

A DEFICIENCY STATE ARISING IN INFANTS ON SYNTHETIC FOODS

BY

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Severe extensive skin eruptions coupled with failure to thrive have been observed in infants fed on a synthetic low-phenylalanine diet (Moncrieff and Wilkinson, 1961; Brimblecombe, Blainey, Stone-man, and Wood, 1961; Wilson and Clayton, 1962). An investigation of this problem by Wilson and Clayton (1962) drew attention to the need to consider all nutrients carefully when constructing synthetic diets. The interdependence of various nutritional factors and the rapidity with which deficiencies could develop in infancy were particularly stressed. The publication of this work led one of us (T.P.M.) to realize that he had observed rashes somewhat similar to those described by Wilson and Clayton in galactosaemic infants receiving the low lactose-containing food, Galactomin (Trufood Ltd.). Similar features have subsequently been observed in 3 infants, one receiving a low sodium milk (Edosol, Trufood Ltd.), another low calcium milk (Locasol, Trufood Ltd.), and a third fed low lactose milk (Low lactose milk food, Cow and Gate Ltd.).

These synthetic milks are prepared by precipitating the casein in cows' milk, washing it to free it from other components and then mixing it with carbohydrate, fat, and a mineral mixture using a spray-drying process. During the initial precipitation and washing procedure, many nutrients are washed out too. Vitamins B₁, B₂, and nicotinamide are added to Edosol and Locasol, but not to Galactomin* or Low lactose milk food. Edosol also contains added vitamins A and D.

The nutritional properties of these four milks have been studied in weanling rats, and in the light of our experiments recommendations can be made for suitable vitamin supplements, their efficacy having been demonstrated in some infants.

* Trufood Ltd. have already taken note of the experimental and clinical findings reported in this paper, and Galactomin now contains added choline, and the label carries detailed advice about vitamin requirements.

Milk Preparations Studied

Galactomin, Edosol, Locasol, and Low lactose milk food were fed to the infants as the preparations available commercially.

Special batches of Edosol and Locasol, in which lactose was replaced by dextrimaltose, were used for the feeding experiments in rats, since lactose causes diarrhoea in this species (Mitchell, 1927). 0.3 g. sodium as sodium chloride and 0.6 g. calcium as calcium gluconate were added to 100 g. of Edosol and Locasol, respectively, in order to increase the amounts of sodium and calcium to the levels present in breast milk. Galactomin and Low lactose milk food were fed to rats as the preparations available commercially.

The percentages of protein in Galactomin, Edosol, Locasol, and Low lactose milk food were 22.3, 27.8, 21.4, and 27.8, respectively of the dried food.

Vitamin Preparations

Details of the preparations of vitamins used for treating the infants, and for the feeding experiments in rats are shown in Table 1. For the purpose of this communication the term 'vitamin' includes choline.

Case Reports

Two galactosaemic infants who developed the deficiency state while receiving Galactomin are described.

Case 1. A.R., a female infant, aged 7 days, was admitted in June 1959, to the Royal Alexandra Hospital for Sick Children, Brighton, for further investigation of galactosaemia. On the 4th day of life galactose had been found in the urine while she was receiving breast milk.

A previous child had been similarly affected, the diagnosis being made on the 10th day of life. On Galactomin there had initially been a good response in this other sib, but vomiting then occurred and she ceased to thrive normally. A soya-bean product was tried with no better response, and while still on this preparation and

TABLE I
COMPONENTS OF PREPARATIONS OF VITAMINS USED IN INFANTS AND EXPERIMENTAL STUDIES

Preparation	A (i.u.)	D (i.u.)	B1 (mg.)	B2 (mg.)	B6 (mg.)	Nicotina- mide (mg.)	C (mg.)	Other Vitamins
Abidec (Parke Davis & Co. Ltd. 0.3 ml.)	2,500	500	0.5	0.2	0.25	2.5	12.5	
Adexolin (Glaxo Laboratories Ltd.) 0.3 ml.	3,000	300						
Becosym elixir (Roche Products Ltd.) 1.0 ml.			1.0	0.4	0.4	4.0		
Betalin complex (Eli Lilly Ltd.) 1.0 ml.			25.0	6.0	10.0	100.0	150.0	
Compound vitamin drops (Paines & Byrne Ltd.) 0.6 ml.	5,000	400	1.0	0.4	0.5	5.0	50.0	
Ketovite tablets (Paines & Byrne Ltd.) One tablet			1.0	1.0	0.33	3.3	16.0	Calcium pantothenate 117 mg. α-tocopheryl acetate 5.0 mg. Inositol 50.0 mg. Biotin 0.17 mg. Folic acid 0.25 mg.
+ Ketovite supplement syrup (Paines & Byrne Ltd.) 5.0 ml.	2,500	400						Choline chloride 150 mg. Vitamin B12 12.5 μg.
Parentrovite (Vitamins Ltd.) No. 1 5.0 ml.			250.0	4.0	50.0	160.0		
+ No. 2 5.0 ml.							500.0	

in hospital she suddenly collapsed and died at the age of 7 weeks. There was no record of skin lesions in this earlier case, and no cause for death was found at necropsy; the liver was large and fatty.

On examination the second affected baby weighed 6 lb. 6 oz. (2,891 g.) at the age of 7 days (birth weight 7 lb. 4 oz. (3,288 g.)). There was slight jaundice of 24 hours' standing and the liver was enlarged, but there were no lens opacities or retinal disease.

Investigations revealed a generalized aminoaciduria, and an excessive accumulation of galactose-1-phosphate. Liver function tests were normal.

On admission the infant was given $6 \times 2\frac{1}{2}$ oz. feeds of Galactomin each 24 hours, increasing to 6×5 oz. feeds on discharge, together with Abidec (Parke Davis) 0.3 ml. daily, throughout. She gained weight steadily and the liver became normal in size. The urine was occasionally positive to Benedict's test. She was discharged aged 7 weeks, weighing 9 lb. 10 oz. (4,365 g.) and in good health. She was readmitted at the age of 4 months in October 1959, having made good progress until a month previously when she had developed soreness of the lips followed by angular fissuring. At the time of her readmission she had a worsening cough, was reluctant to finish feeds, and was vomiting.

On examination her weight was 10 lb. 5 oz. (4,677 g.). Her lips were sore and fissured with angular cracking and ulceration. Similar fissuring and ulceration were present at the outer canthi of the eyelids. The buttocks and groins were red, raw, and weeping. There were bronchitic signs in the chest.

She was now receiving Galactomin as six 6-oz. feeds in 24 hours, together with Abidec 1 ml. daily. An initial 8-day course of tetracycline was given for her chest infection.

A dermatological opinion was obtained 5 days after readmission. Dr. Colin Jones considered the baby had a

seborrhoea with associated cheilosis. He thought a nutritional deficiency likely and advised the administration of vitamin B and topical neomycin with hydrocortisone ointment to eyelids and mouth. In spite of this application, together with Becosym (Roche) (1.5 ml. daily for 48 hours) and then Betalin complex (Lilly) (4 daily injections each of 0.5 ml.), the various skin lesions failed to heal. Two weeks after starting this intensive treatment, a blood-stained purulent discharge was a feature of the various angular lesions. Also at this time weeping sores developed over the ears. At this stage the dose of Abidec was increased from 1 to 2 ml. daily.

A fortnight after her readmission septic lesions appeared in the sacral region, and though she was given chloramphenicol (7 days by the intramuscular route and 7 days by mouth) multiple abscesses requiring incision developed over the buttocks and lower back. *Staphylococcus pyogenes*, type 80, was isolated from the pus and was sensitive to the antibiotic used. There was an associated profound anaemia, the haemoglobin falling from 13.1 g./100 ml. on admission to 4.0 g. three weeks later, notwithstanding a blood transfusion five days previously.

After an initial 14-oz. (396 g.) weight gain during the first week in hospital, the infant failed to thrive. Vomiting, progressive abdominal distension, and nocturnal restlessness became noticeable features as deterioration set in. Her cough returned pre-terminally. The child suddenly collapsed and died 26 days after admission. Necropsy was refused by the parents.

Case 2. T.M., a male infant was admitted to the Royal Alexandra Hospital for Sick Children, Brighton, in September 1962 at 15 days of age, weighing 7 lb. 2 oz. (3,232 g.) (birth weight 7 lb. 11 oz. (3,486 g.)). His parents had been married for 10 years and had two adopted children.

On examination he was irritable and wasted but not jaundiced, with a unilateral purulent ophthalmia, a paronychia of one finger, and a sticky umbilicus: *Staph. pyogenes* was isolated from all three sites. His liver was large and there were lens opacities in both eyes (Mr. D. St. Clair Roberts). The urine gave a positive reaction with Clinitest but a negative one with Clinistix, and paper chromatography showed that galactose was present. Uridyl transferase was absent from the red cells (Dr. V. Schwarz, Manchester). Liver function tests were normal and there was no aminoaciduria.

He was placed on Galactomin and Abidec, 1 ml. daily, with an immediate good response. His urine became free of sugar, the vomiting stopped, his liver decreased in size, and his weight increased. He was discharged after 12 days, weighing 7 lb. 10 oz. (3,458 g.).

He was readmitted in November 1962 at 2 months of age because of failure to thrive and recent diarrhoea. He had been snuffly and coughing for a few days but was not vomiting. Glucose feeds had been substituted for Galactomin just before readmission.

On examination he was emaciated and dehydrated and weighed 8 lb. 3 oz. (3,713 g.). The lenses were normal. There was crusting around the anterior nares. The lips were dry, fissured, and bled easily. He had a napkin erythema extending to his inner thighs. His liver was normal in size. No reducing substances were found in the urine and no pathogens in the stools.

Galactomin was reintroduced the day after admission and continued until five days before death, when Low lactose milk food and Moll's pudding were tried in succession. He was receiving Abidec 1·8 ml. daily at this time. Tube feeding was necessary to maintain an adequate calorie intake.

Ten days after readmission abdominal distension with umbilical protrusion was first observed and this progressed until death a month later. At the same time both lips became more fissured and the skin eruption over the buttocks and thighs spread to the scrotum and penis. The ankles became similarly affected. The skin of the left external ear was noted to be pink and moist.

The cracked lips and extensive skin eruption responded neither to various topical applications (including corticosteroid preparations) nor to 10 mg. nicotinic acid daily (given for the last month of the illness), nor to two intramuscular injections each of 1·0 ml. of Parentovite (Vitamins Ltd.). A dermatological opinion was obtained a month after admission. Dr. S. P. Hall-Smith thought the plaques over the buttocks and elsewhere could be labelled psoriasis, though he preferred to consider the eruption as a seborrhoeic dermatitis. Shortly after this opinion was obtained, fissures appeared for the first time at the corners of the mouth and the outer canthi of the eyelids. Also both ears became pink and moist, the exudate tending to crust. Two days before death the main skin lesions (shown in Fig. 1a, b) were summarized as follows by Dr. Hall-Smith.

- (1) Muco-purulent nasal discharge with crusting of anterior nares.
- (2) External ears pink and glazed especially helices, with a tendency to crusting.

- (3) Haemorrhagic fissures of the upper and lower lip surfaces and the angles of the mouth.
- (4) Eyes: fissuring and scaling at outer canthi.
- (5) A widespread and confluent demarcated pink infiltrated plaque covering the left buttock, with a central island of normal skin. Postero-lateral and postero-medial aspects of left thigh, sacrum, perianal region, perineum, scrotum, and penis all similarly affected.
- (6) Pink moist intertrigo groins with follicular eruption in the pubic area.
- (7) Pink irregular patches on the posterior aspect of the left lower leg with superimposed flaccid blisters.

Restlessness, irritability, reluctance to feed, and vomiting were features noted by the nursing staff during the infant's five-week stay on the ward. Repeated testing failed to detect reducing substances in the urine. He was afebrile until the last three days of his illness when his temperature rose to 100° F. (37·8° C.) and 48 hours later to 102° F. (38·9° C.). During the last week a five-day course of oxytetracycline was administered, followed by oral chloramphenicol 25 mg. 6-hourly pre-terminally, when a heavy growth of *B. pyocyaneus*, sensitive to this second antibiotic, was isolated from the baby's nose, throat, and skin lesions.

Five weeks after readmission to hospital the infant suddenly collapsed and died after passing a fluid stool.

NECROPSY (Dr. R. I. K. Elliott): Salient naked eye and histological features were as follows.

Skin. There was a crusted eruption in the distribution already described. Microscopically the skin in the affected areas showed some hyperplasia of the epithelial layer with elongation of the papillae combined with oedema and considerable vascular dilatation. Great masses of parakeratotic keratin were piled up above these dilated papillae; the bulk of the crust was obviously increased by exudation of serum. Some spongiosis was present though it was less striking than one would have expected. The lesion was interpreted as an active eczematous reaction with some degree of lichenification.

Lungs. There was bilateral *B. pyocyaneus* pneumonia with multiple abscesses. The histology suggested bronchogenic rather than haematogenous spread.

Liver. This looked normal to the naked eye. Microscopy showed a heavy inflammatory infiltration, mainly of lymphocytes and polymorphs, in the portal tracts. In some of the latter there was an increase of fibrous tissue.

Kidneys. These looked macroscopically normal. Microscopically, the lining cells of the first convoluted tubules showed considerable degenerative changes; many of these cells had disintegrated and formed a sponge-like meshwork inside the tubules.

Adrenals. These were normal in size and appearance. Sections showed a broad hyaline zone between the lower cortex and the medullary cells. In this situation the blood vessels were very dilated and there were scattered

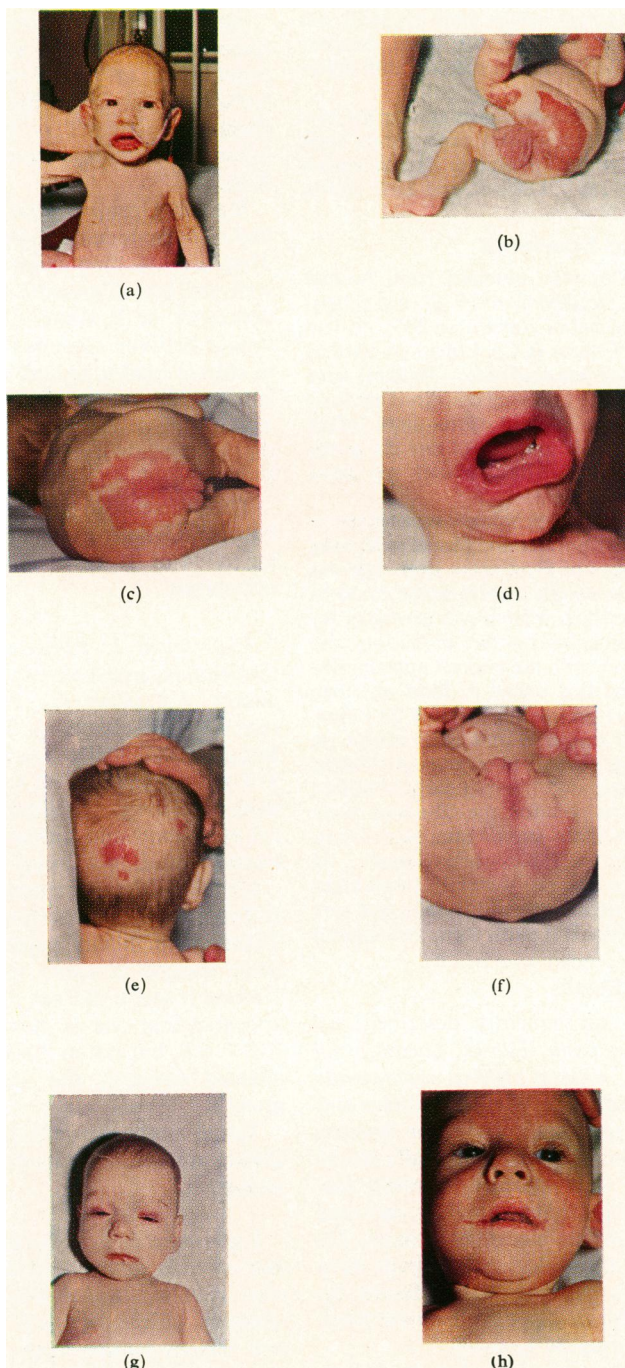


FIG. 1.—(a) (Case 2). Taken a few days before death, showing alert expression, generalized skin pallor, and emaciation. The scabbed external nares, the fissured lips, and the skin lesions at the outer canthi of the eyelids are visible. (b) (Case 2). Well-demarcated pink and glazed buttock eruption suggestive of psoriasis. (c) (Case A). Circumscribed psoriasiform buttock eruption. (d) (Case A). Angular fissuring of the mouth with superimposed whitish film. (e) (Case A). Psoriasiform patches in occipital region. (f) (Case A). The healing buttock eruption one week after the introduction of Ketovite tablets (no topical application), compare Fig. 1 (c). (g) (Case B). Angular fissuring and red eyelids. (h) (Case C). Fissuring of the angles of the mouth and outer canthi of the eyes.

cells containing dark pigment, which were probably not an artefact. In the cortex there was some vascular dilatation and the cells here showed considerable depletion of lipid.

The recognition of a possible deficiency state in the two galactosaemic infants led to animal experiments with Galactomin which we shall now describe. These studies were later extended to Edosol, Locasol, and Low lactose milk food.

Animal Experiments

Female Sprague-Dawley rats, obtained from Animal Supplies (London) Ltd., weighed 60 to 90 g. when experiments were begun. Rat cubs containing 20% protein (number 86, from J. C. Withers & Co. Ltd.) were used as a control diet. Tap water was available. Animals were housed in cages with grids so that they could not eat their faeces, and were kept for at least three days before experiments were begun. The number of rats per group and the duration of feeding with the diet are given subsequently for each experiment.

All foods and their vitamin supplements were mixed to a batter-like consistency with water and placed in troughs in the cages. The amount of food eaten each day was measured so that an approximate calorie intake could be determined. For pair feeding, when it was necessary for all groups to consume an equal number of calories, the amount eaten by the group with the poorest appetite was determined each day, and this weight of food was then given to each of the other groups for the next 24 hours.

The rats were weighed to the nearest gram except on Sundays. The percentage changes in body weight during the experiments were calculated. *t* tests for probability of difference were determined for the absolute body weights of groups of rats at the end of each experiment, and the results are given in the Tables when relevant. At the end of each experiment, the rats were killed with ether and dissected. General appearance of fur, tails, and ears was noted, and the abdominal fat pads, uteri, and vaginae were examined.

Results

In the experiments subsequently described, *all young rats fed on Galactomin, Edosol, Locasol, and Low lactose milk food, without vitamin supplements* had a similar appearance. They failed to thrive and were less lively than controls. Their fur became dull and staring, and in some places, especially round the neck, there were bare patches. Brown discoloration was frequently present on their ears and tails. At necropsy the vaginae were closed, the uteri ill developed, and the abdominal fat pads were absent. The rats were more severely affected by Galactomin (see Fig. 2b) or Low lactose milk food (see Fig. 3a) than by Edosol or Locasol.

When these preparations were supplemented with Ketovite tablets + Ketovite supplement syrup (KT + KS) (see Table 1), the rats thrived, were active, and completely normal in appearance (see Fig. 3b).

Galactomin. *Experiment 1: Effect of feeding Galactomin, with and without a complete vitamin supplement, to young rats.* Three groups of rats were fed *ad lib.* with cubes, Galactomin, and Galactomin + KT + KS. Details of the experiment and the results are shown in Table 2 (Groups a, b, c).

Rats in Group b which received Galactomin had the ill appearance already described (see Fig. 2b). They ate less than those in Group c which thrived well, and loss of appetite was probably the result of a deficiency of B vitamins. The difference in body weight between Groups b and c reflected a difference in calorie intake, as well as a deficiency of vitamins. In a further investigation (Groups d, e, and f, Table 2), Groups d and f were pair-fed with Group e so that all the rats received the same calorie intake (see Fig. 4).

The difference in percentage change in body weight between Groups e and f (23% and 48%) was a true reflection of the effect of vitamin content on calorie utilization.

Experiment 2: Effect of feeding young rats with Galactomin, supplemented with the vitamins given to patient A.R. (Case 1). Patient A.R. at one period received Galactomin + 1.3 ml. Abidec + 1.7 ml. Becosym elixir daily (i.e. 10,000 i.u. A, 2,000 i.u. D, 3.5 mg. B₁, 1.4 mg. B₂, 1.6 mg. B₆, 50 mg. ascorbic acid, and 16 mg. nicotinamide). Groups of rats were fed on Galactomin with and without various supplements, including a group receiving A.R.'s vitamins.

Details of the experiment and the results are given in Table 3 and the growth curves are plotted in Fig. 5. There were highly significant differences in the body weights attained by the groups except that Groups b and c did not differ from each other. It appeared that one or more of the factors present in KT + KS, but not in Abidec + Becosym + choline, affected appetite, the utilization of calories, and growth.

The vitamins prescribed for A.R., while receiving Galactomin, did not support optimum growth in the young rat.

Experiment 3: Effect of feeding young rats on A.R.'s diet of Galactomin + Abidec + Becosym, together with choline and various combinations of other vitamins. Eight groups of rats received Galactomin and various combinations of vitamins. Details of the experiment and the results are shown in Table 4. Adequate amounts of vitamins A, B₁, B₂, B₆, C, D, nicotinamide, and choline were given to all groups.

Rats given supplements which included pantothenic acid achieved considerably greater increases



FIG. 2.—Appearances of young rats after 10 days on a diet. (a) Cubes *ad lib.* (Table 2, Group a). (b) Galactomin *ad lib.* (Table 2, Group b).

TABLE 2

EFFECT OF FEEDING GALACTOMIN WITH AND WITHOUT A COMPLETE VITAMIN SUPPLEMENT, TO YOUNG RATS

Group*	Basic Diet	Supplement to Diet	Approximate Daily Calorie Intake/Rat	% Change in Body Weight During Experiment (Mean \pm Standard Error)	<i>t</i> test for Probability of Difference Between Groups
a	Cubes <i>ad lib.</i>	None	60	76 \pm 1.9	a compared with b: $p < 0.001$
b	Galactomin <i>ad lib.</i>	None	42	17 \pm 3.2	a compared with c: $p > 0.05$
c	Galactomin <i>ad lib.</i>	KT + KS†	59	70 \pm 1.9	b compared with c: $p < 0.001$
d	Cubes, pair fed with Group e	None	36‡	42 \pm 0.6	d compared with e: $p < 0.001$
e	Galactomin <i>ad lib.</i>	None	43	23 \pm 1.6	d compared with f: $p > 0.05$
f	Galactomin, pair fed with Group e	KT + KS†	43	48 \pm 3.5	e compared with f: $p < 0.001$

The experiment was continued for 10 days.

* 6 rats in each group except b, which had 5. † 100 g. Galactomin + 3 Ketovite tablets + 5 ml. Ketovite supplement syrup.

‡ Owing to a technical difficulty, d received slightly fewer calories than e.

TABLE 3

EFFECT OF FEEDING GALACTOMIN, WITH AND WITHOUT SOME VITAMIN SUPPLEMENT, TO YOUNG RATS

Group	Supplement to Galactomin	Approximate Daily Calorie Intake/Rat	% Change in Body Weight During Experiment (Mean \pm Standard Error)	<i>t</i> test for Probability of Difference Between Groups
a	None	34	-3 \pm 3.1	a compared with b: $p < 0.005$
b	Abidec + Becosym elixir* as given to Case 1	40	40 \pm 10.7	a compared with d: $p < 0.005$
c	Abidec + Becosym elixir + choline chloride†	41	59 \pm 9.5	b compared with c: $p > 0.05$
d	KT + KS‡	60	75 \pm 12.1	b compared with d: $p < 0.02 > 0.01$
				c compared with d: $p < 0.05 > 0.01$

3 rats in each group; experiment terminated after 19 days; feeding was *ad lib.*

Supplements to 100 g. Galactomin:

* 10,000 i.u. A, 2,000 i.u. D, 3.5 mg. B1, 1.4 mg. B2, 1.6 mg. B6, 16 mg. nicotinamide, 50 mg. ascorbic acid.

† As group b + 150 mg. choline chloride. ‡ 3 Ketovite tablets + 5 ml. Ketovite supplement syrup.



FIG. 3.—Appearance of young rats after 14 days on a diet. (a) Low lactose milk food *ad lib.* (Table 5, Low lactose milk food, Group a). (b) Low lactose milk food *ad lib.* + KT + KS (Table 5, Low lactose milk food, Group b).

in body weight than the others and were of a healthier appearance. There was a significant difference ($p < 0.01$) between Group a as compared with Groups e, f, g, and h. Group a did not differ from Groups b and d ($p > 0.05$) but was just different from Group c at the $p < 0.05$ level; the reason is not apparent but probably depends on the variation encountered with small numbers of animals.

Amongst the groups given pantothenic acid, Group e did not differ from Groups f or g ($p > 0.05$) but was different from Group h ($p < 0.05$).

No clear-cut trends were evident with α -tocopheryl acetate, B2, folic acid, biotin, and inositol in this experiment.

Edosol, Locasol, and Low Lactose Milk Food.

Groups of young rats were now fed on Edosol, Locasol, and Low lactose milk food with and without vitamin supplements. Details of the experiments and the effects on body weight are shown in Table 5. Fig. 6 illustrates the growth curves obtained with Locasol.

Young rats fed on these preparations, without vitamin supplements, had poor appetites, failed to thrive, and developed appearances similar to those of the rats fed on Galactomin, except that the changes were less marked with Edosol and Locasol. If a supplement of KT + KS was added, caloric intake, growth, appearance, and liveliness were as satisfactory as with rat cubes. *t* tests for probability of differences between the body weights of groups are given in Table 5 and show highly significant differ-

ences between groups receiving the synthetic milk only, and those receiving KT + KS in addition.

Ideally, studies on nutrition should be performed on the human subject, but during infancy this is usually impossible. Soon after the animal studies were completed three infants receiving Edosol, Locasol, and Low lactose milk food came to our notice. The infants had failed to thrive and had developed rashes similar to those of A.R. and T.M. As a result of the conclusions drawn from the animal studies, these infants were given complete vitamin supplements in the form of KT + KS, and the clinical response was in each case dramatic and sustained.

Case Reports

Case A. L.K., a female infant, was first admitted in November 1963 to the Royal Alexandra Hospital for Sick Children, Brighton, at the age of 10 weeks with increasing cough, cyanosis, difficulty with feeding, and failure to thrive.

On examination the infant was ill, febrile, dehydrated, and wasted, weighing 7 lb. 2 oz. (3,232 g.) (birth weight 6 lb. 6 oz. (2,891 g.)). There was consolidation of the right lower lobe, and a systolic murmur along the left sternal border was attributed, after radioscopy and electrocardiography, to a left-to-right shunt through a large ventricular septal defect.

The baby received intramuscular penicillin and streptomycin for 7 days, continuous oxygen for 25 days, and 8 daily 75 mg. doses of chlorothiazide. Feeds of Edosol were commenced 3 days after admission (480 cal. in 24 hours) and compound vitamin drops 1 ml. daily.

TABLE 4

EFFECT OF FEEDING YOUNG RATS ON DIET OF CASE 1, i.e. GALACTOMIN + ABIDEC + BECOSYM, TOGETHER WITH CHOLINE AND VARIOUS COMBINATIONS OF OTHER VITAMINS

Group	No. of Rats	Basic Diet	Additional Supplement Added to 100 g. Diet	Approximate Daily Calorie Intake/Rat	% Change in Body Weight During Experiment (Mean ± Standard Error)
a	6	100 g. Galactomin + 1.2 ml. Abidec + 1.5 ml. Becosym + 150 mg. choline chloride } Case 1's diet	None	39	65 ± 4.9
b	6	As Group a	α-tocopheryl acetate 15 mg.	36	68 ± 1.9
c	5	As Group a	Folic acid 0.75 mg. B12 10 μg.	37	88 ± 4.8
d	5	As Group a	Folic acid 0.75 mg. B12 10 μg.	38	69 ± 2.5
e	6	As Group a	α-tocopheryl acetate 15 mg. Calcium pantothenate 3.48 mg.	42	98 ± 3.3
f	6	As Group a	Calcium pantothenate 3.48 mg. folic acid 0.75 mg. B12 10 μg.	43	102 ± 4.7
g	6	As Group a	α-tocopheryl acetate 15 mg. As for Group f + Biotin 0.51 mg. + inositol 150 mg.	43	96 ± 4.7
h	6	Galactomin	KT + KS	50	108 ± 5.5

The experiment lasted 16 days; feeding was *ad lib.*

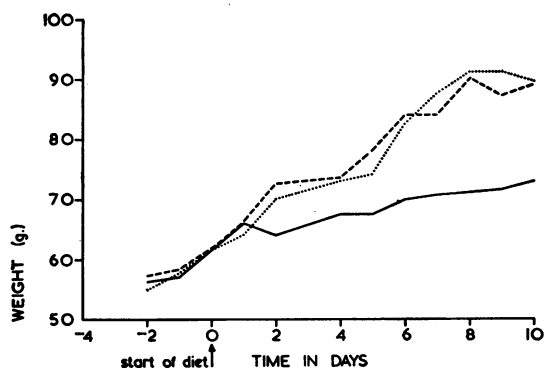


FIG. 4.—Growth curves of groups of weanling rats fed on cubes, Galactomin alone and Galactomin + KT + KS.

--- cubes
 — Galactomin alone
 Galactomin + KT + KS } pair-fed

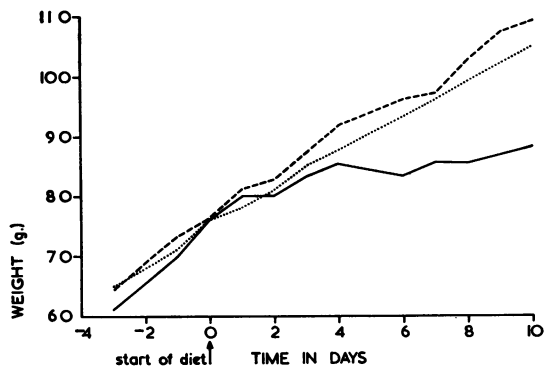


FIG. 6.—Growth curves of groups of weanling rats fed on Locasol; on Locasol + KT + KS; and on cubes.

— Locasol
 Locasol + KT + KS } pair-fed
 --- cubes

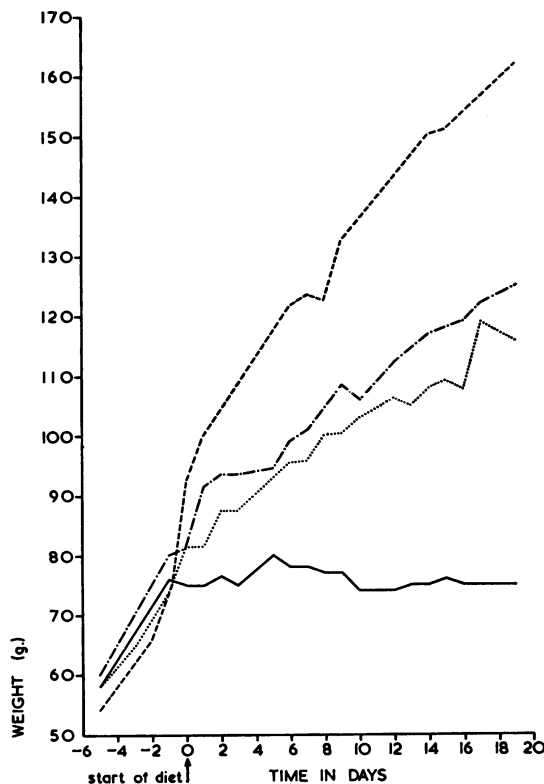


FIG. 5.—Growth curves of groups of weanling rats fed on Galactomin alone; on Galactomin + Abidec + Becosym; on Galactomin + Abidec + Becosym + choline; and on Galactomin + KT + KS. — Galactomin alone; Galactomin + Abidec + Becosym; --- Galactomin + Abidec + Becosym + choline; - · - Galactomin + KT + KS.

TABLE 5
EFFECT OF FEEDING EDOSOL, LOCASOL, AND LOW LACTOSE MILK FOOD TO YOUNG RATS

Group	No. of Rats	Basic Diet	Supplement Added to 100 g. Basic Diet	Approx. Daily Calorie Intake/Rat	% Change in Body Weight During Experiment (Mean \pm Standard Error)	t test for Probability of Difference Between Groups
<i>Edosol</i>						
a	11	Edosol <i>ad lib.</i>	None	34	21 \pm 2.5	a compared with b: $p < 0.001$
b	11	Edosol pair fed with Group a	KT + KS	34	32 \pm 2.2	a compared with c: $p < 0.001$
c	9	Edosol <i>ad lib.</i>	KT + KS	44	45 \pm 3.6	b compared with c: $p < 0.001$
d	9	Cubes <i>ad lib.</i>	None	50	44 \pm 3.5	c compared with d: $p > 0.05$
<i>Locasol</i>						
a	6	Locasol <i>ad lib.</i>	None	42	15 \pm 2.3	a compared with b: $p > 0.001 < 0.005$
b	6	Locasol pair fed with Group a	KT + KS	42	44 \pm 7.1	a compared with c: $p > 0.001 < 0.005$
c	6	Cubes pair fed with Group a	None	42	38 \pm 4.0	b compared with c: $p > 0.05$
<i>Low lactose</i>						
a	6	Low lactose <i>ad lib.</i>	None	38	18 \pm 5.0	a compared with b: $p < 0.001$
b	6	Low lactose <i>ad lib.</i>	KT + KS	63	66 \pm 6.6	a compared with c: $p < 0.001$
c	5	Cubes <i>ad lib.</i>	None	48	56 \pm 2.3	b compared with c: $p > 0.05$

The diet was continued for 10 days.

She was critically ill for the first week with slow improvement subsequently. She was discharged 6 weeks after admission weighing 7 lb. 10 oz. (3,458 g.), on digoxin, Edosol (480 cal./24 hours), and compound vitamin drops 1 ml. daily.

She was readmitted in February 1964, aged 5½ months, i.e. 6 weeks after discharge from hospital, because of failure to thrive, anorexia, vomiting, and cough. Two weeks previously an eruption had appeared over the buttocks and back of the scalp, with no associated pain or irritation. She had periods of irritability and screaming at night possibly due to abdominal pain. Edosol and the drugs were maintained.

On examination her temperature was 101° F. (38.3° C.) on admission, but there were no signs of infection. She was alert, responsive, grossly marasmic (weight 8 lb. (3,628 g.)), and irritable when handled. Her lungs were normal and there were no signs of heart failure. Her lips were cracked and bleeding, and there was an eruption on the buttocks and scalp as described below.

She was given an initial 8-day course of demethylchlor-tetracycline (40 mg./day), and was afebrile within 48 hours of admission.

One week later the striking similarity between this baby and the two galactosaemic ones described earlier led to a diagnosis of a deficiency state associated with Edosol. This synthetic milk (540 cal./24 hr.) was maintained, compound vitamin drops were discontinued, and Ketovite syrup 5 ml. daily was introduced.

Two weeks after admission she was deteriorating and her weight was 8 lb. 1½ oz. (3,670 g.). There were frequent regurgitations and sometimes vomiting after coughing. Her skin lesions were virtually unchanged and, indeed, since being on Ketovite syrup, fissures had appeared at the upper junction of the left ear and scalp. At this point the dermatological picture was summarized by Dr. Hall-Smith as follows.

'Circumscribed psoriasiform lesion with clear-cut edge

involving the sacral and coccygeal regions, both buttocks for a distance of one inch on each side and both labia (see Fig. 1c).

Dry linear intertrigo in depths of groin creases. Minimal fissuring at left outer canthus of eye. Fissuring of left retro-auricular ear adjacent to upper pole of left ear.

Angular cheilosis with superimposed whitish film (see Fig. 1d).

Crescent-shaped psoriasiform patch occiput with two small satellite lesions (see Fig. 1e).'

At this stage, i.e. two weeks after admission, as well as Ketovite syrup (5 ml. daily), compound vitamin drops were reintroduced, 1 ml. daily. In addition, calcium pantothenate 3 mg. and folic acid 0.75 mg. were given daily (i.e. approximate amounts of these nutrients in 3 Ketovite tablets).

48 hours later there was further deterioration with a 3 oz. (85 g.) weight loss and complete refusal to feed. She had implacable screaming and restlessness throughout the night, possibly due to abdominal colic (similar attacks had occurred at home in the fortnight prior to her readmission). One Ketovite tablet daily was then introduced for the first time and the Ketovite syrup was reduced from 5 to 3 ml. daily and compound vitamin drops were discontinued. Edosol (540 cal./24 hr.) was continued by intragastric tube.

48 hours after introducing one Ketovite tablet daily a remarkable change had taken place in the baby's condition. She became contented and peaceful for the first time, and she started to feed hungrily so that the caloric intake was increased from 540 to 660 cal./24 hr. Most dramatic of all was the rapid regression of all the skin lesions without topical applications. A week after starting the Ketovite tablets in addition to Ketovite syrup, all the skin lesions had healed with faint scarring over the buttocks (see Fig. 1f) and scaling over the posterior scalp, and the baby was taking Edosol (780 cal./24 hr.) from the bottle. At this point, she developed styes over both upper eyelids with associated low-grade pyrexia. A

penicillin-resistant staphylococcus was isolated from the pus and methicillin 125 mg. was accordingly given by the intramuscular route 6-hourly for 5 days.

Two weeks after commencing KT + KS the patient looked alert and well, her residual scarring was fading, and her styes were healing. After three weeks she had gained 14 oz. (396 g.) and weighed 9 lb. (4,082 g.), her skin was normal, and she was discharged home. One month later she weighed 10 lb. 5 oz. (4,677 g.) and was changed to a standard dried milk.

Case B. K.Y., a male infant aged 2 months was admitted to The Hospital for Sick Children, Great Ormond Street, in October 1963, for the investigation of vomiting and failure to thrive; a diagnosis of early idiopathic hypercalcaemia was made. He was discharged one month later on Locasol, together with 2,500 vitamin A, 150 mg. choline chloride, 12.5 µg. B12, and 3 tablets of Ketovite daily. He thrived and gained 5 oz. (142 g.) weekly until the middle of January 1964, when he weighed 14 lb. 2½ oz. (6,421 g.). At this stage his Ketovite tablets were stopped but the other vitamins were continued. Two weeks later his weight had dropped to 13 lb. 13 oz. (6,264 g.) and the out-patient notes stated that 'he had developed small red spots on his face and then on his legs'. After a further month he was readmitted because his weight had fallen to 12 lb. 1 oz. (5,471 g.), he had begun to vomit, was anorexic, and had a rash.

On examination he was a very restless, wasted infant of 12 lb. 1 oz. (5,471 g.), with striking pallor. He had a moderate degree of angular fissuring at the mouth, his eyelids were red (see Fig. 1g), and over the napkin area there was a bright red psoriasiform rash with well-demarcated raised edges.

Investigations revealed plasma calcium 6.3 mg./100 ml.; the urinary amino acid pattern showed a raised excretion of glutamine, threonine, serine, and glycine with other amino acids at the upper level of normal; in addition, each 100 ml. of urine contained 500 mg. lactose and 200 mg. sucrose, but less than 5 mg. of galactose, glucose, and fructose.

Two days after admission, the infant was placed on Low lactose milk food, three tablets of Ketovite, and 5 ml. Ketovite supplement syrup daily. Improvement began within 24 hours and five days later the child was feeding well, had gained 12 oz. (340 g.), and the rash was much improved. Three weeks later when he weighed 13 lb. 12 oz. (6,236 g.) he was changed to cows' milk. The lactosuria did not recur and he was discharged well.

Case C. G.R., a male infant, was admitted to The Hospital for Sick Children, Great Ormond Street, at the age of 4 months for surgical correction of a large patent ductus arteriosus. Before operation he developed heart failure and pneumonia, and probably a staphylococcal septicaemia. At the age of 6 months he developed lactosuria and was placed on Low lactose milk food, together with 3 drops of halibut liver oil and vitamin C daily. 10 days later his ductus was successfully ligated. 29 days after commencing Low lactose milk food he developed sore buttocks and then fissuring of the angles

of the mouth and outer canthi of the eyes (see Fig. 1h). The skin lesions failed to respond to topical treatment. Six days later he was given three tablets of Ketovite and 5 ml. Ketovite supplement syrup daily. There was rapid improvement and after four days the rash had almost gone. The development of the rash was not accompanied by a failure to gain weight in this patient.

Discussion

The feeding experiments in young rats reported here demonstrated that the synthetic foods studied were unable to support adequate growth and that this could be corrected by the administration of a complete vitamin supplement. Though great caution must always be exercised in applying the results of animal experiments to man, these investigations supported the hypothesis that there was a vitamin deficiency in the human infants. This was subsequently shown to be so, as evidenced by the prompt and dramatic clinical improvement in Cases A, B, and C when adequate vitamins were given.

Admittedly, with the synthetic foods investigated, the appetite of the rats was poor and hence their total calorie intake was lower than that of controls. However, in pair-feeding experiments with Galactomin and Edosol it was shown that there was an actual inability to utilize the calories provided when there was a deficiency of vitamins.

Although the animal feeding experiments using various combinations of vitamins (see Table 4) gave no clear-cut indication of the cause of the deficiency state which developed in the babies described above, the clinical evidence derived from feeding vitamins to Case A suggested that the missing factor or factors might belong to the tocopheryl—inositol—biotin group. However, the interdependence of various nutritional factors made a precise assessment difficult. Furthermore, because of the critical condition of Case A it became necessary to abandon the piecemeal introduction of the components of Ketovite tablets upon which we had embarked. It could, of course, be argued that had we persisted with the calcium pantothenate and folic acid for longer than 48 hours (she was at this stage still receiving vitamins A, B1, B6, B12, C, D, and choline chloride), the unremitting deterioration would have been halted and reversed with the addition of these two vitamins alone. In other words, the suggestion would be that these particular nutrients were not given enough time to take effect. One thing is certain, and that is that a most dramatic change for the better occurred within 48 hours of introducing Ketovite tablets.

There are few data on the minimal requirements of the human infant for individual vitamins, and these,

TABLE 6
TIME OF APPEARANCE OF THE RASH

	Case				
	1	2	A	B	C
Age of patient when synthetic food and incomplete vitamin supplement first given	7 days	15 days	10 weeks	5 months	6 months
Period on diet before rash appeared	10 weeks	7 weeks	10 weeks	2 weeks	4 weeks

therefore, have to be decided largely on theoretical grounds, after considering the composition of breast milk. The levels of pantothenate, folate, and thiamine have been measured by Baker, Frank, Pasher, Ziffer, and Sobotka (1960), in the foetus, newborn, and mother. They found that the levels rose in the foetus during gestation, so that the values at birth were 3 to 7 times greater than in the mother. It appears then that high levels of vitamins may be necessary for optimal growth in the early months of life when metabolism is proceeding at a very rapid rate. In this connexion we have indicated in Table 6 the ages at which the synthetic food together with the inadequate vitamin supplements were first given, and also the time taken for the rash to appear thereafter. Although it is impossible to assess the part played by the primary disease under treatment in the time taken for the rash to develop, it is of interest that the most rapid appearance of the eruption was in Cases B and C, the oldest of the series, whose vitamin reserves may have been by this time less plentiful.

The clinical picture found in the babies with this deficiency state is a striking one. Most distinctive are the various skin lesions which, in the florid case, may be itemized as follows.

(1) A well-demarcated pink psoriasiform eruption affecting particularly the buttocks. The rash may extend forwards to involve the perineum and the external genitalia and posteriorly to the natal cleft and sacral region. Similar lesions may occur elsewhere; thus they have been seen over the scalp and the lower limbs. The rash could be moist at first, with blistering on occasions, later becoming dry, scaly, and glazed.

(2) A pink, moist, or dry intertrigo of the groins.

(3) Cracking of the lips often associated with exudation and bleeding.

(4) Fissuring at the angles of the mouth and the outer canthi of the eyelids, again with exudation and sometimes bleeding.

(5) Pink exudative lesions over the external ears especially the helices, with a tendency to crusting.

The retro-auricular reflection of skin could be similarly affected, particularly superiorly.

(6) In one fatal case crusting of the external nares was a persistent feature and assumed to be part of the generalized eruption.

Other recurring features noted in the three severe cases were skin pallor, emaciation, anorexia, and fatigue while feeding. Vomiting occurred frequently and was easily induced if milk was pressed on the baby. Coughing could also be troublesome on such occasions and often lead to retching with loss of calories. Irritability and restlessness, particularly at night, were impressive behaviour disturbances, though, contrary to what one might expect from the appearance of the skin lesions, the deeply cracked lips and the sore-looking buttocks did not seem to cause either pain or discomfort. Abdominal distension was a constant development as the child's condition slowly deteriorated. There was a striking tendency for septic lesions to be a late complication. Death in our two fatal cases occurred abruptly and unexpectedly, both babies remaining alert and responsive until near the end. Sudden death was also reported to us in the sib of our first case (Case 1) who had died earlier in another hospital while under treatment for galactosaemia.

The unusual and distinctive lesions affecting the lips and eyes in the present cases are a feature of these nutritionally disturbed infants. While lip fissuring alone has been described in cases of riboflavine deficiency (Spies, Vilter, and Ashe, 1939), it should be emphasized that the patients reported here were not only receiving adequate amounts of this vitamin but failed to respond to additional large supplements.

The Report of the Committee on Nutrition (1963) stressed both the importance of the awareness of composition and nutritional properties of synthetic diets, and the need to give adequate vitamins. The Report also drew attention to the paucity of knowledge concerning the long-term effects of synthetic diets in infancy.

Three recommendations are made as a result of our experience.

(1) The exact composition of synthetic foods, so far as this is known, should be readily available to the clinician.

(2) When the synthetic food is known to be nutritionally incomplete, the label should clearly state this and give definite advice concerning any necessary additions to the diet. It is not sufficient to make the general statement that 'vitamins should be given'.

(3) If an infant is receiving a synthetic food, the clinician should be wary about assuming that the disease under treatment is necessarily the cause of failure to thrive.

Summary

A deficiency state characterized by disseminated skin lesions of a distinctive kind coupled with failure to thrive is reported in 5 infants who received various synthetic milks: 2 deaths occurred before the nature of the disturbance was appreciated.

The synthetic milks were found not to support adequate growth of young rats but this could be corrected by the administration of a complete vitamin supplement, namely Ketovite syrup together with Ketovite tablets (Paines & Byrne Ltd.). These experiments supported the clinical impression that the two infant deaths were due to a hitherto unrecognized deficiency state. This was subsequently shown to be likely when complete vitamin supplements were given to three other similarly affected infants and led to rapid clinical improvement.

The supplements included choline chloride, calcium pantothenate, inositol, biotin, α -tocopheryl-acetate, and vitamin B12 and folic acid in addition to those provided by conventional vitamin therapy.

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