Nutritional advantages of constituents of infant formulae formely called « humanised »

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Terms like « maternized or « humanised » attached to infant formulae are misleading and should not be used anymore. The modifications to cow's milk to adapt it to the nutritional requirements of infants result in a product that is quite far from human milk particularly with respect to the immunological components. The correct term for these products is « adapted formulae ».

Basically there are two kind of adaptations, quantitative and qualitative and almost all categories of nutrients are modified.

Protein adaptation

a) *Quantitative.* — The first adaptation is a reduction of about 50 per cent of the total quantity of protein from 35 g/l in cow's milk (CM) to 15 — 17 g/l for a modern infant formula (IF). The main reasons for this are the limited digestive and absorptive capacities of young infants for protein. The second is to reduce renal solute load since all the proteins in excess of the needs of the baby for maintenance and growth are catabolised with formation of urea needing water to be eliminated by the kidneys. The immature kidney has only limited capacities of concentration (1). The use of non diluted CM has been responsible (2) for hyperosmotic dehydration mainly due to the high level of electrolytes in cow's milk but also partly due to the level of protein. The third reason for reducing the protein level is to minimise the risk of acidosis. The newborn's kidney is unable to buffer an excess of acid produced as a result of the metabolism of sulphur containing amino acids. However, acidosis although frequent in low birth weight infants, is very rare in term infants even with protein level as high as 5,7 g/kg/day (3).

A hypothetical reason would be the stimulation of insulin secretion by excess of amino acids.

Some authors (4) ask for an even greater reduction of the protein level to bring it even closer to the level of HM of about 11 g/l.

This proposal does not take full account of the important physiological variations in humans. The protein level in HM (fig. 1) varies from above 30 g/l at birth to 14 g/l after 1 week to reach the level of 11 g/l only after several weeks (5).
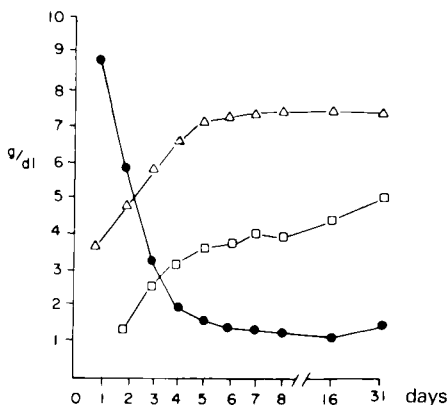
FIG. 1. — *Concentration of protein (●), lipid (⬚) and lactose (△) in human milk* (ref. 5).

Why should manufacturers select the lowest level of the range corresponding to a period of slower growth ? There may be also possibilities of transamination due to the high level of non protein nitrogen in HM which could increase the level of some aminoacids when needed. Absorption of protein in the infant could vary from one day to the other in relation to many factors such as intestinal transit time or infection, presence of fiber from other food etc. The needs could also vary from day to day. Finally we have to remember that even with the latest technologies and in spite of great progress, the heat treatment necessary for conservation of formulae leads to a certain destruction or blockage of some amino acids like lysine (6) whereas in fresh HM the total quantity of amino acids is available.

These are the reasons why industry should keep a certain security margin and not try to go down to the same level as HM, taking also into account the fact that only large quantities of protein given during long periods to uninephrectomized rats (7) have been proven harmful.

The hypermethioninemia observed in infants (8) happened with enormous quantities of protein : 7-16 g/kg/day and there were no clinical symptoms. By contrast Zoppi *et al.* (9) have published deficient immunoglobulin synthesis when the protein diet was insufficient in quantity or in quality.

b) *Qualitative.* — Due to the specificity of the aminoacids necessary to synthesize the new proteins characteristic of rapid infant growth, it is important that the quantity of individual essential or semiessential amino acids present in formulae should be higher or equal to the quantity present in HM. The level of cystine is for example in CM at 60 % of the HM level. Change in casein/whey ratio will raise the level of cystine. On the other hand some amino acids like tyrosine or phenylalanine are considered toxic for the developing brain of the new born when the plasma level reaches 100 micromoles/dl for tyrosine or 60 micromoles/dl for phenylalanine. These levels could be reached in low birth weight infants (10) especially for tyrosine (fig. 2) with formulae too rich in protein and when the ratio casein/whey has not been modified.
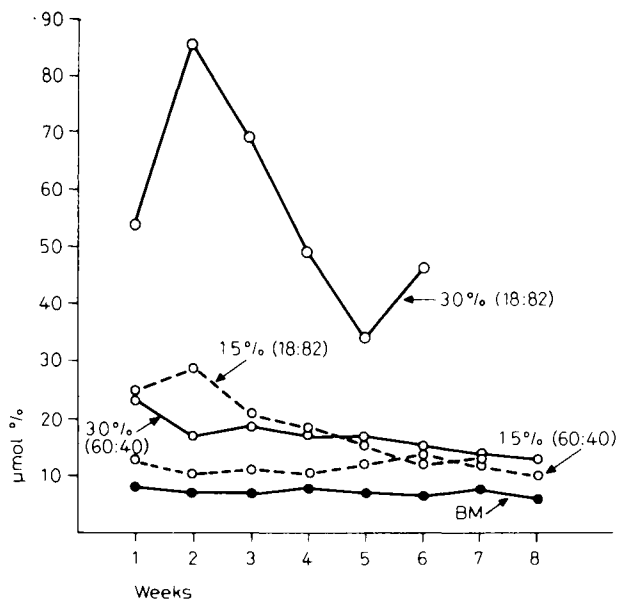
FIG. 2. — *Blood tyrosine levels in preterm infants* (ref. 10).

By extension and as a legitimate precaution, even for the healthy neonate, changes in the casein/whey ratio could be associated with protein reduction to further reduce the level of these amino acids.

Very recently manufacturers have added to IF taurine which could be considered an amino acid even if taurine is not incorporated into protein. Taurine is abundant in human milk and plays a role in synthesis of bile acids. It is also important in some mammals for the normal functioning of the retina. In healthy term infants, and even low birth weight infants (LBW), in spite of numerous studies aimed at proving importance of taurine nothing convincing has been shown (11). By contrast in LBW infant fat absorption seems to be significantly reduced.

Carbohydrate adaptation.

Human milk contains on average about 74 g of carbohydrate (CHO) per litre whereas CM contains only about 48 g/l (12). Adaptation consists of raising the level of CHO up to HM level. The quality of the CHO added to IF has become an issue for 3 main reasons : — Sweetness, — Dental caries, — Osmolarity.

In the old days the CHO usually added was sucrose. In the modern adapted IF the CHO added is either lactose or dextrin maltose (DM). The advantages of lactose are that it is less sweet than sucrose or fructose and doesn't induce over-consumption of IF which could lead to infantile obesity (13). Lactose is a less potent inducer of dental plaque than is sucrose and a less potent acid producer

(table 1) (14), although the first tooth usually does not appear much before the cessation of consumption of these starter IF.

TABLE 1

Acid production rate in dental plaque suspension from different carbohydrates expressed as percent of the rate from glucose.

Substrate	Acid production rate (%)
Glucose	100
Sucrose	100
Glucose syrups (DE 40 and 60)	100
Fructose	80-100
Lactose	40- 60
Maltitol-Sorbitol	10- 30
Mannitol-Xylitol	0

Lactose also enhances net absorption and net retention of calcium as well as absorption of magnesium and manganese (15). It has also been said that lactose (16) probably through lactic acid acidifies the stool of the baby, prevents growth of pathogens or by formation of lactulose (17) working as bifidus factor.

The advantage of DM is based on its low osmolarity in solution which becomes an important issue since necrotizing enterocolitis, mainly in low birth weight infant but sometimes in newborn, has been related to an excessive osmolarity of the IF. The committee on nutrition of the American Academy has issued recommendations (18) related to the osmolarity of infant formulae. Table 2 shows the osmolarity of solutions of lactose or of DM of various degrees of polymerisation. It is clear that at the level usually found in IF replacement of a large quantity of lactose by DM drastically reduces the osmolarity of the solution.

TABLE 2

Osmolarity of a solution of 50 g/l of lactose or of DM of decreasing degree of polymerisation.

Concentration g/l	Osmolarity mOsm/l of water			
	Lactose	MD 02	MD 05	MD 25
50 g/l	150	33	51	77

Due to the fact that lactase activity appears quite late in the ontogeny of the gut in contrast with alpha-amylase and maltase and in spite that the level of lactase is generally adequate in newborn to digest about 50 g of lactose per day, some authors attribute infant colic to the lactose content of HM or IF. Dextrin maltose is thought to be much more easily digested.

Fat adaptation.

The total concentration of fat in HM (36 to 47 g/l) and in CM (38 g/l) are approximately the same (12).

During the adaptation of CM, it is important to keep a high level of fat since fat brings 9 kcal per g when CHO or protein brings only 4 kcal per g. Moreover fat is not responsible for any osmolarity since it is not soluble in water. The addition of fat should take into account not only the fatty acid pattern, the rate of absorption but also the metabolic result or even the potential toxicity.

Fat absorption is inversely proportional to the length of the chain and directly proportional to the number of unsaturated bonds (fig. 3) (19).
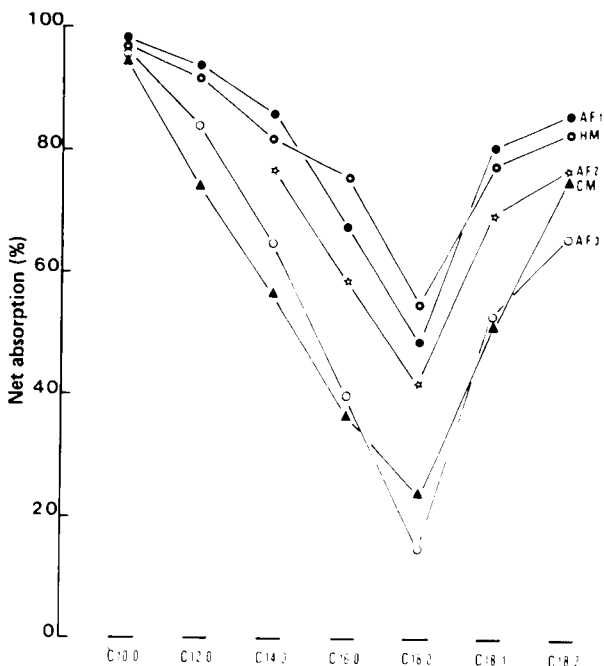

FIG. 3. — *Net absorption of various fatty acids in LBW infants fed pasteurized pooled human milk* (HM), *various adapted formulaes* (AF1, AF2, AF3) *or a cow's milk formula* (CM). (ref. 19).

Despite the large proportions of palmitic acid (C 16 : 0) HM fat is well absorbed (20) probably due to the fact that most of its palmitic acid is esterified in the beta position (21). Among fats available for infant feeding lard is the one with the highest percentage of palmitic acid in the beta position (83 %) followed by CM fat (43 %) whereas vegetable fats contain no more than 10 % of palmitic acid in the beta position. This makes CM fat fairly well absorbed (22). Optimal fat absorption is not only important for energy balance but also for calcium absorption since there is direct relationship between fat and calcium absorption (23).

Regarding the long term potential consequences of early feeding it is clear that the level of plasma cholesterol of infants receiving formulae with vegetable fat (24) is much lower than the level of cholesterol of breast fed infants.

This raises the question of late atherosclerosis when the level of plasma cholesterol remains low during the period of enzyme induction and when the ratio HDL/VLDL (25) is different from the one with HM.

Due to the potential risk of atherosclerosis (26) the EEC scientific committee for food (27) have fixed a maximum level of 15 % of the fat content for lauric and myristic acid in IF.

The essentiality of linoleic acid has been recognised for a long time (28). The level in IF should be in the same range as BM between 6 and 16 % of the total fat (29) varying according to the mother's diet. Linoleic acid is important for maintenance of functional integrity of cell membrane and synthesis of prostaglandins (30). The importance of linolenic acid, arachidonic and C22 : 6 has been recognized lately (31).

Finally one should not forget potential toxicity of some fatty acids contained for example in cotton seed oil (32) like malvalic acid and sternilic acid responsible for deleterious mitogenic effects.

Mineral adaptation.

As previously mentioned the high level of electrolytes in CM opposed to the low level in HM has been responsible for hypernatremic dehydration when dilution instructions were not correctly followed. One important adaptation is to reduce the level of sodium from about 500 mg/l in CM to 150 to 200 mg/l level found in HM (33) (fig. 4).
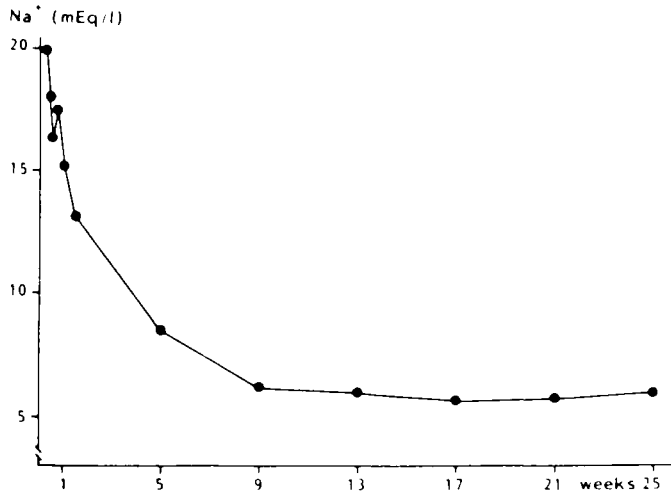

FIG. 4. — *Sodium concentration of human milk in the first six months postpartum* (ref. 33).

Potassium and chloride should be reduced in about the same proportions. The potassium/sodium ratio should be above 2 and to avoid too low a level of chloride which otherwise induces dangerous alkalosis and hypercalciuria (34). Recently (35) the question whether low sodium infant formulae could prevent hypertension in adults has been raised. The long term consequences of early dietary manipulation is still uncertain (36). Other factors like calcium content of diet play an important role in the subsequent development of adult hypertension (37).

Calcium and phosphorus adaptation are very important for bone growth of the infant. Calcium level in CM is about 3 times higher than in HM while phosphorus level is about 6 times higher resulting in a Ca/P ratio of about 1,3 in CM *versus* 2 in HM. Since we know that Ca/P ratio is an important parameter for calcium absorption and retention, manufacturers try to increase this ratio closer to HM ratio.

However we also know that the absorption of calcium is inversely related to the total calcium content of the formulae. In other words increasing the calcium content of a formulae reduces the percentage of calcium absorbed and increases the quantity of calcium in the stool. This calcium will combine with fatty acids to give insoluble salts preventing absorption of fat (38). A good way of increasing Ca/P ratio is to reduce the phosphorus content of CM by two third and calcium by half. Such adaptation allows a calcium absorption and retention of 117 mg/kg/day comparable to HM (114 mg/kg/day) even in premature infants (39).

Trace Minerals.

The iron content of CM is not very different from HM 0.5 mg/l versus 0.76 mg/l. However the absorption is very different (40) : about 50 % in HM and about 10 % in CM. In IF the presence of vitamin C increases iron absorption to about 20 %.

This quantity is certainly sufficient for healthy newborns during the first 4 months of life. It becomes insufficient both for breast and artificially fed infants after 4 months. To avoid anemia supplementation of 8 to 12 mg/l should then be introduced. Copper and zinc have about the same concentration in CM and HM. The mean value of iodine is a bit lower in CM than in HM, but there is a large variation, according to the proximity of the sea. The level is usually sufficient for healthy newborn so addition is generally not necessary.

Vitamins.

Most vitamins are present in CM at a lower level than in HM so a certain adaptation is necessary. This is particularly true for Vit D, 20 times less abundant in CM, Vit E 10 times less and for which a further addition is needed in relation to the level of linoleic acid. Vit C should be added because it is sensitive to heat treatment. Moreover a high level of Vit C is necessary in infant formulae to improve iron absorption (40).

All these nutritional adaptations now give us a very good substitute for HM when breast feeding is not possible for medical, social or economic reasons. However there is still more work to do especially in the field of immunology, to remove the risk of sensitization to foreign protein by use of hydrolysed protein and to provide some non specific protection against enteral infection by addition of substances like lactoferrin, lactoperoxidase, lyzozyme... Even then, it would be difficult to speak of « humanized » formulae since the protection offered by

mother's milk against infection is adapted to the risk through specific immunoglobulins A and through leucocytes activity.

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