Milk Intolerance in Infancy

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Allergy to cows' milk-protein is an occasional cause of persistent diarrhoea (Clein, 1954; Collins-Williams, 1954; Kane, 1957; Bachman and Dees, 1957a, b; Davies, 1958), but in the absence of other overt signs of allergy, may easily be overlooked. The management of milk intolerance often involves the use of synthetic feeds, which in themselves may produce a fulminating illness (Wilson and Clayton, 1962); hence the necessity for vitamin and amino acid supplements stressed by these workers and by Mann, Wilson, and Clayton (1965) and Clayton, Arthur, and Francis (1966).

This paper describes four cases of milk-protein intolerance. Problems encountered with diagnosis and with the use of synthetic feeds are discussed.

Case Reports

Case 1. A male infant, birthweight 3.5 kg., was born to an unmarried mother. He was fed on half-cream dried milk from birth, and remained well until 2 weeks old, when he developed frequent, loose, watery stools, and his weight became static: he was admitted to the City Hospital, Edinburgh, at the age of 1 month, with a tentative diagnosis of gastro-enteritis. However, no pathogenic bacteria were isolated from the stools, and it was noted that the diarrhoea stopped when the cows' milk formula was replaced by a soya bean preparation, Velactin (Wander), and started again with the reintroduction of milk. The infant was transferred to the Royal Hospital for Sick Children, Edinburgh, at the age of 3 months, for further investigation. On admission he weighed 4.65 kg., was well hydrated, and had no skin rashes. A cows' milk preparation was again reintroduced into the feeds, but the onset of severe vomiting and diarrhoea resulted in it again being replaced by Velactin, and the diarrhoea and vomiting again stopped. Some of the investigations carried out are shown in Table I. During the first months after admission, the infant developed a mild stomatitis and a perineal dermatosis; at this stage, a vitamin supplement, Ketovite (Paines and Byrne), was added to the diet.

Six weeks after admission, his weight had again gone down by 0.5 kg. to 4.2 kg. He was thus weaned on to Farex (a cereal containing some cows' milk derivative)

and meat extracts. He at once began to gain weight and within two weeks the rash and stomatitis had completely cleared; shortly after this he was discharged home on a milk diet with solids. At 14 months, milk was again introduced, but there was no recurrence of diarrhoea or vomiting, and when seen at 15 months, he was well and weighed 10.5 kg.

Case 2. Female infant, birthweight 3.7 kg., from birth was fed on a dried milk preparation. At 4 weeks of age, she began to vomit after feeds. The vomiting was non-projectile and not bile-stained, and the stools became frequent and watery. She was admitted to the Royal Hospital for Sick Children, Edinburgh, at 8 weeks of age, weighing 4.5 kg. Apart from the diarrhoea and vomiting, no abnormality was found on examination. Repeated stool cultures for pathogens were negative. Milk feeds were replaced by Velactin and vitamin supplements (Ketovite and Abidec (Parke-Davis)), whereupon the vomiting and diarrhoea stopped within 5 days. A small weight gain occurred, and investigations were carried out (see Tables I and II).

After three weeks on Velactin feeding, the infant developed a red, raw appearance of the tongue and mouth, and a dry, scaly psoriasiform dermatosis in the napkin area. Her appetite was poor, and she ceased to gain weight. A further bout of diarrhoea occurred and she became severely dehydrated, requiring intravenous fluid therapy for 36 hours.

Half-cream dried milk was then introduced into the diet. Her allergic responses were then studied (see Table III). With the reintroduction of milk, the stomatitis and dermatosis began to disappear within 48 hours, the infant became alert and happy, and a rapid weight gain was noted. No recurrence of diarrhoea or vomiting occurred. The patient has continued to thrive on milk and is gaining weight satisfactorily.

Case 3. Female infant, birthweight 3.9 kg., was well and thriving on a dried milk preparation, until 5 weeks old, when she began to vomit and developed loose watery stools: these symptoms started seven days after the onset of an upper respiratory infection. The diarrhoea and vomiting continued for 2½ months, before medical advice was sought because of her failure to gain weight.

On admission to hospital, there were no abnormalities on examination. She weighed 4.25 kg. at 13½ weeks of age. Repeated stool cultures were

TABLE I
Results of Investigations Carried Out

Investigations	Case 1	Case 2	Case 3	Case 4
Rectal swab	Negative	Negative	Negative	Negative
Stool pH	9	6	7	6
Full blood count	Normal	Normal	Normal	Normal
Chest x-ray film	Normal	Normal	Normal	Normal
Barium meal and follow-through	—	Coarse mucosal pattern of jejunum and ileum, with clumping of barium	Disordered mucosal pattern of small bowel, with some clumping of barium	Coarse mucosal pattern of jejunum and ileum, with clumping of barium
Tryptic activity in stool (Emery's method)	1/640	1/640	1/640	1/320
Sodium concentration in sweat (mEq/litre)	—	38	24	25
% Fat absorbed from diet (5-day stool collection)	—	95% of 132 g.	90% of 69 g.	81% of 121 g.
Urinary xylose excretion after 24 hours (% of 5 g.)	—	19	12	11
Jejunal Dissecting microscope biopsy	—	Moderate villous atrophy	Normal mucosa	Villous atrophy
Histology	—	Moderate villous atrophy	Normal mucosa; cellular infiltration into submucosa	Marked blunting and broadening of villi

TABLE II
Comparison of Disaccharidase Activity in Relation to Previously Described Normal Ranges

Case No.	Age (wk.)	Disaccharidase Activity (Units/g. mucosa, wet weight)			
		Lactose	Maltose	Isomaltose	Sucrose
1	12	—	—	—	—
2	8	2.47	13.49	3.91	3.55
3	14	1.34	10.03	2.79	2.62
4	16	0.72	8.12	1.7	1.3
<i>Normal range</i>					
Burgess <i>et al.</i> (1964)		6.6–12.4	43.2–88.9	6.5–6.9	12.4–20.2
Arthur (1966)		4.44–11.65	17.70–24.53	1.98–3.03 (as palatinase)	5.46–9.21

1 Unit = 1 μ mole substrate split/g. wet weight mucosa per min.

TABLE III
Results of Investigations to Establish Allergy of Gastro-intestinal Mucosa to Milk-protein

Case No.	Age (wk.)	Eosinophil Counts (per c.mm.)						Rectal Infiltration of Eosinophils		Antibody Titres	
		Before Milk	After Milk Reintroduction					Before Milk	After Milk	Before Milk	After Milk
			Days								
			1	2	3	5	6-10				
1	12	270	630	320	—	—	—	+	+	+	Not done
2	8	106	406	585	593	1150	1756 (day 6) 200 (day 8)	+	+	+	1/320
									(superficial biopsy)		6-fold increase
3	14	101	325	104	200	281	75 (day 7)	+	+	+	<1/10
4	16	125	267	300	156	238	106 (day 6) 75 (day 10)	+	+	+	1/640
									(superficial biopsy)		8-fold increase
											1/640
											8-fold increase

+ Few eosinophils; ++ marked increase; +++ very marked increase.

negative. Milk feeds were replaced by Velactin, with added vitamin supplements. The diarrhoea and vomiting ceased after 72 hours and the infant began to gain weight. The investigations listed in Tables I and II were then carried out.

During the third week of Velactin feeding, a severe dermatosis in the napkin area and an angular stomatitis occurred. The tongue and oral mucous membrane appeared reddened and 'beefy', and the infant fed less readily. The weight became static. At this stage, milk was reintroduced into the diet, and allergic responses were concurrently assessed (see Table III).

Within 24 hours, the dermatosis and stomatitis began to improve, and there was no recurrence of vomiting or diarrhoea. The infant gained weight rapidly and is presently thriving, being well within the normal weight range for her age.

Case 4. Female infant, born following a normal delivery, birthweight 3.8 kg., was fed on an evaporated milk. She thrived satisfactorily until 6 weeks of age, when she developed acute bronchitis. One week later, she developed loose frequent stools. This was thought by her doctor to have been due to oral tetracycline therapy. However, the diarrhoea persisted after withdrawal of the antibiotic, and the patient began to vomit her feeds.

She was admitted to hospital at the age of 4 months. On admission, her weight was 4.38 kg. She was alert, well hydrated, and examination was normal. Repeat stool cultures were negative. It was noted that the diarrhoea and vomiting stopped upon withdrawal of milk from the feeds, but that reintroduction of milk immediately brought about the return of loose stools. Milk feeds were replaced by Velactin, supplemented with Ketovite and Abidec. The infant improved and gradually gained weight, the diarrhoea stopping within 48 hours. During this time, a series of investigations (see Tables I and II) was carried out.

After three weeks on Velactin feeds, the weight again became static, and the infant developed a severe dermatosis over the napkin area (Fig. 1), and an angular stomatitis with a red, injected mouth. Her general condition began to deteriorate and it was decided

FIG. 1.— Severe perineal dermatosis (Case 4).

to reintroduce milk into the diet. Allergic response to the milk was assessed by the observations recorded in Table III.

Within 24 hours of restarting milk (as half strength, half-cream dried milk), the dermatosis and stomatitis began to disappear (Fig. 2), and the patient became more

FIG. 2.—Two days after reintroduction of milk into feeds: dermatosis has considerably improved (Case 4).

alert. During the next week, the first weight gain for a month was recorded. Stools remained firm and normal. The infant has since continued to thrive on milk and her present weight is normal for her age.

Investigations

In each case, repeated stool cultures excluded the possibility of bacterial infection of the gastro-intestinal tract, no organisms of dysentery, the enteric group, type-specific *Esch. coli* and *Staph. pyogenes* being cultured. The poor general condition of the patients prevented full investigation being carried out immediately upon admission: in fact, it was only possible to do this after two to three weeks of treatment with a soya bean diet (Velactin). A series of tests excluded fibrocystic disease of the pancreas, coeliac disease, and disaccharidase deficiencies. Jejunal biopsy, using the Crosby capsule, was carried out in three cases. Portions of jejunal mucosa were studied under the dissecting microscope, and histological sections examined. Enzyme assay by the method of Burgess, Levin, Mahalanabis, and Tonge (1964) was carried out in three cases: the disaccharides tested for were maltose, isomaltose, sucrose, and lactose.

When it became apparent that the patients were again becoming severely ill as a result of the soya bean diet, it was decided to reintroduce milk into the feeds. The effects of milk-protein on the gastro-intestinal tracts of the patients were then assessed. Absolute eosinophil counts in the blood, before and after the reintroduction of milk, were compared. A Crosby capsule was used to take rectal biopsies before and after milk enemata, the milk being left in the rectum for 30 minutes before a

second biopsy was taken. Assessment of rising 'whole milk antibody' titres, using the method of Boyden (1959), as modified by Rose and Witebsky (1956), Gunther, Aschaffenburg, Mathews, Parish, and Coombs (1960), and J. C. Gould (1966, personal communication), on samples of sera taken before and after the reintroduction of milk, was carried out. 'Whole milk antigen' was prepared using the serum of rabbits inoculated with National Dried Milk preparations (J. C. Gould, 1966, personal communication). No attempt was made to separate the milk-protein fractions into casein, α -lactalbumin, and β -globulin: thus 'whole milk antibody' does not precisely define the fractions in the milk that were associated with the immune responses in each patient.

Investigation of Case 1, admitted 18 months earlier, followed slightly different lines. Good stool tryptic activity was taken to be adequate evidence for the exclusion of fibrocystic disease. The infant had, until admission, taken milk feeds only: thus tests to exclude coeliac disease were not thought necessary. An oral lactose tolerance test, together with estimations of stool pH, was regarded as satisfactory evidence for the presence of lactose activity. In this case, more emphasis was placed on the parameters associated with the diagnosis of allergic reaction in the bowel mucosa (see Table III).

Results

The results in Table I show a striking pattern of absorptive disorder, varying from slight in Case 3, to severe in Case 4. Fibrocystic disease is adequately excluded on the basis of sodium content in sweat and tryptic activity in stools. Abnormalities in D-xylose absorption and excretion, fat malabsorption, barium follow-through, and jejunal mucosa, as seen on dissecting microscope and/or histology, revealed damage of varying severity to the absorptive surfaces of the intestinal mucosa. These abnormalities appeared in patients not exposed to dietary gluten.

The disaccharidase estimations in Table II revealed no absence of sucrase, maltase, isomaltase, and lactase activity, but the activity was not as great as that found in normal infants (Burgess *et al.*, 1964; Arthur, 1966). Enzyme activity was present in the same ratios as normal, thus indicating a non-specific generalized depression of enzyme activity.

The three parameters used in an attempt to assess the role of allergy to milk as an aetiological factor in these cases are shown in Table III.

Blood eosinophil counts. In every case, there was an eosinophil response with the introduction of milk. Case 1 showed a rise to 630/c.mm. within 24 hours. Case 2 showed a marked eosinophilia which continued to rise up to the 6th day

after restarting milk, reaching a level of 1756/c.mm.: almost as dramatic, was the rapid drop in count within 48 hours to 200/c.mm. by the 8th day. In Cases 3 and 4, the absolute rise remained below 350/c.mm., but the actual counts tended to treble in Case 3 and more than doubled in Case 4: both counts dropped to the pre-milk levels by the tenth day.

Eosinophil infiltration into rectal submucosa. Definite increases in eosinophil infiltration into the rectal submucosa were seen in Cases 1 and 3, following milk enemata. The absence of response in Cases 2 and 4 was probably related to the poor quality of the biopsy, since only a superficial shaving of mucosa with little submucosa was obtained.

Milk antibodies. Cases 2, 3, and 4 showed a rising titre after reintroduction of milk, varying from 1/320 (Case 2) to 1/640 (Cases 3 and 4): these rises are significant when compared with the absence of antibody in the pre-milk sera, being sixfold in Case 2 and eightfold in Cases 3 and 4. (The pre-milk sera were sampled after a 2 to 3 month period off milk.) The rising titres all occurred on the third day after milk was restarted in the feeding régime. These increments are well above the levels found in normal subjects, which have never been found to be above 1/40 by J. C. Gould (1966, personal communication). Taylor, Thomson, Truelove, and Wright (1961) found that milk-protein antibody levels remained below 1/20 in healthy subjects. Case 1, where preliminary titres were not done, showed a strikingly high titre subsequently.

Discussion

All the cases presented with vomiting, and 3 of the 4 had diarrhoea. Gastro-intestinal malabsorption of varying severity was evident. The infants had all been fed on dried milk preparations and none were being weaned at the time of admission. In Cases 2, 3, and 4, assay of disaccharidase activity revealed a general depression, when compared with the normal range found by investigators such as Burgess *et al.* (1964) and Arthur (1966); the relative proportions of the various enzymic activities estimated were normal, thus indicating a non-specific abnormality of the intestinal mucosa. Case 1 was investigated 18 months earlier, and enzyme assays were not carried out; at that time, however, an oral lactose tolerance test was found to be normal, no reducing substances were found in the stools, where

the pH remained alkaline, varying between 6 and 9, throughout.

Although the soya bean feed was complemented by the addition of vitamins A and D, choline, cyanocobalamin, aneurine, riboflavine, pyridoxine, nicotinamide, and ascorbic acid, in the form of Ketovite solution (Paines and Byrne) and Abidec (Parke-Davis), as advised by Mann *et al.* (1965) and Clayton *et al.* (1966), severe dermatosis and stomatitis developed in about the third week. The clinical picture of these babies was very similar to that described and illustrated by the latter authors. In Case 1, rapid weaning, with the addition of beef extracts to the soya bean preparation, resulted in a gradual improvement. In Cases 2, 3, and 4, the replacement of soya bean by milk, produced a dramatic improvement, though the allergic response, as seen in Table III, persisted. The evidence suggests that an essential amino acid, rather than a vitamin, was lacking in the soya bean feed. This, when added to the incipient deficiency existing because of the chronic diarrhoea, probably produced the overt syndrome of malnutrition.

Evidence favouring milk-protein allergy in these cases is the eosinophilia in the blood, and the infiltration by eosinophils of rectal mucosa (in 2 cases) following a retention enema of milk. The blood eosinophilia was most obvious in Case 2, but the rise in the absolute eosinophil counts in all cases was significant. A return of the counts to the 'pre-milk' levels occurred in all cases within 10 days, and was particularly striking in Case 2.

Assessment of eosinophil infiltration in rectal submucosa is only satisfactory if the biopsy includes submucosal tissue. With adequate biopsy material, the eosinophil infiltration was marked, and the investigation consequently of great value. A more satisfactory rectal biopsy would probably have been obtained under direct vision of the rectal mucosa, rather than by the use of a Crosby capsule.

A rising titre of 'whole milk antibody' was found to occur in all cases. The significance of this is not clear, but, as stated by Wright, Taylor, Truelove, and Aschaffenburg (1962), there are three possibilities to be considered. (1) High titre serological reactions may represent increased absorption of whole protein either through diminished proteolysis or because the gastro-intestinal mucosa is damaged. (2) A high titre of circulating antibodies may be indicative of a state of hypersensitivity to the particular dietary antigen and this state may be important in either the causation or the perpetuation of the disease. (3) The high titre reactions are a mere epi-phenomenon and bear no crucial relationship to the aetiology of the disease. In the four

cases of this series, it appears that the first two considerations are of importance. Nevertheless, the rising titres were of value in indicating a relation between milk ingested and damage to intestinal mucosa.

All the patients tolerated the reintroduction of milk after about three weeks of the milk-free régime, without recurrence of symptoms. It therefore seems that withdrawal of milk may be only a temporary necessity, which need not be carried out for longer than a few weeks.

Summary

The investigation of four cases of milk allergy, presenting in infancy with diarrhoea and vomiting, is described. Eosinophil infiltration of biopsied rectal mucosa, following a milk enema, was found to provide a possible test for milk allergy in such cases.

The introduction of a soya bean milk substitute relieved the gastro-intestinal symptoms, but within about two weeks a deficiency syndrome with skin rash and stomatitis developed, despite the complementary use of a multi-vitamin preparation.

Reintroduction of milk caused a rapid disappearance of the deficiency syndrome, without any recurrence of the original gastro-intestinal symptoms.

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