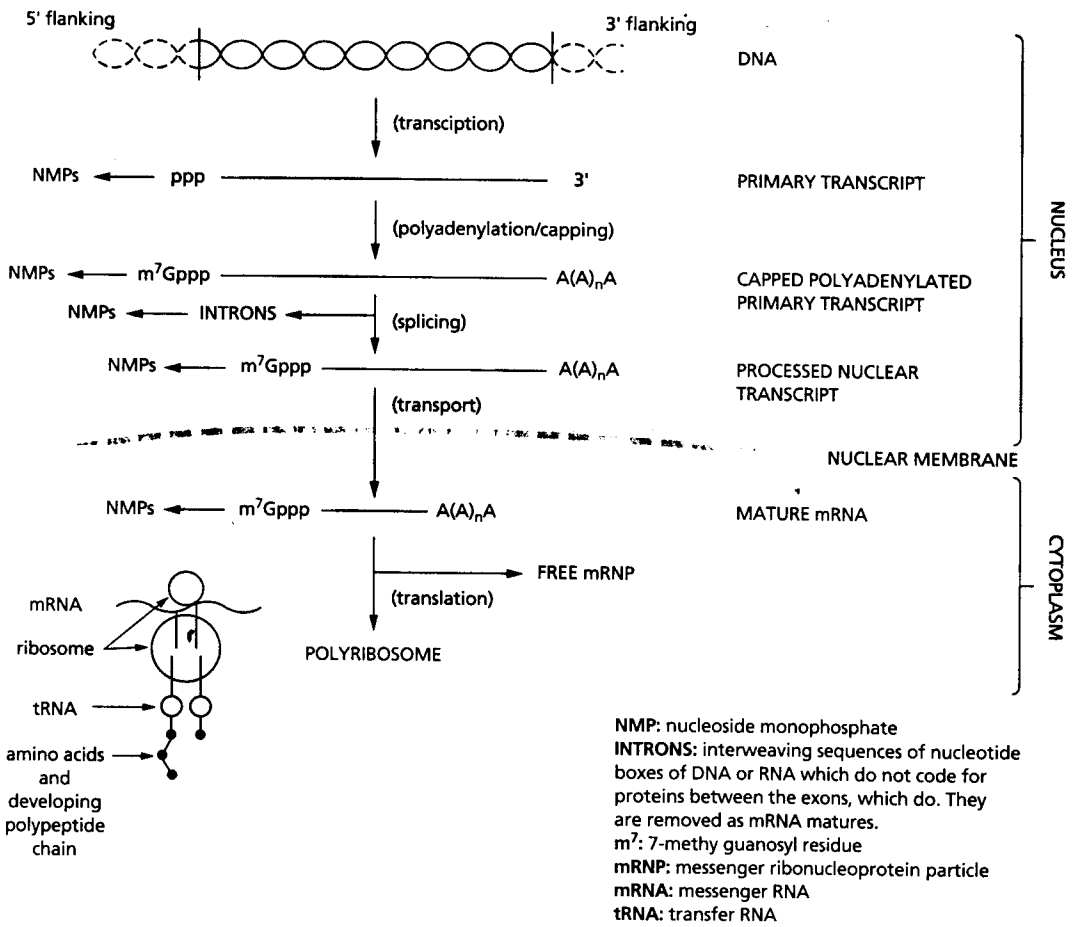

Figure 33.1 The pathway for gene expression: a generalised scheme for the transcription, processing, transport and degradation of intermediate and final products in the synthesis of mRNA (Goodridge, 1987). The translation of m-RNA through tRNA and protein in the ribosome is also shown

influencing the turnover of mRNA will also be important (see Figure 33.1). Examples of genes which can be nutritionally modulated are shown in Table 33.2) (Dice, 1990; Morley, 1988)

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 (e.g. 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).

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

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 over-production 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 52 and 55). There are clearly societal and ethical, as well as economic issues, involved here.

SUMMARY

- 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.

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FOOD AND NUTRITION

Australasia, Asia and the Pacific

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Thanks to Antigone Kouris-Blazos for her editorial and technical assistance.

ALLEN & UNWIN

First published in 1997 by
Allen & Unwin Pty Ltd
9 Atchison Street, St Leonards, NSW 1590 Australia
Phone: (61 2) 8425 0100
Fax: (61 2) 9906 2218
E-mail: frontdesk@allen-unwin.com.au
Web: http://www.allen-unwin.com.au

National Library of Australia
Cataloguing-in-Publication entry:

Food and nutrition: Australasia, Asia and the Pacific.

Bibliography.
Includes index.
ISBN 1 86448 220 6.

1. Food. 2. Nutrition. I. Wahlqvist, Mark L.

641.3

Set in 11/13 pt Bembo by DOCUPRO, Sydney
Index compiled by Russell Brooks
Printed by Dah Hua Printing Press Co. Ltd, Hong Kong

10 9 8 7 6 5 4 3 2 1

Contents

Contributors vii

Part I EVOLUTION, CULTURE AND FOOD

1 Human history and food *Mark L. Wahlqvist* 3
2 Anthropological and sociological approaches to understanding food, eating and nutrition *Patricia A. Crotty* 9
3 Industrialisation and urbanisation *Richard S.D. Read* 25
4 Recent developments in food technologies *David R. Briggs & Louise B. Lennard* 30
5 What is food? *David R. Briggs & Mark L. Wahlqvist* 45

Part II CONTEMPORARY FOOD USE

6 Food supply systems *Guyn P. Jones* 53
7 Trends in the available food supply *Ingrid H.E. Rutishauser* 59
8 Current food consumption *Ingrid H.E. Rutishauser* 67

Part III FOOD COMPOSITION, PROCESSING, REGULATION AND SAFETY

9 Food composition *Guyn P. Jones* 81
10 Food processing *Guyn P. Jones* 89
11 Food preparation *Guyn P. Jones* 97
12 Food microbiology and food poisoning *David R. Briggs & Louise B. Lennard* 104
13 Naturally occurring toxicants and food contaminants *David R. Briggs* 120
14 Food additives *David R. Briggs* 128
15 Real and perceived risks in food *David R. Briggs & Louise B. Lennard* 143
16 Food law, regulation and surveillance in Australia *David R. Briggs* 148
17 Food law and regulation: an international perspective *David R. Briggs & Louise B. Lennard* 157

Part IV THE BIOLOGY OF FOOD COMPONENTS

18 Food energy and energy expenditure *Richard S.D. Read* 167
19 Digestion of food *Richard S.D. Read* 177

20 Protein *Richard S.D. Read* 188
21 Carbohydrates *Gwyn P. Jones* 199
22 Fats *Gwyn P. Jones* 205
23 Dietary fibre and resistant starch *Gwyn P. Jones* 215
24 Vitamins and vitamin-like compounds *Mark L. Wahlqvist* 222
25 Minerals *Gwyn P. Jones* 249
26 Water *Gwyn P. Jones* 255

Part V LIFESPAN NUTRITION

27 Pregnancy and lactation *Ingrid H.E. Rutishauser* 263
28 Infant nutrition *Ingrid H.E. Rutishauser* 274
29 Childhood and adolescence *Ingrid H.E. Rutishauser* 284
30 Foods, physical activity and sport *Richard S.D. Read & Antigone Kouris-Blazos* 293
31 Survival nutrition *Richard S.D. Read and Gwyn P. Jones* 311
32 Requirements in maturity and ageing *Mark L. Wahlqvist* 317

Part VI FOODS AND DISEASE

33 Genetic individuality, diet and disease *Mark L. Wahlqvist* 331
34 Protein energy malnutrition *Madeleine Ball* 335
35 Overweight and obesity *Richard S.D. Read & Antigone Kouris-Blazos* 346
36 Eating disorders *Richard S.D. Read* 366
37 Atherosclerotic vascular disease and hypertension *Madeleine Ball* 373
38 Diabetes *Madeleine Ball* 384
39 Alcohol and alcohol related diseases *Madeleine Ball* 394
40 Nutrition, infection and immune function *Mark L. Wahlqvist* 402
41 Nutrition and cancer *Mark L. Wahlqvist* 407
42 Nutrition and osteoporosis *Mark L. Wahlqvist & Naiyana Wattanapenpaiboon* 416
43 Food sensitivities *David R. Briggs & Louise B. Lennard* 425
44 Nutritional disease related to poverty, famine and organic disease *Madeleine Ball* 434
45 Nutritional problems related to cultural and environmental transition *Mark L. Wahlqvist* 440
46 Nutrition and health problems related to substance abuse and medications *Mark L. Wahlqvist* 454

Part VII NUTRITION MONITORING AND SURVEILLANCE

47 Monitoring food and nutrition status at the population level *Ingrid H.E. Rutishauser* 461
48 Assessment of nutritional status in the individual *Ingrid H.E. Rutishauser* 470
49 Nutritional standards of reference *Ingrid H.E. Rutishauser* 475

Part VIII PRIMARY HEALTH CARE AND NUTRITION

50 Health promotion and nutrition *Patricia A. Crotty* 489
51 Nutrition in primary health care *Madeleine Ball & Iain Robertson* 500
52 Dietary advice and food guidance systems *Mark L. Wahlqvist & Antigone Kouris-Blazos* 508

Part IX FOOD PRODUCTION AND THE ENVIRONMENT

53 Food, population and development *Richard S.D. Read* 525
54 Sustainable environments *Richard S.D. Read* 534
55 Food and nutrition policies *Mark L. Wahlqvist* 541

Abbreviations 549
Index 551