Food and biological clocks

BY BRIAN WHARTON

Department of Human Nutrition, University of Glasgow, Yorkhill Hospitals, Glasgow G3 8SJ

It may be an artificial limitation to discuss the relationship between diet and an individual's biological clock without also considering the two other major modifying influences, his genes and the environment in which he lives. These three influences are anyway interconnected. Biological clocks and events, like all physiological processes, are under genetic control to a large extent, e.g. the fall in jejunal lactase (EC 3.2.1.108) activity in the toddler years of most of the world's children. The stage of development an individual has reached will partly determine his nutritional environment, e.g. whether he is a suckling, weanling or omnivore; the amount of physical activity, etc.

Nevertheless the present review deals entirely with the biological clocks, that is the stages of development from gametogenesis to old age.

GAMETOGENESIS

Ovulation. The story of the Dutch famine during the 1939–45 war is well known (Stein et al. 1975). Amenorrhoea was common and it was followed 9 months later by a substantial fall in birth rate. There was good evidence, therefore, that a sudden reduction in energy intake, probably to less than 6.3 MJ (1500 kcal) per head in the household inhibited ovulation. There is also evidence of a similar mechanism in anorexia nervosa (Parry-Jones, 1991).

Spermatogenesis. The effect of protein–energy deficiency on spermatogenesis has received less attention but the male volunteer prisoners in the Denver study of starvation had reduced sperm counts, with fewer motile forms. Zinc deficiency is thought to be responsible for the delays in testicular development and puberty seen in many boys in the Fars province of Iran and elsewhere in the Middle East (Eminians et al. 1967; Stanstead et al. 1967). Presumably this also leads to a delay in the onset of spermatogenesis, although no direct evidence for this has been collected.

ORGANOGENSES

There is evidence in man to implicate deficiencies of protein–energy, folic acid and Zn during the stage of organogenesis as a factor in the aetiology of congenital malformations.

The incidence of neural tube defects increased in babies conceived during the Dutch famine (Stein et al. 1975).

Folate deficiencies. In Britain there is evidence that multi-vitamin supplementation and in particular folic acid around the time of conception reduces the incidence of neural tube defects in the babies of mothers who have had a previous child with a neural tube defect. Some years ago blood levels of selected vitamins were measured in the first trimester of pregnancy in over 900 women (Smithells et al. 1976). Seven mothers subsequently had babies with neural tube defects and they had significantly lower levels of erythrocyte
Table 1. *Neural tube defects (NTD) v. preconception vitamins.* (From Medical Research Council Vitamin Study Research Group, 1991)

<table>
<thead>
<tr>
<th>Folic acid</th>
<th>Other vitamins</th>
<th>NTD:All</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>—</td>
<td>2:258</td>
<td>1%</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>3:256</td>
<td>0.28 (0.1-0.8)</td>
</tr>
<tr>
<td>—</td>
<td>Yes</td>
<td>11:260</td>
<td>3.5%</td>
</tr>
<tr>
<td>—</td>
<td>Yes</td>
<td>7:257</td>
<td></td>
</tr>
</tbody>
</table>

Folate and leucocyte vitamin C. Following this circumstantial evidence an intervention study was set up (Smithells *et al.* 1980). The subjects were women who had had a child with a neural tube defect, who were considering a possible further pregnancy but who were not pregnant then. Mothers who were already pregnant at the time they sought advice did not receive the supplement and in effect acted as controls. The supplement included folic acid, vitamin C, riboflavin, vitamin D, thiamin, pyridoxine, nicotinamide, iron and calcium. Three of 429 (0.7%) infants/fetuses of fully supplemented women had recurrences of a neural tube defect compared with twenty-four of 510 (4.7%) born to unsupplemented women over the same centres.

The design of this study has been criticized since it was not randomized and those in the treated group were in effect self-selected, i.e. the treated mothers were those sufficiently motivated to seek advice before becoming pregnant again. Consequently the Medical Research Council organized a randomized double-blind control of periconceptional vitamin supplementation in mothers who had already had an affected child. The results are shown in Table 1. They confirm the Smithells *et al.* (1980) observations. There seems no doubt that folic acid deficiency is teratogenic in man.

Zn deficiency. Sever & Emanuel (1973) commented on the higher incidence of congenital malformations of the central nervous system in the Middle East where Zn deficiency in humans was first described. This hypothesis was supported by Cavdar *et al.* (1980) who found lower serum and erythrocyte Zn in Turkish women who gave birth to anencephalic babies. Mothers with acrodermatitis enteropathica, also have babies with congenital malformations (Hambidge *et al.* 1975), but not if they have received Zn therapy (Brenton *et al.* 1981). Jameson (1976) studied 234 women, eight of whom had babies with a congenital malformation and five of these mothers had very low values of serum Zn. It seems probable, therefore, that Zn deficiency is teratogenic in humans.

**HISTIOGENESIS**

All organs are established by the end of the first trimester of pregnancy but further differentiation to form the tissues seen at birth carries on throughout the second and third trimesters. It seems probable that dietary factors could modify this process of differentiation and tissue formation just as it can modify organogenesis.

There is little firm evidence, however, to link diet with this phase of the biological clock. The development of teeth (if they can be regarded as a tissue rather than individual organs) may be an exception. A poor vitamin D status in mothers results not only in neonatal hypocalcaemia in their babies but in enamel hypoplasia of the babies’
teeth when they subsequently erupt and this can be reduced by vitamin D supplementation during pregnancy (Cockburn et al. 1980). Sunlight and diet had, therefore, interfered with histiogenesis in mid and later pregnancy.

One might speculate that the mechanism of the Barker (1992) hypothesis relating intrauterine nutrition to late cardiovascular morbidity might be via the modification of histiogenesis in vascular tissues at this stage of pregnancy.

**BIRTH WEIGHT**

There is little doubt that the mother's state of protein–energy nutrition affects birth weight. The wartime experiences in Leningrad and Holland are well known. In addition in recent years, there have been a series of intervention studies designed to study in more detail the effects of protein–energy supplementation on fetal growth. These have been reviewed elsewhere (Wharton, 1985) but give conflicting results. In the second trimester the mother should normally be laying down stores of fat in anticipation of later fetal demands (Hytten & Leitch, 1971). Protein–energy undernutrition at this stage as shown by a failure to lay down adequate amounts of fat may compromise later fetal growth (Bissenden et al. 1981; Viegas et al. 1987). In the third trimester most of the mother's weight gain is due to the increase in size of the fetus and she herself is no longer storing food. However, if undernutrition has been recognized in time, e.g. because her skinfold thickness has not increased normally, then improved nutrition during this remaining third trimester can prevent poor fetal growth (Viegas et al. 1982a,b).

These concepts may explain the apparently conflicting results of various supplementation studies in pregnancy. In those showing a positive effect (e.g. Birmingham at risk group, Guatemala, Colombia, Gambia during the wet season, Aberdeen) the mothers had probably failed to lay down adequate stores during the second trimester, whereas in those showing no effect (e.g. Birmingham not at risk group, New York, Taiwan, Gambia in dry season) fat stores were probably adequate.

The concept of birth weight as an important biological event might be questioned, but the hypotheses and evidence developed by the previous paper (Barker, 1992) relating size at birth to disease in later adult life is sufficient evidence. Moreover, in the short term birth weight is related to survival in infancy throughout the world, and to the risk of suffering from protein–energy malnutrition during later infancy and the toddler years in developing countries.

**FOOD FOR THE SUCKLING**

The short-term effects of breast-feeding are well known. From the point of view of biological clocks the concept of a 'priming or conditioning' stimulus is relevant. By this hypothesis early feeding experiences act as a priming stimulus which if they are followed by some later environmental stimulus will result in the development of a particular disorder. Had the later stimulus occurred without the earlier priming stimulus it would not have resulted in disease.

There is some evidence that absence of breast-feeding may be a priming stimulus for later development of certain diseases. Table 2 summarizes three studies relating breast-feeding to the later development of Crohn's disease. The findings are not consistent and so not convincing, but there is sufficient evidence to support further...
Table 2. Crohn's disease in children and adults, and breast feeding or diarrhoea during infancy

<table>
<thead>
<tr>
<th>Study</th>
<th>Crohn's</th>
<th>Matched controls</th>
<th>Siblings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whorwell et al. (1979)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Southampton</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>57</td>
<td>114</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>33</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Never breast-fed</td>
<td>11 (19%)</td>
<td>22 (19%)</td>
<td></td>
</tr>
<tr>
<td>Gastroenteritis &lt;6 months</td>
<td>6 (11%)</td>
<td>1 (1%)</td>
<td></td>
</tr>
<tr>
<td>Bergstrand &amp; Hellers (1983)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stockholm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast-feeding (months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>36</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>1-3</td>
<td>100</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>4-6</td>
<td>96</td>
<td>106</td>
<td></td>
</tr>
<tr>
<td>&gt;6</td>
<td>74</td>
<td>121</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>308</td>
<td>308</td>
<td></td>
</tr>
<tr>
<td>Koletzko et al. (1989)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toronto</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>114</td>
<td>180</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>16-1</td>
<td>18-1</td>
<td></td>
</tr>
</tbody>
</table>

Relative risk

Not breast-fed 3.8 Had diarrhoea 2.9

investigation of the concept. The relationship of early feeding experiences to later gastrointestinal disease has recently been reviewed (Wharton & Edwards, 1992). There seems, then, sufficient evidence to regard the suckling's choice of food (breast milk or an infant formula) as an important event in the biological clock.

GROWTH AND VULNERABLE PERIODS

The long-term effect of nutritional stress depends at least partly on its timing. The importance of timing was demonstrated in a variety of animals in Cambridge many years ago, and was reviewed by McCance (1962) in his memorable *Food, Growth and Time*. These, and similar observations, have been used to support the critical period hypothesis of development. This was probably first stated by Moulton in 1923, but was refined by Dobbing (1968) 'if a developmental process be restricted by any agency at any time of its fastest rate, not only will this delay the process, but will restrict its ultimate extent, even when the restricting influence is removed and the fullest possible rehabilitation obtained'.

The hypothesis is well known to embryologists where undoubtedly a 'restricting agency' applied at a critical period will have a permanent effect and this has been discussed under 'organogenesis' above. It is clear that the hypothesis cannot be applied so absolutely to situations where the restricting agency is more gradually perceived by the individual, and the developmental process has fewer discrete and marked changes than in embryological life. Nutritional stresses occurring during post-natal life and after the first trimester of pregnancy in the human might, therefore, not follow the hypothesis as closely as embryological events.
Fig. 1. Nutrition and the stage of development; the effects of nutritional stress in an early period (a and b), in the mid term (c and d) and at a later stage (e) on distance travelled, velocity, and biological events (from Wharton, 1976).

The concept of the vulnerable period hypothesis is developed further in Fig. 1. The stage of development modifies the effect of nutritional stress on first the 'distance' the individual has reached at a certain age, e.g. in height, number of cells in various organs, and second, the velocity or rate at which the 'distance' is covered, e.g. height velocity, peaks of growth rate in cells and tissue. Some aspects of development seem to occur in one stage only; others may occur in two or more stages; height and weight velocity have two peaks during infancy and at puberty, and probably a peak occurs also earlier still in the mid trimester of pregnancy. Superimposed on these continuous variables, and partly programmed by them, are discrete biological events, such as eruption of teeth, the arrival and departure of fertility. Fig. 1 shows a theoretical measurement (it might be height or cell number) which has two peaks of velocity and a biological event (e.g. menarche) occurring during the second peak.

Early stress. Insult ‘a’ occurs during part of the first growth spurt but when it is over there is still time for an acceleration in velocity which, although delayed, is sufficient for the individual to experience ‘catch-up growth’ on the distance chart. By the time insult
‘b’ has ceased, however, the opportunity for a substantial acceleration of velocity has passed by, and so although there is some acceleration and some catch-up growth, it is too little to make up for what has been lost. An example of ‘a’ is the light-for-dates baby in whom growth retardation occurs only in later pregnancy. The prolonged undernutrition occurring throughout infancy and into the early toddler years which occurs in a number of developing countries, particularly in urban areas, is an example of ‘b’.

Mid-term stress. Insults ‘c’ and ‘d’ occur during a period of steady velocity. In addition to altering the velocity rate the stress also advances or retards the biological clock so that the second peak velocity and its associated biological events are moved in time. Obesity in childhood leads to an early puberty while undernutrition delays it.

Later stress. Insult ‘e’ occurs throughout the second peak velocity. The velocity and distance charts are both affected and immediate biological events are delayed, but what happens after then? Our observations of biological events occurring some time after growth is over are limited.

GROWTH SPURT AND PUBERTY

The prepubertal growth spurt is not merely a matter of increase in size. Body shape and composition also change. Boys start with about one-sixth of their weight as body fat; they develop muscle so that fat falls to one-tenth of weight. Girls also start with one-sixth body fat increasing to about one-quarter of the body-weight. The increase in growth velocity and changes in body composition are related to the various biological events of puberty.

The timing of menarche has been studied in detail. Frisch & Revelle (1971) have developed a ‘hypothesis’ of menarche (see Fig. 2). They showed that girls who experienced menarche relatively early (the earliest quartile) when compared with ‘later’ girls, had also started their growth spurt earlier. At the time of menarche ‘early’ girls were shorter than ‘later’ girls; attained height seemed little to do with the onset of menarche. However, weight at menarche was similar in both the ‘early’ and ‘later’ groups; perhaps weight had to some extent programmed, or was the trigger, for menarche.

This concept has been developed further. The onset and maintenance of menstruation depend on a minimum weight-for-height, and a minimum fat of 17% of body-weight (Frisch, 1977). On a population basis this hypothesis of menarche fits well, but it is not accurately predictive in individuals.

Clearly diet affects weight-for-height and the proportion of body fat, and perhaps via this mechanism diet affects the biological clock of the growth spurt and the biological event of menarche.

The hypothesis or at least the observations that led to it are of practical day-to-day value in the management of anorexia nervosa in adolescent girls. One psychodynamic theory of this condition is that the development of extra body fat heralds the onset of development of sexual maturity. This is subconsciously unacceptable to some girls, the extra fat is threatening and so pathological slimming is the solution. The Frisch (1977) data provide minimal and average weights-for-height, for the correction of primary or secondary amenorrhoea in anorexia nervosa. The data can then be used, with some discretion, for setting a ‘target weight’ for the treatment of girls with anorexia, which is based on concepts of development and maturity rather than mere size (Parry-Jones, 1991).
IMPACT OF DIET ON DEVELOPMENT

1.70 r

1.30 t

1.1 1.4 1.8
Age (years)

50
40
30
20
10
0

Fig. 2. Heights and weights of girls experiencing menarche 'earlier' and 'later' (based on data of Frisch & Revelle, 1971).

LATER LIFE

The biological clocks and associated events in later life have received less study than earlier on.

Menopause. The influence of diet on the timing of menopause is not known. Gynaecologists have the impression that the menopause is occurring later in life in Britain than it did some years ago; also that it occurs earlier in developing countries than in more developed ones (World Health Organization, 1969), but is this genetic or environmental? The timing of the menopause has important implications for one nutritionally-related disorder, osteoporosis.

Osteoporosis. Bone mass begins to fall rapidly after the menopause. The greater the bone mass initially, however, the greater the post-menopausal fall may be before a dangerously low level is reached when the risk of fracture increases substantially. Bone mass reaches its peak at about 30–40 years of age, but 90% of this peak bone mass has been reached before the pubertal growth spurt is over.
To what extent these events are nutritional is unclear. In view of the relationship between diet and the timing of menarche a relationship between diet and the timing of the menopause is at least plausible. What about Ca and the many dietary factors affecting its absorption (e.g. fat, fibre) and excretion (e.g. dietary protein)? Following the menopause a much greater dietary intake of Ca is necessary to achieve positive Ca retention. Boyle (1991) in a recent review has concluded that 'the bulk of evidence supports the view that the negative Ca balance found in post-menopausal osteoporosis is a consequence (of the bone loss) not a cause and that dietary Ca can only, if at all, influence the course of events if pushed up to unusually, and for many intolerably, high levels'.

Looking to earlier years does dietary Ca affect the size (height) of the peak bone mass? The pattern of Ca accretion (e.g. in mg/d) is similar to that of weight velocity, i.e. high in infancy, then falling with a secondary rise and fall around puberty; peptide hydroxyproline excretion which reflects collagen turnover has a similar pattern (Wharton et al. 1972). But as with the post-menopausal Ca changes, is this a consequence or a cause of the changes in bone mass? There is some evidence in that Ca supplementation (718 mg daily) for 3 years in girls aged less than 14 years led to a 10% increase in bone mass (Miller & Johnston, 1990). It is not known whether this hastened the timing of the peak mass or actually increased its ultimate size. Was the effect of the Ca as in 'd' in Fig. 1? Nevertheless it is a clear example of dietary Ca as a cause (rather than a consequence) of changes in bone mass.

THE HARMONY

The biological clock of the individual is mainly under genetic control but it is slowed or speeded up by environmental factors one of which, probably the most important, is nutrition. A person's clock may dictate many features of his nutritional environment such as his choice of food, energy expenditure via work and play, his exposure to sunlight. Biological clocks, food and nutrition are indivisible; in Scottish terms a true ceilidh (a concert, dance).

REFERENCES

IMPACT OF DIET ON DEVELOPMENT


Printed in Great Britain