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Response of Premature Infants to Human Milk and Two Types of Cow's Milk Formulae

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Summary. The response of thirty-four premature infants to human breast milk and two types of cow's milk formulae has been investigated. The three milk formulae were well tolerated. There was no significant difference among the babies in the bulk, frequency and consistency of their stools. The average daily weight gain among infants fed on a 'humanized' cow's milk formula (S-26) closely paralleled that of another group of infants fed on human breast milk. The average daily weight gain among infants fed on a non-humanized cow's milk (Lactogen) was generally satisfactory although lower than that obtained from the other two groups of infants. It is concluded that human breast milk or a cow's milk formula with composition similar to human milk contains the optimal contents of nutrients necessary for the rapid growth of premature infants.

Résumé. La formule, répondant à 34 cas d'allaitation d'enfants prématurés, en deux types de lait de vache, a été trouvée.

Les trois formules de lait étaient acceptables. Il n'y avait pas de différence significative, fréquemment et constamment, entre les enfants dans le ventre, et ceux de la couveuse.

Le poids convenable, quotidiennement obtenu parmi les enfants nourris à l''humanised' formule de lait de vache (S-26) est sensiblement le même que celui (d'un groupe) d'enfants nourris au lait maternel.

Le poids convenable quotidiennement obtenu par des enfants nourris au lait de vache artificiel (Lactogen) était généralement satisfaisant bien que, au-dessous, du poids obtenu dans les deux autres groupes.

Il est à conclure que le lait maternel ou le lait de vache formulé à partir d'une composition similaire au lait maternel contient des éléments nutritifs optimum nécessaire pour une rapide croissance d'enfants prématurés.

A decline in breast feeding has been reported from several developing countries: Uganda (Welbourn, 1958), Kenya (Bell, 1955), Trinidad (Jelliffe, Symmonds & Jelliffe, 1960), and

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Nigeria (Adeniyi-Jones, 1955; Wenn-Van Der Mey, 1969). Because of the prevailing poor standard of sanitation, and low level of maternal education, the substituted practice of bottle feeding has often resulted in increased morbidity and mortality from bacterial contamination of the bottle feeds (Welbourn, 1958; Wenn-Van Der Mey, 1969). Ideally, breast feeding should therefore be the advisable method of infant rearing in developing countries. There are, however, circumstances when artificial feeding of infants is strongly indicated. Such circumstances include severe illness or death of the mother, diseased maternal breast, abnormalities of the mouth and palate in the infant, and extreme feebleness or prematurity of the infant.

In developing countries, prematurity is common and in our experience this condition is the commonest indication for artificial feeding. These infants are poor suckers, and consequently the mother's milk supply tends to dry up because of inadequate stimulation. Prolonged hospitalization and therefore separation from their mothers is common with premature infants; in such a situation financial and transport difficulties tend to limit the frequency of visit to hospital by mothers to supply expressed breast milk (EBM) for use by the babies. Wet nurses are sometimes available, but supply from this source is usually limited and human milk banks are beyond the financial and organizational capacity of most centres in developing countries. In practice, therefore, paediatricians in developing countries often resort to artificial milk preparations, for feeding premature infants under their care. The purpose of the present study was to compare the response of premature Nigerian infants to human breast milk and two types of cow's milk formulae. To the best of our knowledge, there has been no previous report of such a study in premature African infants.

SUBJECTS AND METHODS

The study was carried out on premature babies admitted to the Special Care Baby Unit (SCBU) of the University College Hospital, Ibadan, Nigeria. The period of the study was from April to September 1970. The unit admits premature infants with birth weights mostly below 4 lb (1·8 kg). On admission infants were randomly allocated to three different milk formulae. A (human breast milk), B (Lactogen—Nestlé) and C (S-26—Wyeth). Infants who had repeated apnoeic or cyanotic attacks during the first 6 days of life, or required oxygen therapy for more than a few hours on or after the sixth day of life, or became seriously ill from whatever cause during the period were excluded from analysis.

Formula B has been in wide use for many years. Formula C was recently introduced into the Nigerian market. The manufacturers of this milk formula claim that when the milk powder is reconstituted a percentage composition similar to that of human milk is obtained. Undiluted breast milk was obtained from lactating mothers attending the University College Hospital. The commercial formulae were reconstituted according to the manufacturers' directions.

The approximate composition of the three types of milk are as shown in Table 1. Feeding and nursing care of the infants were undertaken by the same nursery staff, all of whom had had between 3 and 5 years' experience in the unit. Infants were offered their respective milk preparation, first at 12–18 hr of age, and thereafter at 2–3 hourly intervals, depending on the size of the baby. Infants who were too feeble to suck from the breast or bottle were fed through a nasogastric tube and the quantity of feed ranged from 3 to 4½ oz/lb (85–128 ml/

kg) body weight/day. Those infants who were strong enough to suck were fed *ad libitum* each infant being offered the largest amount of feed it was able to accept.

Each infant was weighed on alternate days throughout the period of study. In addition, a record was kept of the number, size, consistency and colour of stools, regurgitation of feeds and excoriation of the buttocks. Daily clinical assessment of each infant was carried out by one of us (J.B.F.).

The following investigations were done on the sixth day of life, and thereafter at 3 weekly intervals until the infant was discharged:

(1) Total serum proteins and fractions (albumin and globulins) by the Biuret method (Gornall, Bardawill & David, 1949).

(2) Serum cholesterol, by the digitonin-precipitation method (Ferro & Ham, 1960).

(3) Serum calcium by the method of Trinder (1960).

(4) Serum inorganic phosphorus by the method of Gomori (1942).

(5) Serum transferrin by the antibody-incorporated agar-plate method of Mancini *et al.* (1964). The immunoplates were obtained from Hyland Laboratories, Los Angeles, California.

(6) Packed cell volume (PCV) was determined with the aid of a portable centrifuge as described by Dacie & Lewis (1968).

TABLE 1. Approximate composition of the various milks used in the study

	Human milk*	Lactogen†	S-26†
Protein (g/100 ml)	1·6	2·4	1·5
Fat (g/100 ml)	5·9	3·5	3·6
Carbohydrates (lactose) (g/100 ml)	7·2	7·6	7·2
Phosphorus (mg/100 ml)	9·5	39‡	33
Calcium (mg/100 ml)	20·5	54‡	42
Iron (mg/100 ml)	0·2‡	0·75	0·8
Total mineral (mg/100 ml)	235‡	840	250

* Data obtained from Nigerian women (Bassir, 1956).

† Data given by the manufacturers.

‡ Unavailable data from sources * and † above. These were obtained from human breast milk (Nigerian women) and from the two artificial milk formulae by H. McFarlane, Chemical Pathology Laboratory, UCH, Ibadan.

Infants who developed jaundice were fully investigated to determine possible aetiological factors, and serial estimation of serum bilirubin was also carried out to determine the course of the jaundice. Infants with unconjugated bilirubin ranging between 18 and 20 mg/100 ml received exchange blood transfusion. An infant was discharged when its weight reached between 4½ and 5 lb (2·2·27 kg).

RESULTS

During the 6-month period of the study, 110 infants were admitted into the unit; thirty-four (sixteen male and eighteen female) of these satisfied the criteria for analysis. Of the thirty-four infants, twelve were on Formula A, twelve on Formula B and ten on Formula C.

All the three milk formulae were well tolerated. There was no significant difference in the bulk, frequency and consistency of stools. Simple redness of the buttocks or excoriation occurred in most of the infants during the first week or two of life when they were in incu-

TABLE 2. Mean birth weight of premature infants receiving three different milk formulae

	Milk formula		
	A	B	C
Mean birth weight in pounds (kg in parenthesis)	3·38 (1·53)	3·63 (1·65)	3·71 (1·68)
SD	±0·33	±0·40	±0·32
SE	±0·10	±0·12	±0·10
No. of infants	12	12	10

TABLE 3. Differences between the mean daily weight gain

			Milk formula		
			A	B	C
Mean daily weight gain (g)			23·58	19·39	24·49
SD			±3·91	±3·94	±2·57
Number of infants			12	12	10
Pair under test	*t* value	df	*P* value		
A vs B	2·61	22	0·025 > *P* > 0·01		
A vs C	0·65	20	*P* > 0·5		
B vs C	3·65	20	0·005 > *P* > 0·001		

bators. No particular milk formula was associated with excoriation of the buttocks in any significant frequency. During the first 12 days of life, there was an initial loss of weight in all the babies irrespective of the milk formula. Thereafter weight gain proceeded steadily in the three groups.

Table 2 summarizes the mean birth weight of the infants. There was no significant difference between the mean birth weight in the three groups. The average daily weight gain for each infant was obtained by dividing the difference between the birth weight and the

TABLE 4. Biochemical and haematological values in premature infants fed on various milk formulae*

Milk formula	Age								
	6 days			3 weeks			6 weeks		
	Formula A	Formula B	Formula C	Formula A	Formula B	Formula C	Formula A	Formula B	Formula C
Total serum protein (g/100 ml)	5·39± 0·40	5·86± 0·74	6·06± 1·02	5·17± 0·40	5·46± 0·48	5·83± 0·69	5·53± 0·80	5·18± 0·75	5·35± 0·42
Albumin (g/100 ml)	3·47± 0·47	4·31± 1·07	3·69± 0·52	3·63± 0·71	3·50± 0·63	3·83± 0·75	4·05± 0·42	4·03± 0·48	3·85± 0·35
Globulin (g/100 ml)	1·79± 0·44	1·51± 0·59	2·36± 0·59	1·58± 0·77	2·00± 0·79	1·79± 0·65	1·66± 0·35	1·20± 0·37	1·60± 0·50
Serum cholesterol† (mg/100 ml)	110·0 ±28·3	127·8 ±20·1	118·8 ±20·1	129·8 ±22·2	143·5 ±21·5	132·9 ±29·6	99·7 ± 8·6	136·3 ±36·8	116 ±18·9
Serum calcium (mg/100 ml)	8·9 ± 1·13	8·8 ± 0·8	9·2 ± 1·1	10·1 ± 1·7	9·0 ± 2·1	10·4 ± 1·5	12·1 ± 2·0	10·0 ± 1·1	11·37± 1·2
Serum phosphorus (mg/100 ml)	6·0 ± 1·2	7·3 ± 0·7	7·1 ± 0·8	7·0 ± 1·4	7·0 ± 1·4	7·1 ± 2·2	6·23± 1·1	6·4 ± 1·6	5·6 ± 1·2
Serum transferrin (mg/100 ml)	1·8 ± 0·8	1·8 ± 0·8	1·4 ± 0·8	2·0 ± 0·7	2·1 ± 0·6	2·6 ± 0·3	2·6 ± 0·5	3·3 ± 0·8	2·3 ± 0·2
Haematocrit or packed cell volume‡ (PCV)%	55·4 ± 5·5	56·2 ± 5·5	48·0 ± 4·2	40·8 ± 4·0	42·8 ± 8·1	30·5 ± 2·6	27·0 ± 3·9	30·1 ± 1·9	25·7 ± 3·3

* Mean values ±SD.
† Serum cholesterol at 6 weeks significantly higher ($P < 0·05$) in infants on Formula B compared with those on Formulae A and C.
‡ PCV significantly lower ($P < 0·05$) at 6 days and 3 weeks of age in infants on Formula C compared with infants on Formulae A and B.

weight on discharge by the total number of days spent in hospital. The means of the average daily weight gain per infant on Formulae A and C were comparable (Table 3), while the mean for infants on Formula B was significantly lower (Fig. 1).

The laboratory values in the three different groups at 6 days, 3 weeks and 6 weeks of age respectively are summarized in Table 4. There was no statistically significant difference between the groups in respect of the total serum protein, serum albumin, globulin, transferrin, calcium and inorganic phosphorus. There was, however, a gradual increase in the serum transferrin value in all the groups throughout the study. There was no difference in the serum cholesterol values during the first 3 weeks of life, but at 6 weeks of age, serum cholesterol values in babies on Formula B were significantly higher ($P<0{\cdot}05$) than in those on Formulae A and C. The cholesterol values fell in all groups at 6 weeks, although the fall was not significant. There was also a significantly lower PCV ($P<0{\cdot}05$) at 6 days and 3 weeks of age among infants who received Formula C than among those who received Formulae A and B. However, at 6 weeks of age, no further significant difference existed in the PCV in the three groups.

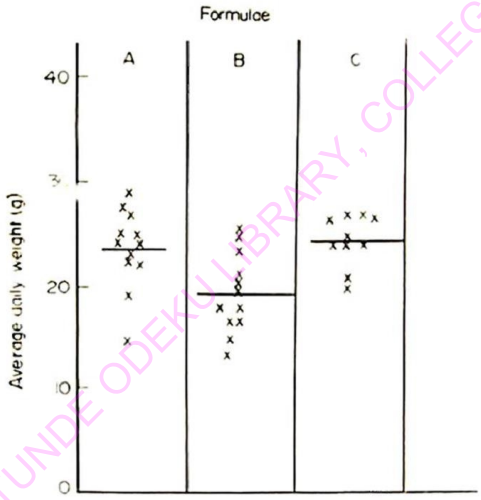

FIG. 1. Weight gain in groups of premature Nigerian infants fed various types of milk. Individual values and mean shown. Average daily weight gain calculated as in text.

DISCUSSION

The ideal food for premature infants remains a controversial issue. Advocates of cow's milk formulae maintain that human milk is not ideal for the rapidly growing premature infant because of its low protein and mineral salt and the high fat content. Gordon, Levine & McNamara (1947) obtained a significantly better weight gain in premature infants fed on evaporated and skimmed milk formulae than in those on human breast milk; they also stressed that partially skimmed cow's milk was particularly indicated for the smaller premature infants. Similarly, Mackay & Levin (1953) have observed a better mean weight gain in premature infants receiving half or more of their total calorie intake in the form of sweetened half-cream milk from birth. In contrast, Crosse *et al.* (1954) compared the performance of premature infants fed human milk with that of those fed other milk prepara-

tions and obtained the best all round results with human milk as judged by rate of weight gain, serum protein, haemoglobin level, mortality and infection rates. Similar findings to those of Crosse have been reported by others (Ford, 1949; Lelong & Rossier, 1951).

Our findings of better weight gains in infants fed human milk and a cow's milk formula with similar composition to human milk are in agreement with the findings of Crosse and others. The findings would suggest that human milk and cow's milk Formulae C contain optimal nutrients necessary for the growth of the premature human infant. The better weight gains with Formulae A and C are unlikely to be due to fluid retention since these formulae contain less total mineral content and fluid-retaining potential than Formula B. The favourable weight gain would seem to be due partly to the relatively high content of lactalbumin with a high ratio of essential amino acids. The lipid contents of Formulae A and B are probably also contributory. Although premature infants in general tolerate fat poorly, Gordon & McNamara (1941) have shown that the fat content of human milk is more easily utilized than that of cow's milk. Furthermore, linoleic acid which is present in higher quantities in human than in cow's milk has been shown to possess growth-promoting ability (Hansen *et al.*, 1962).

In most feeding studies, total serum protein and albumin levels have been used as reliable indices of nutritional adequacy. Although normal concentration of serum albumin may not reflect normal nutrition, abnormally low concentration strongly implies inadequate nutritional status (Fomon, 1967). The level of protein and albumin in the present study is comparable to that obtained by Fomon. There was no significant difference in the total serum protein and albumin between the groups of infants studied. Low serum transferrin (siderophilin) has been shown to be associated with protein–calorie malnutrition in children (Antia, McFarlane, & Soothill, 1968; McFarlane *et al.*, 1969). In the present study serum transferrin was comparable among the three groups of infants. Therefore, according to these parameters, Formula B does not appear to be nutritionally inadequate for premature infants, although its growth-promoting ability is less than that of Formulae A and C.

Recently the association between serum cholesterol and atherosclerosis has been the subject of considerable interest. In the present study, the serum cholesterol was significantly higher at 6 weeks of age ($P<0{\cdot}05$) among infants receiving Formula B than among those who received Formulae A and C. This finding is in agreement with that of Fomon & Bartels (1960) and may be explained by a higher composition of butter fat in Formula B. These authors have also shown that essential fatty acids present in human milk tend to reduce blood cholesterol levels. Serum cholesterol in the average Nigerian adult of low socio-economic status is lower than in the Caucasian (Edozien, 1965) and the incidence of pathological atherosclerosis is low in Nigerian adults (Williams, 1969). Prolonged breast feeding in childhood and low intake of cow's milk may explain these observations.

Phosphorus content is higher in cow's milk than in human milk and because of this, the use of cow's milk may produce hyperphosphataemia. Gittleman & Pincus (1951) and Gardner (1952), have considered this to be the most important factor in the genesis of neonatal tetany. The hyperphosphataemia induced by ingestion of cow's milk may be associated with hypocalcaemia (Oppe & Redstone, 1968). In contrast to these facts Von Sydow (1946) has shown that radiological signs of rickets are more frequent in premature infants on human milk than in those on cow's milk. In the present study, there was no statistically significant difference in the levels of calcium and phosphorus in the infants on the various milk formulae.

It is of interest that at age 6 days and 3 weeks the haematocrit among infants receiving Formula C was significantly lower than among infants on Formulae A and B. The difference in the iron content of the three milk formulae is unlikely to account for this observation since exogenous iron has been shown to have little influence on early anaemia of prematurity (Wolff & Goodfellow, 1955). Haemolytic jaundice occurred in five of the infants who received Formula C and in three each of those fed on Formulae A and B and this is possibly the cause of the low PCV in the babies on Formula C. In three of the infants on Formula C and one each of those on Formulae A and B, the jaundice was due to ABO incompatibility. In the two other jaundiced infants on Formula B and one of those on Formula C, the jaundice was associated with glucose-6-phosphate dehydrogenase (G6PD) deficiency. In three instances (one infant on Formula C and two others on Formula A) no associated aetiological factor (besides prematurity) was found. Exchange blood transfusion was necessary in two infants, namely, one in group B with G6PD deficiency, and another in group C with ABO incompatibility. Neonatal jaundice in association with the above stated factors is extremely common among Nigerian babies and it would appear that the type of milk formula was unrelated to the cases of jaundice in the present study. However, further study on this problem is indicated in view of the recently reported association of neonatal jaundice with human milk (Arias *et al.*, 1963; Newman & Gross, 1963).

The response of premature infants on Formula C closely parallels that of the infants fed human breast milk. There seems to be no doubt that this similarity is due to the quantitative and qualitative similarity in the composition of these two types of milk. Our results would support the conclusions of previous workers that human milk contains the optimal contents of nutrients required for the growth of premature human infants. In the absence of adequate milk however, it would appear that the best substitute is a cow's milk formula which approximates as much as possible to human milk.

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REFERENCES

Adeniyi-Jones, O. (1955) The etimological and medical significance of breast feeding: with special reference to the Yorubas of Nigeria (Correspondence). *J. trop. Pediat.* **1**, 123–124.

Antia, A.U., McFarlane, H. & Soothill, J.F. (1968) Serum siderophilin in Kwashiorkor. *Arch. Dis. Child.* **43**, 459–462.

Arias, I.M., Cartner, L.M., Seifter, S. & Furman, M. (1963) Neonatal unconjugated hyperbilirubinaemia associated with breast-feeding and a factor in milk that inhibits glucuronide formation *in vitro*. *J. clin. Invest.* **42**, 913.

Bassir, O. (1956) Nutritional studies on breast milk of Nigerian women. *J. trop. Med. Hyg.* **59**, 139–144.

Bell, S. (1955) The Ameru people of Kenya. *J. trop. Med. Hyg.* **58**, 249–259.

Crosse, V.M., Hickmans, E.M., Howarth, B.E. & Aubrey, J. (1954) The value of human milk compared with other feeds for premature infants. *Arch. Dis. Child.* **29**, 178–195.

Dacie, I.V. & Lewis, S.M. (1968) *Practical Haematology*, 4th edn, p. 48, J. & A. Churchill, London.

EDOZIEN, J.G. (1965) Establishment of biochemical norm for the evaluation of the nutritional status in West Africa. *J. W. Afr. Sci. Ass.* **10,** 3–21.

FERRO, P.V. & HAM, H.B. (1960) Rapid determination of total and free cholesterol in serum. *Amer. J. of clin. Path.* **33,** 545–549.

FOMON, S.J. (1967) *Infant Nutrition*, pp. 63–65. W. B. Saunders, Philadelphia and London.

FOMON, S.J. & BARTELS, D.J. (1960) Concentrations of cholesterol in serum of infants in relation to diet. *Amer. J. Dis. Child.* **99,** 27–30.

FORD, J.F. (1949) Feeding of premature infants. *Lancet*, **i,** 987–994.

GARDNER, L.I. (1952) Tetany and parathyroid hyperplasia in the new-born infant: influence of dietary phosphate load. *Pediatrics*, **9,** 534–543.

GITTLEMAN, I.F. & PINCUS, J.B. (1951) Influence of diet on occurrence of hyperphosphataemia and hypocalcaemia in newborn infants. *Pediatrics*, **8,** 778–787.

GOMORI, G. (1942) Modification of colorimetric phosphorus determination for use with photoelectric colorimeter. *J. Lab. clin. Med.* **27,** 955–960.

GORDON, H.H., LEVINE, S.Z. & MCNAMARA, H. (1947) Feeding of premature infants: A comparison of human and cow's milk. *Amer. J. Dis. Child.* **73,** 442–452.

GORDON, H.H. & MCNAMARA, H. (1941) Fat excretion of premature infants: Effect on fecal fat of decreasing fat intake. *Amer. J. Dis. Child.* **62,** 328–345.

GORNALL, A.G., BARDAWILL, C.J. & DAVID, M.M. (1949) Determination of serum proteins by means of biuret reaction. *J. Biol. Chem.* **177,** 751–766.

HANSEN, A.E., STEWART, R., HUGHES, C. & SODERHJELM, L. (1962) The relation of linoleic acid to infant feeding. *Acta paediat.* Suppl. **137,** 1–41.

JELLIFFE, D.B., SYMMONDS, B.E.R. & JELLIFFE, E.F.P. (1960) The pattern of malnutrition in early childhood in Southern Trinidad. *J. Pediat.* **57,** 922–935.

LELONG, M. & ROSSIER, A. (1951) L'elevage des prematures. *Nourirson*, **39,** 49–55.

MACKAY, H.M.M. & LEVIN, B. (1953) Proceedings of the Twenty-fourth General Meeting of the British Paediatric Association. *Arch. Dis. Child.* **28,** 245.

MANCINI, C., VAERMAN, J.P., CARBONARA, A.P. & HEREMANS, J.F. (1964) *Protides of the Biological fluids* (Ed. by H. Peeters), p. 370. Proceedings of the XIth Colloquium, Bruges, 1963. Elsevier, Amsterdam.

MCFARLANE, H., OGBEIDE, M.I., REDDY, S., ADCOCK, K.J., ADESINA, H., CURNEY, J.M., COOKE, A., TAYLOR, G.O. & MORDIE, J.A. (1969) Biochemical assessment of protein–calorie malnutrition, *Lancet*, **i,** 392–395.

NEWMAN, A.J. & GROSS, S. (1963) Hyperbilirubinaemia in breast-fed infants. *Pediatrics*, **32,** 995–1001.

OPPE, T.E. & REDSTONE, D. (1968) Calcium and phosphorus levels in healthy newborn infants given various types of milk. *Lancet*, **i,** 1045–1048.

WENN-VAN DER MEY, C.A.M. (1969) The decline of breast feeding in Nigeria. *Trop. Geog. Med.* **21,** 93–96.

WELBOURN, H.F. (1958) Bottle feeding: A problem of modern civilization. *J. trop. Pediat.* **3,** 157–166.

WILLIAMS, A.O. (1969) Atherosclerosis in the Nigerian. *J. Path.* **99,** 219–235.

WOLFF, J.A. & GOODFELLOW, A.M. (1955) Hematopoiesis in premature infants with special consideration of the effect of iron and of animal protein factor. *Pediatrics*, **16,** 753–762.

TRINDER, P. (1960) *Analyst*, **85,** 889.

VON SYDOW, G. (1946) Study of development of rickets in premature infants. *Acta Paediat.* **33,** Suppl. 2, 3–122.