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From early nutrition and later development . . . to underlying mechanisms and optimal health

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'Life is a country that the old have seen, and lived in.
Those who have to travel through it can only learn the way from them.'
Joseph Joubert, 1842

This quotation is perhaps especially appropriate when considering the extensive contributions made by Professor McCance and Dr Widdowson to the field of early nutrition and later development. A detailed knowledge of their work in this area is of undoubted value both in interpreting many recent findings and in the design of new investigations. The first part of this paper presents a brief overview of some of their most significant studies. Their implications at both the fundamental and applied levels are then discussed, especially in relation to the role of nutrition in health and disease. Finally, potential mechanisms by which development may be modified by early nutrition are considered.

THE WORK OF PROFESSOR McCANCE AND DR WIDDOWSON

The pioneering research carried out by McCance and Widdowson on early nutrition and later development stems from their investigations into undernutrition in the German population during the 1940s (Widdowson, 1951; Widdowson & McCance, 1954). During the ensuing 20–30 years they undertook a series of studies in a wide range of animal species. Especially significant were those in the rat and pig on (1) varying litter size, and hence food intake, immediately after birth; (2) long-term postnatal undernutrition and subsequent rehabilitation; (3) the effects of slow prenatal growth and small size at term on subsequent growth and development.

Early postnatal undernutrition (1950s)

In the 1950s Gordon Kennedy introduced Dr Widdowson and Professor McCance to the idea of rearing rats in groups of different size, so that by weaning at 3 weeks those in small groups were two to three times as heavy as those in large groups. Kennedy used this model for a wide range of studies and found, for example, that even though all animals had unlimited access to food after weaning, the rats from large litters remained small and there was no sign of the catch-up growth which is characteristic of rehabilitation after undernutrition at older ages (Widdowson & McCance, 1960; Widdowson & Kennedy, 1962).

Long-term undernutrition (1960s)

In studies on undernourished pigs, carried out initially by Professor McCance, the undernutrition from 10 d after birth was so severe that by 1 year their body weight was only 3 % that of their well-fed littermates (McCance, 1960). When, after 1 year they were offered plentiful food they ate it and began to grow. Then, to use Dr Widdowson's words: 'In 1966, Professor McCance went to Uganda for two years and I became more adventurous. I continued the undernutrition for two and three years before I rehabilitated the pigs'. Even after careful rehabilitation, the animals did not catch-up body weight completely but it was found that they carried on growing at a later age than either control littermates or piglets undernourished before birth (McCance & Widdowson, 1974; Widdowson, 1974). It was also found that the previously undernourished females produced good litters and their piglets bore no obvious mark of 'the nutritional adventures their parents had undergone'.

Prenatal undernutrition (1970s)

Dr Widdowson then turned her attention to another aspect of nutrition and development for which the pig was again a particularly suitable experimental animal: the effect of slow prenatal growth and small size at term on subsequent growth and development (Widdowson, 1971). Within a litter of piglets there is sometimes a runt or small-for-gestational-age (SGA) animal, which is only about a half or even a third the weight of its appropriate-for-gestational-age (AGA) littermates. This naturally occurring form of intrauterine growth retardation probably results from a reduced placental blood supply, associated with a specific position in the uterine horn, leading to prenatal undernutrition (Widdowson, 1976). Not only is the SGA animal small but its muscle weight is less than that of younger AGA fetuses with the same body weight. After growth to maturity, the SGA pig is still smaller than its larger littermate. By contrast with undernutrition in later life, however, SGA and AGA animals stop growing at the same chronological age.

During the 1970s I joined Dr Widdowson's laboratory and undertook parallel studies on early nutrition and later development of the human infant, with Douglas Gairdner and Jonathan Shaw (Dauncey, 1974). These studies revealed that by 1 year of age SGA infants, especially boys, did not attain the size of AGA infants born either pre-term or at term.

IMPLICATIONS

Fundamental

These pioneering studies by Dr Widdowson and her colleagues have many far-reaching implications. General principles concerning critical periods of development, during which the long-term development of the individual may be permanently affected, were established. Moreover, they also highlighted important species differences which were linked with the stage of maturity at birth. For example, 'a full-term infant has reached a fairly advanced stage of development by the time it is born, as has a pig, and even more so a guinea pig or a horse. Even a very premature baby is in a more advanced stage of development than a rat born after its normal period of gestation' (Widdowson & McCance, 1975).

Many biological systems, including appetite control, are affected by early nutrition, and since they each have unique patterns of development, the precise response to undernutrition is dependent on chronological age, stage of development and the length of

time during which the individual is undernourished. Clearly, if a nutritional insult occurs during a critical period of cellular differentiation, it is reasonable to postulate that there will be long-term and permanent changes in cell numbers, cell types, and the functions of their associated tissues and systems. Moreover, these fundamental observations suggest that long-term development, in terms of health and disease, may also be affected by undernutrition. Evidence is now accumulating to support this suggestion and this is discussed briefly in the next section.

Applied

Epidemiological studies. Recent evidence suggests that many adult diseases, such as non-insulin-dependent diabetes mellitus (NIDDM) and cardiovascular disease, may originate from an adverse environment during early development (Barker, 1995). Epidemiological studies have shown that both small size and disproportionate size at birth are related to later disease. In a study of over 15 000 men and women born between 1911 and 1930, death rates from CHD fell progessively between those who weighed less than 2·5 kg at birth and those who weighed 4·3 kg (Barker *et al.* 1989; Osmond *et al.* 1993). There is also a steep fall in prevalence of glucose tolerance or NIDDM between men who were small and those who were large at birth (Hales *et al.* 1991). Moreover, it is thinness at birth and not simply small size that is associated with the insulin-resistance syndrome, which includes impaired glucose tolerance, raised blood pressure and disturbed lipid metabolism, in later life (Phillips *et al.* 1994). Adult lifestyle does, however, add to intra-uterine effects; the highest prevalence of impaired glucose tolerance and NIDDM is seen in those who were small at birth but obese as adults (Hales *et al.* 1991).

Prospective/experimental studies. Experimental work on nutritional programming is enabling more-detailed exploration of the significance of the correlations obtained from epidemiological studies. It will, however, be many decades before their long-term implications can be investigated thoroughly. It has already been shown that the early nutrition of pre-term infants has long-term effects on mental abilities and bone mineralization (Lucas, 1994). In the 1980s, pre-term infants were randomly assigned to either standard term formula milk or special nutrient-enriched pre-term formula. At 18 months, infants on the special diet did better in developmental tests, especially those involving physical coordination (Lucas *et al.* 1990), and at 8 years they have a raised performance on verbal IQ tests (A. Lucas, R. M. Morley, C. E. S. Leeson-Payne and G. Lister, unpublished results).

Although a poor maternal diet is not the only cause of poor fetal development, it may play a role: studies in rats from mothers fed on a low-protein or low-energy diet indicate adverse programming effects on many variables including glucose and lipid metabolism (Desai *et al.* 1995) and hypertension (Langley-Evans & Jackson, 1994). It has been proposed that this maternally-induced programming of hypertension is mediated by increased fetal exposure to glucocorticoids (GC) through insufficiency of placental 11β-hydroxysteroid dehydrogenase activity (Seckl & Brown, 1994; Langley-Evans *et al.* 1996). The role of maternal nutrition in the development of later disease is a subject of intense current interest and as yet evidence is not entirely clear-cut. Thus, with other variables such as plasma cholesterol and triacylglycerol, a low maternal protein intake is not necessarily a disadvantage (Lucas *et al.* 1996). Moreover, by constrast with rats given a low-protein diet during both pre- and postnatal life, in those exposed to a low-protein diet only *in utero* there is neither decreased pancreatic islet vascularization nor decreased islet perfusion (Iglésias-Barreira *et al.* 1996).

MECHANISMS

These epidemiological and prospective/experimental studies, taken together with those of Dr Widdowson and her colleagues, raise a number of important questions including: what determines the potential for catch-up growth? What are the mechanisms underlying nutritional programming? Can the adverse effects of early environment be reversed or ameliorated by subsequent optimization of nutrition? The last is especially important if early undernutrition cannot be avoided e.g. because of illness of the mother and/or young. An understanding of mechanisms underlying nutritional regulation of development will help to provide answers to these questions. Consideration should be given to (1) direct effects of nutrients on gene expression, (2) indirect effects of nutrition via hormones and growth factors acting as nutritional signals, (3) the extent to which responses may be specific at either the tissue or cellular level (Dauncey, 1995).

Specific nutrients can influence gene expression directly e.g. long-chain polyunsaturated fatty acids are potent inhibitors of the expression of hepatic lipogenic enzyme genes (Girard *et al.* 1994). However, under conditions of altered energy status, such as undernutrition, it is probable that hormones and/or growth factors act as especially potent mediators of the response.

Hormones and growth factors as mediators of nutritional response

Nutrition has profound effects on many anabolic and catabolic hormone and growth factor systems such as those involving thyroid hormones (TH), growth hormone (GH), insulin-like growth factor-I (IGF-I), GC, insulin and glucagon. Effects occur at many levels including rates of secretion and utilization, binding proteins and receptors. To give a few examples from my own laboratory, in collaboration with many international colleagues: TH, which are especially important mediators of growth and development, are affected by energy status at the levels of the hypothalamus, pituitary and thyroid gland, and also within the peripheral tissues at the deiodinase and receptor levels (Dauncey, 1990; Morovat & Dauncey, 1995; Berthon *et al.* 1996). Moreover, at the level of gene expression, increased energy intake markedly increased hepatic GH receptor mRNA abundance (Dauncey *et al.* 1994*b*) and, assuming increased GH receptor protein levels, this would result in increased synthesis and plasma concentration of IGF-I, and hence lead to an increased potential for growth (Dauncey *et al.* 1993; Straus, 1994; Thissen *et al.* 1994). In this context, the marked differences in growth factor content of infant foods may be especially important in relation to early postnatal development (Dauncey *et al.* 1994*a*; Donovan & Odle, 1994; Burrin *et al.* 1995). Maternal milk, and especially colostrum, has very high concentrations of growth factors such as IGF-I, whereas there are virtually none present in infant formula feeds.

The decrease in hepatic GH receptor gene expression induced by undernutrition is tissue-specific; in muscle, conditions of low energy status induce an increase in GH receptor mRNA abundance (Dauncey *et al.* 1994*b*). This response may reflect the lipolytic and diabetogenic actions of GH, in increasing fatty acid oxidation and limiting glucose utilization. The extent to which this response may have particular relevance to the nutritional programming of impaired glucose tolerance and insulin resistance is highlighted in Fig. 2.

Development, hormones and nutrition. There is now considerable evidence to suggest that patterns of hormone secretion, sensitivity and turnover are related to age and stage of development (Fowden, 1995; Dauncey & Harrison, 1996). One can therefore postulate that (1) the timing, duration and amplitude of a nutritional challenge will alter responses at the cellular and molecular levels; (2) defects in normal maturation of the many hormonal axes

will affect the response to nutrition. Taken together, these ideas would explain both the responses to optimal nutrition and defects in development due to poor nutrition. Especially important also are the many interactions between the different hormone systems (Fowden, 1995) e.g. GH receptor gene expression is modulated in a tissue-specific manner by both TH and cortisol (Duchamp *et al.* 1996; Li *et al.* 1996).

Nutrition–gene–cell interactions in development. Despite the complexity of this system, we need to obtain an integrated view of the field. Attention is often focused on control of the initial point, of hormone secretion, but perhaps we should also focus on the end-point, of tissue responsiveness. Fig. 1 therefore presents a model by which early nutrition can influence later development, with interactions between nutrition and nuclear hormone receptors playing a pivotal role. The critical point is that nutrition can influence the expression of those hormone receptors which act as nuclear transcription factors, such as GC and TH receptors. These have the potential to influence the expression of a vast array of genes involved in growth, development and differentiation, including those concerned with cell surface receptors, intracellular signalling, and cell structure and function. Moreover, these developmentally-programmed events are tissue- and perhaps also cell-specific. For example, prenatally there is evidence for the GH receptor gene being expressed at a very much earlier stage of development in muscle than in liver, and postnatally there are also marked differences in the ontogenic profiles of GH receptor in these two tissues (Duchamp *et al.* 1996; Schnoebelen-Combes *et al.* 1996). Thus, a given circulating level of GH has the potential for exerting strikingly different types of developmental control in different tissues during fetal and postnatal life.

Particularly intriguing in the context of nutrition–hormone interactions is the following observation on long-term undernutrition and rehabilitation: 'in the animals rehabilitated after 2 and 3 years undernutrition, the muscles were so infiltrated with fat that the muscle fibres were completely embedded within it' (Widdowson, 1974). This could certainly be explained by changes in hormone balance, secretion and responsiveness, and not least in GH receptor abundance, and associated changes in metabolic fuel utilization, at different stages of development. In collaboration with many co-workers, Dr Widdowson undertook a number of studies on muscle development (e.g. Dickerson & Widdowson, 1960) and the next section discusses in more detail the extent to which cell structure and function may be affected by nutrition, by reference to the development of muscle.

Muscle development

Nutrition, hormones and growth factors. Not only is muscle essential for movement, breathing, thermogenesis, cardiovascular and intestinal function, but skeletal muscle plays a key role in determining nutrient oxidation rates and is the main peripheral site of insulin action. Nutrition can have major effects on muscle structure and function, with functionally distinct muscles differing in their responsiveness (Dauncey & Gilmour, 1996). These effects are in turn dependent on age and stage of development. Thus, changes in energy status before birth affect myofibre hyperplasia (Handel & Stickland, 1987), postnatally they can affect the proportions of type I slow oxidative and type II fast oxidative-glycolytic myofibres (Harrison *et al.* 1996*a*), and in adults there are myofibre type-specific effects on hypertrophy (Polla *et al.* 1994). Moreover, organ-selective growth retardation occurs in rats with protein-restricted mothers, and muscle is one of the tissues showing a marked reduction in weight (Desai *et al.* 1996).

Hormones and growth factors including TH, GC, GH, insulin-like growth factors (IGF) and insulin, play a central role in normal muscle development and function, and their actions are in turn dependent on stage of development (Dauncey & Gilmour, 1996; Harrison *et al.*

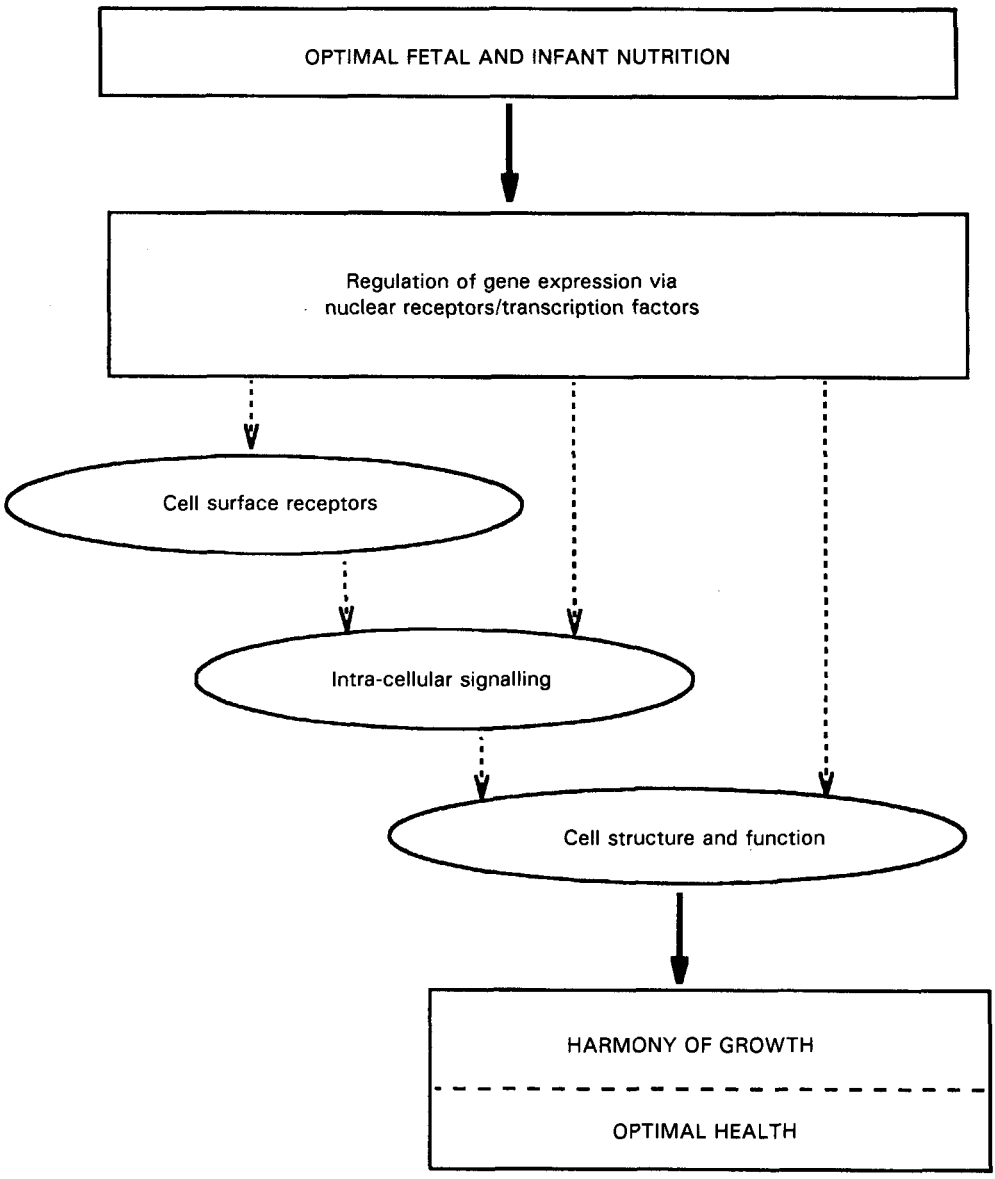

Fig. 1. Nutrition–gene–cell interactions in development. This flow-chart presents an overview of one of the mechanisms by which nutrition may affect development, and can be applied to many different systems. Note that developmentally-programmed events are both tissue- and cell-specific, and each system has its unique ontogenic profile. Therefore, nutrition must be optimal at each stage of development for harmony of growth (Widdowson, 1970) to occur.

1996*b*; Herpin *et al.* 1996). For example, early in development TH induce myoblasts to leave the cell cycle whereas later they are involved in switching between myofibre types, and similarly, IGF stimulate stem cell proliferation and terminal differentiation of myoblasts into myotubes at different stages of fetal development. Myofibres also differ in their responsiveness to insulin, GH, TH and GC, and in adults the hypoinsulinaemic states of diabetes and starvation result in selective atrophy of type II fast fibres.

Early nutrition and later disease: muscle development and insulin resistance. The age-, tissue- and cell-specific differences in nutritional and hormonal sensitivity may be highly relevant to the development of the SGA infant. It has been suggested that undernutrition in mid- to late-gestation alters the normal pattern of muscle development, leading in turn to modifications in muscle metabolism and insulin resistance (Barker, 1995; Taylor *et al.* 1995). Fig. 2 indicates one of the series of pathways by which this response could be mediated. We now need to determine whether early undernutrition results in tissue- and cell-specific defects in the nuclear receptors for TH and GC, members of a super-family of transcriptional regulators. Such a response would trigger a cascade of defects, by influencing the tissue- and cell-specific expression of numerous genes. Both the direct effects of these nuclear receptors, and those mediated by e.g. GH intracellular signalling pathways, would affect many aspects of muscle development including vascularization via changes in IGF, and glucose sensitivity via the GLUT family of facilitative glucose transporters. This would lead inevitably to impaired muscle development and function.

Responses to undernutrition may be age-dependent because they are mediated by programmed differences in hormone and/or growth factor sensitivity. Because there are marked age-specific differences in phenotypic plasticity, changes at critical stages of development would have long-term or permanent effects and, especially with continued malnutrition, would result in insulin resistance, NIDDM and cardiovascular disease in later life.

To highlight the complexity of this scheme and how much remains to be investigated, I shall briefly consider two of the aspects mentioned in Fig. 2: TH receptors and JAK2 phosphorylation.

Nuclear hormone receptors. All members of the hormone receptor super-family of transcriptional regulators contain two highly conserved domains which can bind respectively the specific hormone or ligand and a region of DNA on the target gene (Lazar, 1993). There are two distinct α and β TH receptor genes which in turn encode a family of receptor isoforms. These each have different affinities for TH and their localization is tissue-specific. Moreover, ligand-independent activation has been reported in mammalian cells, and *in vitro* assays show that unliganded TH receptors can repress transcription of normally TH-inducible genes. Much remains to be determined about the precise functions and cellular localization of these isoforms and the extent to which they are developmentally and nutritionally regulated in a tissue- and cell-specific manner. Evidence suggests, for example, that the molecular species of nuclear TH receptors are differentially expressed in liver and muscle during fetal life (Duchamp *et al.* 1994). Moreover, we have recently observed marked effects of postnatal nutrition on TH receptor α isoform gene expression (White & Dauncey, 1998).

Signalling pathways activated by growth hormone. The GH receptor belongs to the cytokine family of receptors and its signal transduction pathways have been the subject of intense investigation in recent years (Xu & Sonntag, 1996). Two major pathways currently identified for GH action are those for JAK2-STAT (janus kinase 2-signal transducers and activators of transcription) and ras-raf (proto-oncogene proteins). Thus, the first stage in activation of the receptor stimulates JAK2 and facilitates association of the receptor with JAK2 into a complex, with subsequent phosphorylation of both proteins. This can result ultimately in increases in c-*fos*, c-*jun*, serine phosphatase inhibitor-1 and IGF-I gene expression (Bichell *et al.* 1992). Recent studies suggest a decline in JAK2 phosphorylation with age (Xu & Sonntag, 1996). We now need to know the extent to which nutritional status is involved in this modulation of GH action and whether the receptor signalling pathways are modulated in a tissue-specific manner.

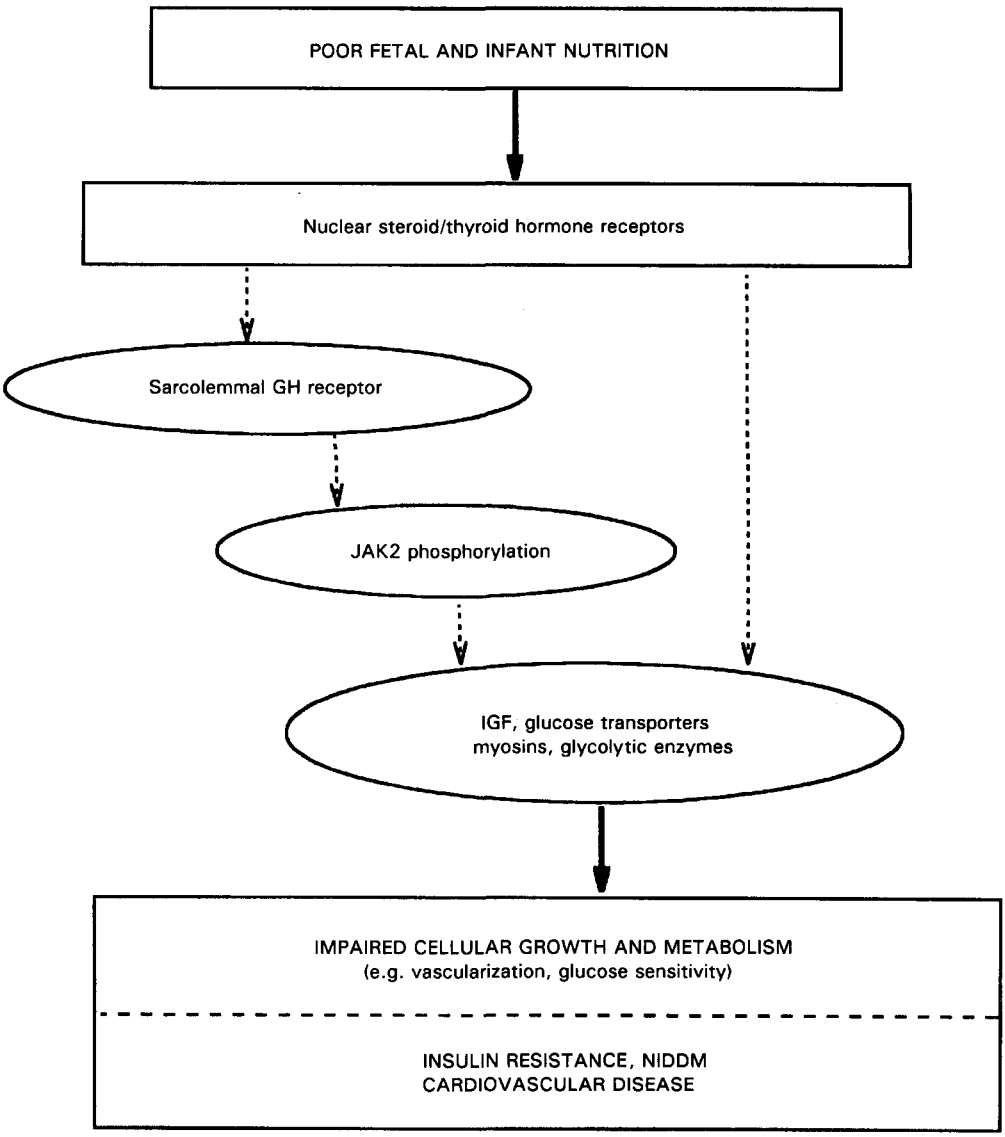

Fig. 2. Early nutrition and later disease: muscle development and insulin resistance. This flow-chart indicates one of the mechanisms by which poor nutrition may programme disease in later life. Note that because there are marked age-specific differences in phenotypic plasticity, changes in nutrition at critical stages will have long-term or permanent effects on development. GH, growth hormone; JAK2, janus kinase 2; IGF, insulin-like growth factors; NIDDM, non-insulin-dependent diabetes mellitus.

PERSPECTIVE

Many aspects of development are affected by early environment. Dr Widdowson's studies in Germany on nutrition, mental contentment and physical growth showed that psychological stresses due to harsh and unsympathetic handling may seriously curtail growth rates (Widdowson, 1951). Results from a prospective epidemiological study

published less than 6 months ago also indicate that emotional problems during youth may act as predictors of stature during early adulthood (Pine *et al.* 1996). One can speculate that at least part of this response is mediated by changes in hormone and growth factor function, not least by changes in nuclear GC receptors affecting GH receptor gene expression.

The enzyme JAK2 was named after the Roman god Janus; the patron of gateways and the beginning of things. There is no problem in predicting a myriad of studies which should be undertaken in the future. My hope is that the start of the new millenium brings increased understanding of the mechanisms underlying tissue and cellular sensitivity to nutrition during critical periods of development. This would enable us to prevent, reverse or ameliorate the adverse effects of early environment in later life.

Janus had two faces and looked both ways. I feel justified, therefore, in finishing by looking back almost 500 years to a quotation which is relevant to a celebration of the 90th birthday of arguably the world's most eminent nutritionist:

'If you understand that old age has wisdom for its food,
you will so conduct yourself in youth that your old age will not lack for nourishment'.
Leonardo da Vinci c. 1500

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