proved,[8 14 15] but positive lymphocyte transformation[16] and the occurrence of eosinophilia in these cases is suggestive.

The prevention of direct toxicity depends above all on monitoring by frequent blood counts: these must include platelet as well as leucocyte counts, and preferably the results should be charted on a flow sheet with the dose of gold given. Any pronounced fall or continued falling trend is a danger signal even if the blood count is still within the normal range. Gold should then be stopped and resumed only with great caution. All the dose schedules were within the accepted safe range, but all but nine of the dyscrasias occurred before 1 g of sodium aurothiomalate had been given; some of these patients were already in remission and still receiving 50 mg weekly. Lower or less frequent dosage may be safer and just as effective in maintaining disease control.

Treatment of established aplasia depends on vigorous supportive measures, and possibly in rare circumstances bone marrow transplantation may be considered. There is little positive evidence that specific measures such as treatment with dimercaprol or penicillamine are of benefit, but doubtless they will continue to be used, as will corticosteroids, which seem to help in some cases of thrombocytopenia.[10]

I thank Dr W H W Inman and the Committee on Safety of Medicines; all the clinicians and haematologists who generously allowed me to include their cases; the late Dr H J A Richards, of May and Baker Limited; and Dr H E M Kay for reviewing the marrow specimens and for advice and criticism.

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Problems of Childhood

Infant feeding: a current view

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The recent report[1] by the Department of Health and Social Security (DHSS) has emphasised the superiority of breast milk and advocated renewed efforts in promoting breast-feeding by educating schoolchildren, parents, and mothers-to-be and by the appropriate instruction of medical students and student nurses. In this respect, and in noting the possible dangers associated with bottle-feeding, the report agrees with recent trends.[2-7]

Superiority of breast-feeding

Infant feeding is an emotive subject and advocates of breast-feeding have sometimes relied more on a personal belief in its naturalness, and therefore rightness, than on the evidence, and there has consequently been a widespread belief, even among paediatricians, that artificial milks are just as good.[8] Recently, however, evidence showing the unique character of human milk in the nutrition of the human infant has accumulated to an extent where it is now difficult to deny that "breast is best."

Some of the reasons for advocating breast feeding are listed in table I, in which an attempt is made to assess the reliability of the evidence incriminating artificial feeding for each of the conditions listed.

TABLE I—*Factors incriminating artificial feeding*

Sound evidence:	
Infection	— gastrointestinal
	— other
Chemical disturbance	— hypocalcaemia
	— hypernatraemia
Obesity	
Cows' milk allergy in infancy	
Necrotising enterocolitis	
Some evidence—not conclusive:	
Cot death	
Atopic diseases	
Equivocal evidence:	
Ulcerative colitis	
Coronary vascular disease	
Multiple sclerosis	

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INFECTION

Gastroenteritis

Over 14 000 infants were admitted to hospital in England and Wales in 1972 with gastroenteritis.[9] Of these, 306 died[10] and the infant mortality rate from this cause was 0·4 per 1000 live births or about 1 in 40 deaths in the first year of life.[10] The disease is much more common in bottle-fed babies.[11 12] In a recent hospital series from Manchester[13] only one of 339 infants, of whom 170 were under 6 months, was breast-fed. The opportunity for bacterial contamination during the preparation of the feeds is a constant risk with bottle-

TABLE II—*Comparison of milk feeds*

	Breast milk	Cows' milk	Ostermilk Complete Formula	Cow and Gate Premium	SMA S26	National Dried Milk	Ostermilk Two	Cow and Gate Baby Milk 2
Calcium in mg/100 ml (mmol/l) ..	33 (8·2)	125 (31·3)	60 (15·0)	55 (13·8)	44 (11·0)	83 (20·8)	114 (28·5)	106 (26·5)
Phosphorus in mg/100 ml (mmol/l)	15 (4·8)	96 (31)	50 (16·2)	40 (12·9)	33 (10·7)	67 (21·6)	91 (29·4)	88 (28·4)
Calcium:phosphorus ratio	2·20	1·30	1·20	1·38	1·33	1·24	1·25	1·20
Sodium in mg/100 ml (mmol/l) ..	15 (6·5)	58 (25·2)	33 (14·4)	23 (10·0)	15 (6·5)	40 (17·4)	56 (24·4)	56 (24·4)
Protein in g/100 ml (g/l)	1·2 (12)	3·3 (33)	1·8 (18)	1·8 (18)	1·5 (15)	2·5 (25)	3·3 (33)	3·3 (33)
Fats in g/100 ml (g/l)	3·8 (38)	3·7 (37)	3·0 (30)	3·3 (33)	3·6 (36)	2·4 (24)	3·3 (33)	3·4 (34)
Carbohydrate in g/100 ml (mol/l) ..	7·0 (0·39)	4·8 (0·27)	9·3 (0·52)	6·9 (0·38)	7·2 (0·40)	5·9 (0·33)	6·7 (0·37)	7·5 (0·42)
Energy in kcal/100 ml (kJ/l) ..	67 (280)	66 (276)	71 (297)	63 (263)	65 (272)	55 (230)	69 (288)	72 (301)
Cost per packet			62p (500 g)	78p (454 g)	65p (454 g)	20p (567 g)	57p (454 g)	56p (454 g)

Chemical data taken from DHSS report and, for Cow and Gate Premium, from manufacturers' promotional booklet. (SI values are given in parentheses.) Prices given for proprietary milks were quoted by a central Birmingham branch of a leading retail chemist on 1 December 1975.

feeding[14] but breast milk may confer immunity to gastrointestinal infection in many ways.

IgA antibodies—Immunoglobulin A of secretory type is present in large amounts in colostrum and lesser amounts in mature breast milk[15] and carries antibody specificity to enteropathogenic *Escherichia coli* and other bacteria and viruses.[15–17] Secretory IgA is resistant to digestion within the gut and serves to protect mucosal surfaces.

Lactobacilli—The predominant organisms in the stools of breast-fed babies are lactobacilli, whereas *E coli* tends to predominate in the stools of the bottle-fed baby.[18 19] This difference, which is thought to confer protection from gastroenteritis on the breast-fed infant, probably results from the high-lactose, low-protein, low-phosphate content and poor buffering capacity of breast milk.[19] There may be a further factor in human milk, the "bifidus factor," encouraging the growth of *Lactobacilli*.[20]

Lactoferrin—The iron-binding protein of milk is present in breast milk in quantities 10 to 20 times greater than in cows' milk.[21 22] In association with specific antibodies lactoferrin strongly inhibits the growth of *E coli*. This property is inhibited by saturating the protein with iron.[21]

Other factors—Leucocytes,[23] lysozyme,[24] and vitamin B_{12} binding protein[25] are all potentially protective against infection and more available to the breast-fed infant.

Other infections

Respiratory tract—Bottle-fed babies appear to be some 50 to 100% more likely than breast-fed babies to suffer from respiratory infections[26–28] and are over four times as likely to die of such infections.[26 27] The increased incidence of respiratory disease in the bottle-fed baby may be related, at least partly, to obesity,[29] but some of the infants who are thought to be suffering from respiratory infection may be allergic to cows' milk.[30]

Otitis media—Middle ear infection is more common in bottle-fed babies.[28 31] In Eskimo infants in the Canadian Arctic otitis media was found to be five times less common in the breast-fed.[32]

Neonatal septicaemia and meningitis—Breast-fed infants are protected against neonatal septicaemia and meningitis possibly because breast milk suppresses the growth of coliform organisms in the gut.[33]

Viral infection—Human milk possesses antiviral activity against many viruses including polio virus and herpes simplex.[17 34] Breast-feeding interferes with oral polio vaccination in the newborn[35] but not in older infants.[36]

Thrush—Monilial infection is much less common in breast-fed infants.[37] Lactoferrin strongly inhibits the growth of *Candida albicans*[38] and cellular immunity, possibly conferred by leucocytes in breast milk,[39] may provide protection against monilia[40] and tuberculosis.[39]

CHEMICAL DISTURBANCE

Hypocalcaemia

In recent years hypocalcaemia has been the most common cause of neonatal convulsions. In a series reported from Manchester convulsions occurred in 8·7 per 1000 newborn babies, and, of these, 34% were attributed to hypocalcaemia alone.[41] Occurring towards the end of the first week of life, it is seen almost exclusively in babies fed on cows' milk preparations. The way in which cows' milk feeding leads to hypocalcaemia is incompletely understood[42] but the high phosphate content of such milks appears to be important.[43]

Hypernatraemia

Hypernatraemic dehydration in infancy is well known to be associated with a serious risk of permanent brain damage.[44] Cows' milk and the older cows' milk preparations contain nearly four times as much sodium and three times as much protein as human milk (table II). This presents the infant kidney with an unduly high solute load for excretion, resulting in a high obligatory renal water loss, and, although the healthy infant can usually cope with this without harm,[45] further water loss from diarrhoea or overheating may result in hypernatraemia.[46] The problem is compounded by the tendency of mothers and nurses to make up feeds more concentrated than is intended by the manufacturers by compressing the powder in the scoop.[47 48]

OBESITY

Artificially fed babies gain weight more rapidly than breast-fed ones.[49] This may be caused by the high solute load of cows' milk leading to thirst and increased demand for fluid, which is interpreted by the mother as a desire for more milk and possibly for solid foods. Obesity in infants is undesirable because of its association with respiratory problems,[29] and it has been claimed that obesity in infancy leads to obesity in later life,[50 51] with its associated dangers of coronary disease, hypertension, and diabetes, but this may not be so.[52]

COWS' MILK ALLERGY

Estimates of the incidence of allergy to cows' milk in infancy have varied from 0·3 to 7%.[30] The presenting features may include diarrhoea, vomiting, respiratory problems, failure to thrive, anaemia, or rashes and the diagnosis is a clinical one based on the withdrawal and re-introduction of cows' milk. Changes similar to those of coeliac disease may be seen in the jejunal mucosa.[53 54]

NECROTISING ENTEROCOLITIS

Necrotising enterocolitis, which is seen particularly in premature infants and after exchange transfusion, occurs almost exclusively in artificially fed babies. Experiments in rats have shown a specific protective effect of breast milk.[55] Although uncommon, necrotising enterocolitis is associated with a high mortality.

COT DEATH

Sudden unexpected death in infancy occurs in about two babies per 1000 live births, and over 1800 babies die in this way each year in Britain.[56] The cause of death is often unknown but there are data to suggest that the risk is about twice as high for bottle-fed babies.[57–59] Two recent reports, however, have cast doubt on this.[60 61] Gunther[62] has stressed that breast-feeding should be regarded as an important part of the baby's immunological defence mechanism, filling in the gap between the period of total antigenic isolation in utero and the time when the infant becomes immunologically independent. She suggests that breast-feeding may provide protection against cot death by limiting the access of both infective agents and allergens, the latter possibly being the more important.

ATOPIC DISEASES

Feeding the children of atopic parents on a soybean-based "milk" rather than an evaporated milk for the first nine months of life reduced the incidence of asthma and eczema to a third and of perennial allergic rhinitis to a fifth of that seen in the control group up to the age of 10.[63] There appears to be no evidence on the effect of early feeding on atopic disease in later life but it has been claimed that prolonged breast-feeding delays the onset of asthma.[64]

Another study on the infants of atopic parents[65] showed that those who developed evidence of atopy in the first year had serum levels of IgA which were lower than the rest at 3 months of age and higher at 12 months. It was suggested that transient IgA deficiency in early life might give a susceptibility to the ingress of allergens. Breast-feeding would both limit the supply of allergens to the infant and, by providing secretory IgA, strengthen the mucosal barrier to such allergens.

ULCERATIVE COLITIS

In a retrospective inquiry Acheson and Truelove[66] found that about twice as many patients with ulcerative colitis as controls had never been breast-fed. After considering social and other factors involved they concluded that early breast-feeding provided protection against the later development of this disease.

CORONARY VASCULAR DISEASE

Osborn[67] showed that in young adults early evidence of atheroma is more common in those who were bottle-fed in infancy and Davies[68] has strongly supported the view that early cows' milk feeding may be an important factor in the later development of coronary disease. He believes that coronary disease has an immunological basis and has shown that patients with myocardial infarction have serum antibodies to milk proteins more commonly than do controls.[69] Giving cows' milk early in life might prime the immunological system.

MULTIPLE SCLEROSIS

There is no hard evidence relating multiple sclerosis to early feeding of cows' milk. Nevertheless, Agranoff and Goldberg[70] have introduced the hypothesis from epidemiological data that geographical variations in the prevalence of multiple sclerosis could be due to regional variations in milk consumption and infant feeding practices, possibly as a result of the different fatty acid compositions of human and cows' milk fats.

Effect of social class

The babies of parents in higher social classes are less prone to infection[26] and to sudden unexpected death.[57] They are also more likely to be breast-fed,[71 72] so that the babies in most need of breast-feeding because of adverse social circumstances are the least likely to get it. Undoubtedly mothers of lower social class should be strongly urged to breast-feed whenever possible, and the DHSS Working Party[1] has recommended that the period during which maternity allowance is payable should be adjustable to allow working mothers to spend longer at home after the birth of the baby.

What of the middle class mother who says: "My baby is unlikely to suffer from severe infection whether I breast feed or not"? What she says is true, but it may be explained that early hypocalcaemia is no respecter of social class and neither are obesity or an allergy to cows' milk. Her baby's stools will become colonised with coliform bacilli rather than lactobacilli, with an increased risk of neonatal septicaemia and meningitis. Atopic diseases, ulcerative colitis, coronary disease, and multiple sclerosis occur throughout the social scale and, although the evidence linking these conditions with bottle-feeding is not conclusive, most parents would surely wish to give their babies the benefit of the doubt.

Duration of breast feeding

The DHSS report[1] recommends breast-feeding for four to six months. During this time breast milk provides adequate amounts of protein and calories tailored to the needs of human growth,[73] and the infants' need for the protection provided by breast milk against infection and the ingress of allergens is maximal.[74] Breast-feeding beyond this time apparently confers little advantage in terms of infant mortality.[7] Mothers who cannot breast-feed for a prolonged period should be encouraged to do so for at least two weeks, as this would virtually eliminate dietary neonatal hypocalcaemia and might prevent neonatal septicaemia and meningitis. The DHSS Working Party also recommended that solid foods should not be introduced before the age of 4 months.

Supplements

Breast-fed babies are more prone to develop haemorrhagic disease of the newborn and an injection of vitamin K soon after birth is a wise precaution. Human milk contains little vitamin D or iron. Vitamin supplements should be given to breast-fed babies in larger doses than to bottle-fed ones (see below) and iron will be needed. Nevertheless, in view of the possible harmful effect of saturating the lactoferrin in milk with iron, it may be advisable not to give supplemental iron for the first month or two.

Bottle feeding

Several new milk preparations introduced in the last few years are intended to reduce the risk of biochemical disturbance and might conceivably contribute to reducing the incidence of obesity but would not be expected to have any appreciable effect on infection or allergy. The main changes made have been a reduction in the contents of sodium, protein, and phosphorus in order to simulate breast milk and thus prevent hypernatraemia and dietary neonatal hypocalcaemia. Babies fed on the "adapted" milks have been shown to have values of serum calcium,[43] urine osmolality,[45] and plasma urea[75] similar to those of breast-fed babies.

In Britain now there are three main proprietary milks of this kind: Cow and Gate Premium, Ostermilk Complete Formula, and SMA S26. Table II compares these milks with some of the older milks, fresh cows' milk, and breast milk. The new milks also differ in the composition of their fat and sugar components, but there is no convincing evidence that these differences are important. Ostermilk Complete Formula contains only butter fat but Cow and Gate Premium and SMA S26 have added vegetable fat in an attempt to bring the fatty acid composition nearer to that of breast milk. Vegetable fat is more completely absorbed that butter fat, but this may not represent any real advantage to the baby.[76] Cow and Gate Premium and SMA S26 have lactose added, whereas Ostermilk Complete Formula has added maltodextrins. This results in babies fed on Ostermilk Complete Formula having rather firmer stools. There appears to be no clear reason for preferring one sugar to another.[77]

It is hoped that by diminishing the baby's thirst the low solute milks will lead to less overfeeding and consequently less obesity. The milks should be satisfactory as a sole nutrient from birth up to the time of weaning and there is no need for a different milk for the newborn such as the half-cream milks. Solid foods should be unnecessary before the age of 4 months.

The DHSS Working Party recommended that to minimise the risk of contamination only water should be added when reconstituting the milk. All the new milks have sugar added by the manufacturers.

FORTIFICATION

Most milks are "fortified" by adding iron and vitamins A, C, and D. Iron is added to all except the evaporated milks and Cow and Gate Trufood. The possible disadvantage of added iron for younger infants has been mentioned. Vitamin D is added to all milks so that the reconstituted milk contains 320 to 440 IU/l. The Government provide a vitamin supplement which provides in seven drops: vitamin D 400 units (10 μg), vitamin C 30 mg, and vitamin A 300 μg. The recommended dose for breast-fed babies is three drops daily in the first month, increasing to seven drops at 4 months. For bottle-fed babies the recommendation is two drops daily in the first month and four drops at 4 months.

The position of National Dried Milk has been debated.[78 79] It is

provided by the Government at a much cheaper price and contains less sodium and phosphorus than the older proprietary milks. It would be better for the Government to provide a cheap low solute milk similar to the new proprietary preparations, but until this is done the present National Dried Milk could be recommended to mothers who cannot breast-feed and for whom the cost is a major consideration.*

Conclusions

(1) Breast-feeding should be more strongly advocated than in the past for at least two weeks and preferably four months.

(2) When breast-feeding is not possible one of the new low solute milks should be recommended.

(3) The introduction of solid foods into the diet before the age of 4 months should be discouraged.

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*Since this article was written, the Government have recommended that high solute milks, including National Dried Milk, should not be given to babies under the age of 6 months and have promised to make available a cheap low-solute dried milk.

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There appears to be a relationship in women between insulin requirements and the oestrogen/progesterone levels in the menstrual cycle. With anovulation the control is more difficult and hypoglycaemic coma has developed twice in a patient of mine. Is there any explanation? Can progestins be used in the second half of the cycle?

The question of relating insulin requirements to sex hormone levels either during the menstrual cycle or in women taking the pill is a difficult one. The association of severe insulin resistance on a cyclical basis with menstruation has been well recorded[1] but the mechanism is not clearly understood. In most insulin-requiring diabetics there is no consistent pattern of control through the month and usually changes due to other factors, such as diet and exercise, are far more prominent. Anovulatory cycles are certainly associated with low progesterone levels during the latter part of the cycle, and synthetic progestins exert a mildly diabetogenic effect in normal people, although this finding cannot necessarily be extrapolated to patients treated with insulin. There is little evidence that progesterone itself, even in enormous parenteral doses, influences carbohydrate metabolism in normal people. It is difficult to identify occasional spontaneous anovulatory cycles promptly enough to normalise the hormonal situation by giving progestins, unless the patient is taking daily temperature records. I doubt, therefore, whether the practical value of progestin administration to maintain normal diabetic control would be very great. The question of anovulation may also refer to patients taking a combined oral contraceptive. There is no general agreement whether these raise or lower insulin requirements, or are without consistent effect. Probably the latter is generally the case. Although some physicians do not regard diabetes as a contraindication to combined oral contraceptives, their effects on lipid metabolism and vascular episodes are often regarded as contraindications to their use in diabetic populations already liable to premature degenerative disease.[2]

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