Review article

Evolution of infant nutrition

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Homo sapiens has developed during the course of over two million years. The social and physical conditions of life, the availability of milk and infant foods as well as the presence of diseases have all undergone radical transformations from the Stone Age, at first without and then with fire, to the hunter–gatherer, farmer–herder, agricultural and, now, developed societies. These changes in the human environment may have induced modifications in the length of pregnancy, the development of the neonate at birth, the duration of lactation, the composition of breast milk and use of weaning foods and milk substitutes. Darwinian selection for the nutrient, anti-infective and other components of breast milk may have been determined by the effects of nutrition, through genetic variations in milk composition, on the survival of infants and perhaps also on fecundity and disease resistance in later adult life. Today Darwinian selection may no longer be effective in maintaining or modifying human mammary function, because modern hygienic environments, together with the availability of nutritionally adequate breast-milk substitutes, permit infant survival even under conditions of total lactational failure. National and international promulgations strictly control the composition of infant formulas offered as breast-milk substitutes or as weaning foods. These recommendations are modified as beliefs suggest, and research indicates, the effects of nutrients and other factors on the health and well-being of the child. Preliminary observations on child health have often proved valuable in furthering research. Unquestioning acceptance of apparently desirable, but untested, epidemiological associations have led to unexpected but dangerous iatrogenic problems. Recommendations for change cannot safely be made without proper comparisons with present products and procedures under practical conditions. Such tests are time consuming and require protocols of appropriate statistical design and power while still meeting the required sociological and ethical constraints, but are essential to identify possible harmful effects of any proposed change. It is suggested that no novel ingredients should be added, or major changes permitted in any component, until appropriate trials have established the value and safety of the proposed modifications. Breast-feeding is vital to maximize infant survival in developing countries. There are major difficulties in assessing any differences in morbidity and mortality of breast-fed *v.* artificially reared infants in the developed world. Carefully controlled studies with comparisons of health and well-being, not only in infancy but throughout life, are desirable if the effects of infant nutrition on adult well-being, suggested by epidemiological studies, are to be validated and ultimately applied. There are considerable variations in the composition of breast milk. This variance suggests that it may ultimately be possible to design formulas better able to meet the needs of individual infants than the milk available from the mother's breast.

Evolution: Infant nutrition: Breast-feeding

Evolution

Two million years to develop: but what of the future?

Most would agree that breast milk is the best food for the suckling infant, particularly when there are risks of infection. Human milk is presumed to have evolved, over about 2–2·5 million years, to meet the varying circumstances of Hominid species and their environments. In the last few generations, during the course of only 100 years, there have been major changes in living conditions for

Homo sapiens, at least for the fortunate few in North America and Western Europe; this novel environment is having a major impact on the need for breast-feeding. Will it be maintained and evolve by natural selection as in past millions of years or will it be replaced by a substitute designed by nutritionists to meet the needs of the new world we are making?

Breast milk differs from most products known to the developed nations in that it is highly variable and not in any way standardized, but it is none the less admirable because of its individuality. There are major differences between mothers in their ability to lactate. The amount and composition of milk secreted have long been known to vary greatly (Kon & Mawson, 1950; Macy *et al.* 1953; Hytten, 1954*a,b,c,d,e*; Insull *et al.* 1959; Department of Health and Social Security, 1977; Allen *et al.* 1991; Neville *et al.* 1991), the milk from one mother even varies during the period of a single feed by the suckling (Hytten, 1954*a*), from day to day (Hytten, 1954*b*) during the course of a lactation (Hytten, 1954*c*) and from one lactation to another (Hytten, 1954*d*) as well as from one mother to another (Hytten, 1954*e*). The nutritional value of breast milk may also vary greatly: 'a plentiful milk supply with a baby losing weight seems to be a not uncommon clinical syndrome' (Hytten, 1954*d*).

The development and maintenance of different breeds of farm stock, e.g. dairy cows, beef breeds, and goats *inter alia*, shows that hereditary factors are important in determining length of lactation, period of gestation and milk yield, as well as milk fat and protein contents. The genetic control of the various bovine and caprine milk proteins, particularly of the α-, β- and κ-caseins and β-lactoglobulins, has been studied because of the effects of these substances on the technological properties of milk, e.g. suspension stability, coagulation and curd strength (Aschaffenburg & Drewry, 1957; Ng-kwai-hang, 1997; Tziboula, 1997). These characteristics may be of significance in determining the physical and chemical behaviour of milk in the infant gut and so may modify digestion and availability of nutrients (Wells, 1998).

Thus, heredity may be expected to play a major part in the reproductive cycle of other mammalian species, including our own, in determining the length of pregnancy and the period of lactation as well as the composition of breast milk. Some features of the mother's milk depend on the mother's diet, e.g. the nature of the lipids, as noted by Insull *et al.* (1959) and by Read *et al.* (1965*a,b*). Other factors, such as the nature and amount of immunoglobulin, may be determined by the mother's exposure to infectious agents (Allardice *et al.* 1974).

Evolution and Darwinian selection

The evolution of species is believed to depend on the Darwinian selection of characteristics favouring 'fitness', i.e. the probability that individuals carrying such traits will be more likely than others to bear fertile offspring and so be represented in subsequent generations.

Two paired organs, the internal cerebral hemispheres and the external mammary glands, have played special roles in the development of *Homo* species. The emergence of *Homo*

sapiens to its present status has depended on several factors. Perhaps the most important have been the evolution of the cerebral hemispheres and consequent developments in brain function which have permitted better interpersonal communication and improvements in the transfer of knowledge to increase control of the environment and food supply. These changes in turn have led to a need for a longer time for training, which is essential if children are to be able, as adults, to act as parents and provide for the future of the community.

Darwinian selection for breast-milk composition and volume as well as the length of lactation and pregnancy may depend on compromises, by both mother and child, to maximize overall 'fitness'.

Nutrient content of breast milk

An increase in the nutrient content, volume or duration of lactation, while benefiting the baby, could, by depriving the mother of nutrients, increase parental morbidity and mortality thereby decreasing fitness of both mother and child. Decreasing milk volume, nutrient content or period of lactation could increase survival of the mother but decrease overall fitness by increasing infant morbidity and mortality. Infants born with a lower growth potential or offered less nutritious milk, would make a smaller drain on parental resources but only at the cost of a longer developmental period. It is difficult to predict the net influence of such changes on 'fitness'.

Physiology of the neonate

Having precocial offspring, as in guinea-pigs and ungulates, may relieve problems of lactation and dependence but may severely handicap the mother by increasing physical problems at parturition and hindering her mobility during pregnancy. Altricial young minimize these latter difficulties but demand more specialized milk because certain organs, the infant gut and kidney for instance, are immature and limited in their ability to assimilate nutrients or eliminate waste (ESPGAN Committee on Nutrition, 1977). Altricial young, because of limitations in size and maturity are vulnerable to hypothermia, infection and predation, thereby demanding a long period of close attention. Human infants are relatively immature. *Homo sapiens* may be unusual in that, because of cooperative defence (and aggression), this species may be able to rear their altricial offspring without protective burrows, or marsupial-type pouches.

The incidence of certain diseases seen in later life

Nutritional deficiencies at an early stage of development *in utero* can lead to permanent impairment of certain vital structures, e.g. malformation of the neural tube because of folic acid deficiency in the early stages of pregnancy (Schorah & Smithells, 1991). Several bodily systems are not fully developed at birth, e.g. renal and digestive functions. It should not then be surprising to find that the incidence of certain diseases in later life may be thought to result from inadequate nutrition at the time (*in utero* or infancy) when the body organs and functions concerned

would normally mature. Barker (1994) has reported that, in the UK, the incidence of certain diseases, notably heart disease in the adult, is strongly associated with a low birth weight and slow growth during the first year of life.

Moore *et al.* (1997) carried out epidemiological studies under very different circumstances, in a developing country. These investigations also revealed a clear association between infantile nutrition and later, adult, mortality in that persons born in the 'hungry' season, and therefore nutritionally deprived in early life, showed an increased mortality, as adults, even though no greater mortality or morbidity was apparent in childhood or youth. Inheritance, by the infant, of a decreased tendency towards these handicaps or of increased ability by the mother to meet the offspring's needs, *in utero* or at the breast, would be expected to show an increased 'fitness' if these diseases became apparent during the reproductive phase of life. However no Darwinian selection against them would be anticipated if these 'degenerative' conditions occurred in the post-reproductive phase.

The menopause

Homo sapiens is unusual in that there is a menopause after which the female becomes unable to bear offspring. It is difficult to understand how the menopause could arise because failure to multiply would appear to lead to loss of Darwinian fitness. It has, however, been suggested that the menopause could possibly maximize fitness (Holliday, 1996). For *Homo sapiens* the ability to produce fertile offspring (Darwinian fitness) depends greatly on the resources diverted to child rearing during the long period of growth and preparation for adult life.

Studies of the !Kung hunter–gatherers of the Kalahari desert show that under their harsh conditions the ability of the parents to find food is severely limited by the need to carry an infant over a wide search area. Marshall (1976) and Lee (1979) report that in these societies the long intervals between births, and infanticide, are critical in permitting parents successfully to rear an infant, because the survival of fertile offspring depends more on the care devoted to existing children than on the production of more babies for whom food cannot be procured.

Heritable factors inducing the menopause to decrease fertility late in life might then maximize Darwinian fitness of parents and grandparents by increasing the number of carers and food gatherers the better to provide for the survival of their descendants. Selection on this basis could be linked to decreased morbidity of one sex if that sex is particularly concerned with education and training of the young. Loss of fertility and decreased morbidity in the post-reproductive phase might then, if at all heritable, be anticipated in the female rather than the male of *Homo sapiens*.

Stages in the development of mankind

Homo species are believed to have been in existence for over two million years (Brace *et al.* 1979; Lewin, 1993, 1998). There is evidence that the earliest known hominid species, *Australopithecus afarensis*, existed about 3·5

million years ago. By about 2·5 million years ago stone tools were being fabricated in Africa. Associated skeletal remains provide evidence for tool production and use by the first *Homo* species and also for a rapid expansion of brain volume at about this time. Approximately 500 000 to one million years later, marks of cutting tools on animal bones provide evidence of meat eating by early man (Lewin, 1998).

The first use of fire is believed to have been about 700 000 (Lewin, 1993) or perhaps less than 500 000 years ago (Weiner *et al.* 1998). The living conditions and social organization of mankind have been subject to change during this total of over two million years. Assuming a generation time of about 20 years, or somewhat less, there could then have been over 120 000 generations during which natural selection could have taken place.

Studies of the composition of the milk of our near relatives, the great apes and the monkeys, and their modes of existence might indicate the ways in which characteristics of human milk developed to meet changing needs. The milk of these animals generally resembles that of mankind in that the content of nutrients essential for growth (notably protein, essential amino acids and micronutrients) is low relative to that in the milk of other animals while the energy content (fat and carbohydrate) is higher than average (Buss, 1968; Lonnerdal *et al.* 1984; Oftedal, 1984). These are features which might be anticipated in species characterized by a long period of slow growth before weaning. This observation, that the composition of human milk may not differ grossly from that of our near relatives, may merely indicate that for most of our existence our mode of life may have resembled that of these species and that there has been insufficient time for Darwinian selection to have modified the composition of breast milk, i.e. a mere 500 generations, or even less, since our way of life significantly differed from that of the apes. It is also likely that breast milk may differ in subtle ways, which have not yet been detected, to meet new selection pressures during the 500 or so generations of agricultural–urban lifestyles.

Hunter–gatherer

Some developments about which little is known (language, social structures and use of perishable substances; Lewin, 1988) almost certainly had major influences on the development of hominid species. Hunter–gatherer existence would be impossible without the use of twine, rope, thread and straw. These fibrous materials are essential for fabrication of shafted tools and snares to catch game, nets and bags in which to carry infants safely and to collect food, as well as body coverings and thatch to protect the 'naked ape' against the weather.

Until fire was first used about 700 000 years ago (Lewin, 1998) only raw foods could have been eaten. The ability to cook must have immensely increased the safety and availability of these foods by destroying thermolabile poisons in otherwise inedible plants as well as the parasites and toxins common in flesh and carrion. However, it is unlikely that this, possibly the greatest invention of mankind, would have had much effect on the composition of breast milk though it may have greatly increased the

chances of survival, territorial expansion and nutrition of our species.

The hunter–gatherer existence then offered better opportunities for infant protection and food procurement but required a longer period of support and training to permit transfer of knowledge from one generation to the next. These developments would be expected to have had major effects on length of infancy, social structures and development of language.

It is at present impossible to evaluate mortality and its causes during this phase of human existence but infant mortality in the wild gorilla and chimpanzee is reported to be about 250 per 1000 live births (Harcourt *et al.* 1981; Courtenay & Santow, 1989; Holliday, 1996). Death would almost certainly have followed lactational failure so that heritable factors controlling the mother's ability to lactate and the child's resistance to starvation and hypothermia may have been major factors in determining survival during the first year of infant existence.

The hunter–gatherer mode of existence, as exemplified by the aboriginal inhabitants of Australia or !Kung of the Kalahari desert, may have dominated for over 90 % of our period of existence, over 100 000 generations until the advent of agriculture and stock raising about 10 000–12 000 years ago (Smith, 1996; Lewin, 1998). During the whole of this time infectious diseases would have occurred but may not have been common. The environment and low population density, absence of livestock and limitations on the contacts between small bands, would be expected to have minimized the spread of contagions. Starvation and hypothermia may well have been common causes of infant morbidity. Their lifestyle and the changing seasons would have exposed people to wide ranges of plant and animal foods from a variety of soil types. Deficiency of micronutrients, whether vitamins or minerals such as I or Fe, would therefore have been unlikely, as would also have been the risk of excess consumption of toxic elements such as F or As.

Lactational failure would have been a major hazard with 100 % infant mortality because, in small groups, there would be scant chance of finding a wet nurse, and in the absence of domestic animals, there would be little or no possibility of preparing an artificial milk from the available foods with the facilities then available. Selection pressure would have been very strong for adequate lactation in this period, as in the whole of mammalian evolution. It is likely that weaning from the breast began then, as now, at about 6 months and lasted for 1–2 years. Mouth-to-mouth feeding (Marshall, 1976; Fildes, 1986) was probably the only way to feed the young weanling, while a cupped hand could have been used to assuage thirst.

Anthropological studies (Marshall, 1976; Lee, 1979) show that present hunter–gatherer societies existing in marginal subsistence economies with no reserves of territory or stores of food often suffer periods of food shortage. Archaeological evidence suggests that men and women increased in height and size until the advent of the herder–farmer economies (Ruff *et al.* 1997). This may imply that hunter–gatherers then had better access to food when not restricted to marginal territories by more 'advanced' cultures!

Farmer–herder, village and urban cultures

The growth of crops and herding of animals began about 10 000–12 000 years ago (Smith, 1996; Lewin, 1998) i.e. about 500–600 generations ago, and has now spread to almost all areas of the world. These agricultural practices permitted settlement into villages and towns and led to major changes in the incidence of disease. Though starvation may have been avoided, the dependence on crops (often only one cereal) and herds grown in one locality, restricted the variety of foods eaten and so led to deficiency diseases (e.g. cretinism, pellagra), or toxicoses (e.g. fluorosis, ergotism).

Failure of lactation could more easily be overcome by the increased likelihood of finding a wet nurse amongst the larger village and urban populations. Artificial feeding also became possible with paps from cereals and milk available from domesticated animals lactating during the spring. Although such foods would have been most inadequate by modern standards they could permit the survival of about two-thirds of babies even under unhygienic conditions (Howarth, 1905).

Large village and urban centres rapidly arose. With overcrowded accommodation, and without adequate sewage disposal, they presented many new opportunities for transmission of disease from microbial infections of the gastrointestinal and respiratory tracts, of helminths or insect-borne infections.

Infantile mortality was very high in such urban societies, about 140 per 1000 live births, from 1840 to 1900 in, for instance, Victorian England (Howarth, 1905) which was then an undeveloped country! Similar child mortalities were often commonly encountered in developing areas. As recently as the 1950s it was found in a study of 500 consecutive births in a village in tropical Africa that only half the babies born survived for 5 years (D Morley, personal communication). In another country of the developing world, The Gambia, Lamb *et al.* (1984) reported infant mortality in 1974–5 to be over 100 and total mortality, at 5 years, over 250 per 1000 live births. Such high death rates during the 600 or so generations of village or urban life would be expected to have enhanced Darwinian selection for hereditary factors combating disease, e.g. the high prevalence of haemoglobin variants in populations exposed to malaria (United Nations Educational Scientific and Cultural Organization & World Health Organization, 1965). Milk has long been known to display a variety of anti-microbial activities (Reiter & Oram, 1967; McClelland *et al.* 1978). If selection pressure (from, for instance, increased infectious disease), favoured modified breast milk during this period, differences would be expected between breast-milk samples from the few remaining hunter–gatherer groups and peoples from the centres at which the agricultural–urban ways of life were initiated (the Middle East, China and Meso-America). Detailed analyses of breast milk are needed to investigate the possibility that exposure to increased microbial risk during 500–600 generations may have led to increases in the anti-microbial action of breast milk in these populations.

Developed cultures

Reduction in infant morbidity and mortality

More recently, within the last 100 years (about five or six generations), major modifications in housing, water supply, sewage disposal, food production, storage and processing, together with advances in medicine, have immensely decreased infant and child morbidity and mortality in the more fortunate populations of the world. In a typical Western country such as the UK, infant mortality dropped from about 150 per 1000 live births in the 19th century (Registrar General, 1908) to less than ten per 1000 in 1990 (Central Statistical Office, 1990), a fall of over 90 % in less than 100 years. This has resulted from a variety of factors, a literate population with hygienic facilities and vaccination to minimize risk of infectious disease coupled with the availability of nutritionally adequate breast-milk substitutes (Cuthbertson, 1994).

Much faster control of infant mortality is now possible. Lamb et al. (1984) have shown in The Gambia that: 'Even under conditions of extreme poverty, under-nutrition, and primitive hygiene ..... a professionally run upcountry out-patient clinic can achieve a rapid and dramatic effect on maternal and child mortality'. In less than 10 years infant mortality was reduced sixfold, from about 150 per 1000 in 1974–5 to less than twenty-five per 1000 in 1982–3, while childhood mortality during that decade was also decreased, from about 110 to about twenty per 1000 live births (Lamb et al. 1984).

Breast-feeding

There is no doubt of the value of breast-feeding in developing countries or under unhygienic circumstances. Howarth (1905) in Derby, UK, noted that in 1900–3, infantile mortality amongst the artificially reared babies was 200–250 per 1000 live births, i.e. over three times

that, at seventy per 1000, amongst the breast-fed. In disadvantaged conditions typical of developing countries breast-feeding still offers the best chance for infant survival. Darwinian selection pressure will be high for breast milk better able to meet the needs of mother and child. This condition continues for the great majority of infants and mothers on Earth today. However, in developed societies such as those of North America and Western Europe the benefits of breast-feeding are not so clearly demonstrable.

Major problems in attempting to assess the effects of breast-feeding in developed societies. Bauchner et al. (1986) observe that: 'Studies of the anti-infective properties of breast milk *in vitro* as well as most of the clinical studies of the effects of breast feeding in underdeveloped countries, have provided convincing evidence that breast feeding protects against infections. In contrast, clinical studies in industrialised countries have produced conflicting results about the protective effects of breast feeding'. These authors suggest that: 'such discordant reports are caused by the fact that, for ethical reasons, it is impossible to conduct randomised controlled trials of infant feeding. As a consequence comparisons between the two regimes must depend on ethically acceptable but non-experimental epidemiological studies susceptible to many forms of bias'. Bauchner et al. (1986) describe the methodology of cohort and case–control studies and the need to meet four methodological standards: (1) to avoid detection bias in assessing outcomes in one v. the other group; (2) to adjust for potentially confounding variables (e.g. social and/or economic status of the groups); (3) to define the outcome events (if a disease, which disease?); (4) to define breast-feeding (e.g. exclusive or for how long).

On examining twenty recent comparisons between breast- and formula-feeding in developed countries (Tables 1 and 2). Bauchner et al. (1986) found only six trials that met three or four of these methodological standards. Four of the six studies found that breast-feeding was

Table 1. Assessment of fourteen cohort studies of breast-feeding *v.* formula-feeding according to four methodological standards (From data of Bauchner *et al.* 1986)

Reference	Avoidance of detection bias	Control for socio-economic status	Breast-feeding defined	Outcome(s) defined
Studies showing a protective effect of breast-feeding:				
Chandra (1979)	+	+	+	+
Cunningham (1979)	−	+	+	−
Cussen (1978)	+	−	−	−
Fergusson *et al.* (1981)	−	+	+*	−
France *et al.* (1980)	−	−	+	+
Paine & Coble (1982)	−	−	+	−
Saarinen (1982)	−	+	+	+
Watkins *et al.* (1979)	+	+	+	−
Studies not showing a protective effect of breast-feeding:				
Adebonojo (1972)	−	−	+	−
Cushing & Anderson (1982)	+	+	+	+
Frank *et al.* (1982)	+	+	−	+
Holmes *et al.* (1983)	−	+	+	−
Research Subcommittee of the South-East England Faculty (1972)	+	+	+	−
Taylor *et al.* (1982)	−	+*	−	−

+, Trial met standard; −, trial did not meet standard, as defined by Bauchner *et al.* (1986).
* Adjustment made for additional confounders.

Table 2. Assessment of six case–control studies of breast-feeding v. formula-feeding according to four methodological standards (From data of Bauchner et al. 1986)

Reference	Avoidance of detection bias	Control for socio-economic status	Breast-feeding defined	Outcome(s) defined
Studies showing a protective effect of breast-feeding:				
Downham et al. (1976)	–	+	–	+
Fallot et al. (1980)	–	–	+	–
Larsen & Homer (1978)	–	–	–	–
Tripp et al. (1977)	–	–	–	+
Studies not showing a protective effect of breast-feeding:				
Pullan et al. (1980)	+	+*	–	–
Weinberg et al. (1984)	–	–	+	+

+, Trial met standard; –, trial did not meet standard, as defined by Bauchner et al. (1986).
* Adjustment made for additional confounders.

not protective and, in three studies, when adjustments were made for confounding variables in the test groups, family size, mother's cigarette smoking and level of education, the apparent protective effect of breast-feeding against respiratory tract infections disappeared. Bauchner et al. (1986) conclude: 'We found that most of the studies have major methodological flaws that may have compromised their conclusions. The studies that met important methodological standards and controlled confounding variables suggest that breast-feeding has, at most, a minimal protective effect in industrialised countries'. Heinig & Dewey (1996) discuss and support the four criteria proposed by Bauchner et al. (1986) and discuss and note eight others listed as essential by Kramer (1988): '(a) non-reliance on maternal recall, (b) blind ascertainment of infant feeding history, (c) blind ascertainment of outcome, (d) information on severity of the outcome, (e) age at onset of outcome, (f) assessment of dose–response effect, (g) assessment of effect in children at high risk, and (h) adequate statistical power.'

Heinig & Dewey (1996) reviewed work later than that of Bauchner et al. (1986) and 'selected studies, conducted primarily in industrialised countries that met at least three of the four criteria described by Bauchner et al. (1986). Although it would have been ideal to screen studies using the criteria listed by Kramer (1988) as well, this would have drastically reduced the number of studies to be considered.'

Heinig & Dewey (1996) conclude that evidence is strong that breast-feeding protects against diarrhoeal and lower respiratory disease as well as otitis media and may also protect against a number of other infections. It is clear from these reviews that few studies meet the criteria essential if the benefits of breast-feeding are to be unambiguously demonstrated in conditions typical of industrialized societies. However, they do strongly suggest that, even under modern conditions of housing and hygiene, breast-feeding leads to a small, but statistically significant, difference in infantile morbidity and mortality. In the developed countries under present circumstances (when infant mortality is about ten per 1000 live births) such a small apparent advantage is to be gained that there may be little Darwinian selection for breast-feeding.

Breast-milk substitutes, infant formulas

Breast-milk substitutes are essential if infants are to survive lactational failure. If mothers are unable to breast-feed and cannot afford to buy or prepare a breast-milk substitute, their infants will surely perish unless a wet nurse can be found. Thus, breast-feeding alone, for infants surviving up to 5–6 months, is the norm in many developing countries (King & Ashworth, 1994). Most clinicians agree that almost all mothers could breast-feed. In one very careful study about 85 % of patients booked into Aberdeen Maternity Hospital left hospital fully breast-feeding. Of those who failed, 39·4 % did so primarily because of inability to produce milk while others failed for other conditions e.g. conditions of the breast or nipples (Hytten, 1954f).

Although most mothers can breast feed, many, for economic or social reasons, choose not to do so. In the UK, in Victorian times, about 80 % of mothers breast-fed their infants during the first year of life (Cautley, 1896; Howarth, 1905). The number of breast-feeding mothers has varied very much from town to town and time to time in the UK but on average the number breast-feeding fell during the 20th century to about 60 % in the 1920s and even lower, to 24 % in the 1970s (Department of Health and Social Security, 1988). In the decades immediately before and after the Second World War there was little encouragement in Great Britain, even from health professionals, for mothers to breast-feed. During this period, from the 1930s to the mid 1970s the feeding regimen for most infants in this country was based on dried full-cream milk powder with added sucrose which was reconstituted, by the mother, with water to the required concentration. Infants were also given oral supplements to provide ascorbic acid and vitamin D. Many believed that there was no benefit to be gained from breast-feeding, indeed an investigation for the Medical Research Council (Levin et al. 1959) had failed to find any differences between the serum protein levels, weight gains or health of infants whether breast-fed or reared on the infant-feeding regimen then available (Levin et al. 1959).

Taitz & Byers (1972) reported the dangers of hypertonic dehydration of infants, a condition commonly induced by mothers feeding their babies excess energy and solutes because heaped scoops of milk powder instead of the recommended level measures had been used in preparing

the formula. These authors concluded that: 'The careless preparation of feeds which results in solute and calorie concentrations substantially in excess of the recommended level which in itself is uncomfortably high, must be considered a potential hazard to health'. The high concentrations of electrolytes and protein in the infant milks then available were also investigated by others, e.g. Shaw *et al.* (1973) and Tripp *et al.* (1973). These authors contrasted the high concentrations of electrolytes in the then available infant foods with the much lower and safer levels characteristic of breast milk.

These findings were rapidly appreciated by all concerned with mother and child welfare. As a result of their encouragement, there was a rapid increase in breast-feeding. In England the proportion of infants breast-fed at 3 months rose within the next decade, from about 20 % in 1975 to about 40 % by 1985 (King & Ashworth, 1994; Paul *et al.* 1994). In another of the more affluent countries, the USA, about 60 % of mothers were breast-feeding their infants at 3–4 months in the 1980s (King & Ashworth, 1994).

Campaigns to encourage breast-feeding have been indubitably successful but the data of King & Ashworth (1994) and Paul *et al.* (1994) show that the majority of mothers (60–80 %) are still not willing to breast-feed, even for a short term of 3 months. Scowen (1989) has presented an excellent review of the changing incidence of breast- and formula-feeding in the UK over the decades from 1964 to 1989 and notes why a majority of mothers then preferred to use formula rather than breast-feeds. Further investigations may be needed more precisely to define the reasons, perhaps social or economic, that prevent the implementation of the advice now widely disseminated by health professionals.

The manufacturers of baby foods rapidly responded to the reports of Taitz & Byers (1972). Novel infant food formulas with lower electrolyte contents and reduced renal loads were quickly devised and offered to meet the new needs. By 1976 all infant milk formulas were of the low-electrolyte type, those based on full-cream cows' milk had been withdrawn and were no longer available (Mettler, 1976).

Control of infant milk formula. The relative safety in the use of breast-milk substitutes in the developed areas of the world depends on greatly improved standards of hygiene and living conditions in the home as well as on the availability of infant foods made to exacting standards of manufacture, nutritional quality and packaging (Cuthbertson, 1994). Because such a large proportion, often the majority, of mothers in the developed world are unwilling to breast-feed, the possible effects of these artificial foods is of considerable concern and has been discussed by numerous international and national committees and conferences, e.g. American Academy of Pediatrics, Committee on Nutrition (1976), Codex Alimentarius Commission (1976), Department of Health and Social Security (1974, 1980*a,b*, 1988), ESPGAN Committee on Nutrition (1977, 1982, 1991), Department of Health (1996). The recommendations of these bodies are rapidly implemented by the infant-food industry (Mettler, 1982) and modified as new findings are established. These expert groups generally agree that an infant formula should resemble breast milk as, for instance, noted by a working party (Department of Health and Social Security, 1980*a*) which stated: 'Although human

milk, because of its variability, cannot be used as an exact chemical model for the composition of an infant feed, the Working Party is of the opinion that human milk does provide the most useful reference "standard". The further the composition of any artificial feed departs from that of average mature human milk, the greater is the possibility of untoward effects in the infant to whom it is fed. It is important to ensure that infants are safeguarded from unsuitable foods.' The general recommendation is that the artificial milk should: 'approximate to the composition of breast milk as nearly as is practicable' (Department of Health and Social Security, 1974, 1977) or 'should resemble human milk as far as is possible' (ESPGAN Committee on Nutrition, 1977).

Artificial milks made to the early recommendations of the Codex Alimentarius Commission (1976) were satisfactory in practice but the enthusiasm of the Committee to provide a sufficiency of nutrients ensured that breast milk from an average mother would fail to meet the commission's requirements in ten out of the twenty-seven specified constraints while a large proportion would fail to meet twenty of them! (Cuthbertson, 1978). Most mothers could however, apart from Ca, phosphate and vitamin D contents, meet the more recent recommendations (ESPGAN Committee on Nutrition, 1977, 1982, 1991; Department of Health and Social Security, 1980*a,b*, 1988).

Dangers of change without adequate trials. The butterfat of cows' milk was partially or completely replaced by vegetable oils in order to meet the new recommendation (Codex Alimentarius Commission, 1976; ESPGAN Committee on Nutrition, 1977; Department of Health and Social Security, 1980*a*) to increase the content of the essential fatty acid linoleic acid ($18:2n$-6; LA) of baby foods to one often found in breast milk but above a level which could be provided by butterfat. The need to change from the traditional butterfat to novel levels of highly unsaturated fats was questioned (Cuthbertson, 1976) but these comments were vigorously refuted (Crawford *et al.* 1978).

The ESPGAN Committee on Nutrition (1977) and Department of Health and Social Security (1980*a*) both agreed the increased level of LA even though some hesitation was noted in their reports: 'It is recognised that the reasons for regarding the concentration in human milk as optimal are not strong, as the level is dependent on the mother's intake of polyunsaturated fat' (ESPGAN Committee on Nutrition, 1977) and: 'There is no proof, as yet, that the lipids of the infant's brain would be altered by feeding a milk containing a fat rich in linoleic acid (LA), but the results of animal feeding experiments suggest that this cannot be ruled out' (Department of Health and Social Security, 1980*a*).

At that time it was known that major increases in the LA content of the blood lipids and body fat were to be found in infants fed on some of the new foods meeting Codex Alimentarius specifications (Widdowson *et al.* 1975). These authors remarked that: 'The results of studies on animals . . . . . suggest that the lipids of the central nervous system are not easily altered but until the effect of an excess (of LA) has been investigated we cannot be sure.' Unfortunately no investigations were made as to the likelihood of any adverse effects.

The importance of LA as an essential fatty acid in human nutrition had been known for many years from the investigations of Hansen *et al.* (1963) but the need for a dietary source of another essential fatty acid, i.e. α-linolenic acid ($18:n$-3; LNA), the parent of the n-3 fatty acid series, was not widely recognized until the late 1980s (Neuringer *et al.* 1988).

The n-6 and n-3 essential fatty acids are LA ($18:2n$-6) and LNA ($18:3n$-3) respectively. The essential nature of LNA as the parent of the n-3 series had not been widely recognized (Innis, 1991) at the time the advisory bodies (Codex Alimentarius Commission, 1976; ESPGAN Committee on Nutrition, 1977; Department of Health and Social Security, 1980*a*) made their recommendations. As a consequence the new formulations were prepared by the manufacturers to meet the required levels of LA, the n-6 essential fatty acid, but with much lower relative proportions of the essential n-3 fatty acid LNA than in breast milk or even in the previously employed infant foods based on butterfat.

The essential fatty acids LA and LNA are not interconvertible but are respectively the parents of the n-6 and n-3 series of fatty acids from which all of the n-6 and n-3 fatty acids can be derived, e.g. the long-chain polyunsaturated fatty acids (LCPUFA) including arachidonic acid ($20:4n$-6; AA), eicosapentaenoic acid ($20:5n$-3) and docosahexaenoic acid ($22:n$-3; DHA). LA and LNA play important roles not only in providing LCPUFA which act as components of cellular membranes but also as precursors of other essential metabolites such as the prostacyclins and prostaglandins controlling a variety of body functions.

Normal neurological development is now thought to depend on the availability of DHA derived from LNA (Neuringer *et al.* 1988; Farquharson *et al.* 1992; Carlson *et al.* 1993; Van Aerde & Clandinin, 1993; Sargent, 1997). Both LNA and DHA are present in breast milk and in butterfat and hence, albeit in low concentrations, in the old-fashioned infant foods based on full-cream cows' milk. The novel infant foods, made to meet the recommended compositions (Codex Alimentarius Commission, 1976; ESPGAN Committee on Nutrition, 1977; Department of Health and Social Security, 1980*a*), contained vegetable fats (Mettler, 1976) to provide sufficient LA to meet increased recommendations. Some vegetable oils are excellent sources of LNA, e.g. linseed, soyabean and rapeseed, but are prone to rancidity and so avoided in infant formulas.

DHA is a major component of brain and retinal rod lipid membranes and has been shown, by animal studies, to be required for normal retinal and brain function (Fliesler & Anderson, 1983; Neuringer *et al.* 1988). The depletion of tissue DHA requires diets with both low levels of n-3 fatty acids and high levels of the n-6 fatty acids. The degree of deficiency induced is largely determined by the LA : LNA ratio because high levels of the n-6 series fatty acids depress conversion of LNA to DHA by competitive inhibition of the $\Delta 6$ desaturase enzyme (Neuringer *et al.* 1988; Farquharson *et al.* 1992; Sargent, 1997). The LNA content is low in the vegetable oils commonly used to meet the LA requirement in infant foods. The LA : LNA ratio in these oils was also very high, about 150 : 1 for safflower, sunflower and arachis oils and 50 : 1 in maize oil, i.e. ratios that largely suppress the conversion of LNA to the other necessary LCPUFA of the n-3 series (Neuringer *et al.* 1988).

The need for LNA in infant formula was not officially recognized until the 1990s (ESPGAN Committee on Nutrition, 1991), thus many infant formulas, from the mid-1970s to the early 1990s, may have provided much less of the n-3 essential fatty acids than would now be advised.

Observations in very carefully controlled, multicentre trials by Lucas *et al.* (1990, 1992) have shown that preterm infants given a formula feed had significantly lower intelligence quotients at 1·5 and 7·5–8 years of age than those receiving breast milk as the total or partial source of nourishment and that this difference was still evident after accounting for possible confounding factors such as, *inter alia*, parental smoking and/or drinking or socio-economic status.

The formula feed used in these studies met the then accepted recommendations (Department of Health and Social Security, 1980*b*), i.e. high levels of n-6 with low levels of n-3 essential fatty acids. The authors noted that the differences in neural development reported might have resulted from a deficiency in long-chain lipids essential for development of the nervous system but not present in the preterm formula, or alternatively, it might be that human milk contains hormones and trophic factors influencing brain growth as well as pre-formed AA and DHA (Lucas *et al.* 1992).

If this neurological problem resulted from a deficiency in LNA the difficulty could be overcome by increasing the LNA content of the formula. However addition of pre-formed DHA to the formula would be expected to relieve the condition whether resulting from LNA deficiency or from an absence, in the immature, preterm infant, of the functional enzyme system essential for formation of LCPUFA from their precursors.

Many trials have been carried out to determine if the observations of Lucas *et al.* (1992) resulted from a deficiency of the DHA and AA required to supply the needs of the brain and visual systems in the rapidly growing preterm infant. In a recent review Morley (1998) notes that there is good evidence that use of conventional formulas leads to depression of LCPUFA status, especially in the preterm baby, and that this fall can be reduced by addition of DHA to the formula. However, the inconsistencies of the published findings on neurological function are such that it is not possible yet to say whether addition of DHA to a formula will be of benefit, though one report (Innis *et al.* 1996) suggests that the absence of dietary AA and DHA is without effect on visual acuity and recognition memory in full-term infants at 9 months of age. This uncertainty, Morley (1998) suggests, may well be caused by inadequate sample size, confounding factors or variations in the LNA content of the formula used. Morley (1998) also discusses the experimental design and numbers of propositi needed to ensure differences of means with 80 % power at 5 % significance. Morley (1998) and Lucas (personal communication) note that three large studies are now in progress to determine the effects of formulas containing added AA and DHA in comparison with breast milk on

neurological development in preterm and full-term infants. (Lucas and co-workers based at the Institute of Child Health, London, UK, are conducting three large-scale, multicentre trials, one on full-term infants and two on preterm infants, and are taking part in a further collaborative international study on preterm infants. These trials involve over 1300 infants and include subjects randomly assigned to infant formulas with and without LCPUFA together with breast-milk-fed reference groups. Two of these studies, one on term infants and another on preterm infants, have passed an 18-month developmental assessment follow-up period.) These are calculated to be of sufficient size to determine what effects (whether beneficial or adverse) may be anticipated to follow LCPUFA additions to formulas, but so far as the work has progressed, there is no evidence of benefit to full-term infants from the addition of LCPUFA to a formula of the type now advised.

The change in the fat content of infant formula made with such enthusiasm in the mid 1970s did carry some considerable risk; it encouraged use of formulas with low n-3 contents and high n-6 : n-3 ratios. Had the full-term as well as the preterm infant needed extra LNA then there could well have been subnormal mental development in the many thousands of children reared on the newly approved formulas between about 1975 and 1992. The available evidence is insufficient to determine whether or not neurological development of normal full-term infants had been significantly depressed as a result of the use of such formulas in the past; it would now be very difficult to investigate this possibility! This brief note of infant feeding practices should act as a warning not to advise modifications without full trials even if no risk can be foreseen. The apparent urgency of a problem should never be used as an excuse to advise changes in practice without adequate investigation.

Addition of supposedly beneficial substances. Present enactments in the UK and in the European Union are designed to prevent the use of untested novel processes or ingredients in the manufacture of infant formula (Wells, 1998). Numerous non-nutrient substances with a variety of biological activities, e.g. promotion of intestinal flora, protection against infection, anti-inflammatory agents, intestinal tissue growth factors, have been detected in breast milk (Wells, 1998). Problems previously encountered with vitamin A, vitamin D, protein and electrolytes as well as with LCPUFA should remind us that general recommendations for change should not be made without proper trial to ensure absence of adverse effects under practical conditions of use!

Carlson *et al.* (1996) reported that, compared with the control group, there was a higher incidence of necrotic enteritis amongst the preterm infants given a formula fortified with fish oil to provide LCPUFA. This difference was not statistically significant but does suggest the need to determine the safety of LCPUFA additions to infant foods. Properly conducted randomized trials of any novel introduction should be made in order to determine whether the introduction may lead to unexpected adverse effects. Such trials are particularly important in this instance because of the wide range of actions (not always beneficial) displayed

Table 3. Scores allocated to particular types of evidence by the Canadian Task Force on the Periodic Health Examination (From Table 1 of Goldbloom, 1997)

Score*	Evidence
1	At least one randomized controlled trial
2-1	Well-designed controlled trial without randomization
2-2	Well-designed cohort or case–control analytical studies, preferably from more than one centre or group
2-3	Multiple time series studies with or without intervention
3	Opinions of respected authorities, clinical experience, or opinions of expert committees

* Information provided is scored according to origin, most weight (score 1) being given to evidence-based data, least weight (score 3) being given to opinion without experimental observations.

by LCPUFA, fish oils, essential fatty acids and the metabolites (including prostaglandins and prostacyclins) derived from them (Sanders, 1993).

Current UK recommendations on the composition of infant foods define the LA : LNA contents and ratios permissible in infant formulas and also permit, within limits, the presence of LCPUFA, notably AA, DHA and eicosapentaenoic acid in infant formulas (Statutory Instruments, 1997).

Examination of nutrient declarations on infant food containers shows that LCPUFA from a variety of sources are present in most infant formulas now (i.e. 1998) sold in Europe even though no firm statement can be made as to benefits thought to follow their use or the safety of some of the sources (fish and fungal lipids) used to provide them.

Assessment of evidence before general recommendation for change. The nature of the evidence required to demonstrate the effect of a change on a health problem and consideration of the value of any proposed action, are well summarized by Goldbloom (1997) in his brief review of the methodology of the Canada Communication Group (1994) and US Preventive Services Task Force (1996).

Table 3 shows the relative importance placed by the Canadian body responsible for Periodic Health Examination (Goldbloom, 1997) on the types of trial commonly available. Recommendations for changes in treatment or practice of the general public should only be made after very careful consideration of the evidence for, and against, the proposed novel practice. Evidence from well planned randomized trials should be given the highest attention while proposals

Table 4. Classification of proposals for changes in treatment or practice of the general public, according to putative benefits (From Table 2 of Goldbloom, 1997)

Classification	Evidence
A	Good evidence to support inclusion in the Periodic Health Examination (PHE) (e.g. polio vaccine)
B	Fair evidence to support inclusion in the PHE (e.g. Pap smear)
C	Poor evidence to support inclusion in the PHE but recommendation possible on other grounds
D	Fair evidence to support exclusion from the PHE
E	Good evidence to support exclusion from the PHE (e.g. pneumococcal vaccination for entire population)

without experimental justification should be given less support. Finally, Table 4 (from Goldbloom, 1997) notes that the evidence should be rigorously examined to ensure its validity and to indicate important unanswered problems. Careful consideration must also be given to the likely costs and potential harm as well as putative benefits of the proposed change.

Importance of nutrition in the first year of life

Epidemiological observations in the UK on persons born in the 1910–30 period (Barker, 1994) and in The Gambia (Moore *et al.* 1997) suggest that adult mortality from chronic degenerative disease may be greatly modified by early development *in utero* and in the first year of life. Thus, nutrition in infancy may be a major determinant of health in later life, whether in a developed country or a disadvantaged community. It is almost certain that the type of milk required to maximize health and 'fitness' of *Homo sapiens* infants reared under modern conditions will be very different from that previously needed. Exposure to changed circumstances for a period of five or six generations, with reduced selection pressure, is clearly unlikely yet to have modified inheritable features of breast milk better able to meet present needs.

An ideal infant food?

The volume and composition of breast milk can vary greatly (Kon & Mawson, 1950; Macy *et al.* 1953; Hytten, 1954*a,b,c,d,e,f*; Department of Health and Social Security, 1977; Allen *et al.* 1991; Neville *et al.* 1991). Its nutritional value may also differ; Hytten (1954*d,e*) reported that: 'a plentiful milk supply with a baby losing weight seems to be a not uncommon clinical syndrome' and that this failing may be caused by a low fat content. It is also very likely that some mothers, because of certain features of their milk, may be better able to provide for the future health of their offspring by, for instance, providing known nutrients in better proportions, or metabolites, enzymes, hormones or other unidentified agents to facilitate optimal maturation and development of the infant's faculties to permit full health in the adult.

An unanswered problem is to find out if differences in the composition of breast milk (or infant formula) affect the health and well-being of the infant and perhaps even the quality of life of the adult. Investigation of these possibilities could involve epidemiological studies of relations between breast-feeding and subsequent child and adult health. There would be technical difficulties in determining nutrient intakes as well as in the subsequent lifelong studies from infancy to ultimate demise. There would also be a need to retain samples for investigation for substances as yet unrecognized, by methods not now available. Application of the methods of multivariate analyses (Chatfield & Collins, 1980) now commonly employed to determine the combined interactive effects of numerous variables (e.g. of diet in farm stock, or sensory appreciation in human subjects) might reveal associations between nutrition of the juvenile and health of the adult.

Could a milk be devised better able to meet these varied needs than present artificial formula or even of breast milk itself?

Long-term feeding trials might also be employed, but for ethical reasons it would not now be possible to carry out comparisons between the progress of infants on deficient *v.* supplemented formulas as in the classical investigations reported by Hansen *et al.* (1963) on essential fatty acid requirements.

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