valvular heart disease but no rheumatic history. Generally, the main distinguishing characteristics of this subgroup are a more equal sex distribution, isolated mitral valve disease, a relatively short history of symptoms before surgery, and, in many cases, the need for surgery at a comparatively early age.

These findings are difficult to equate with the generally accepted concept of the aetiology of acquired valvular heart disease. This traditional view is that virtually all cases are rheumatic. In patients with no history of rheumatic fever or chorea their valvular disease is usually attributed to subclinical rheumatic carditis. Since it is not possible to investigate patients at the time of onset of subclinical carditis, however, the assertion that all such cases are rheumatic is speculative. It could, nevertheless, be argued for the traditional view that patients with no rheumatic history—that is, those with allegedly subclinical rheumatic carditis—differ fundamentally from those who have had classical rheumatic fever and that this may, in some way, account for clinically observed differences between those with and those without a rheumatic history. In this context the AW19 antigens might be a factor predisposing to the development of subclinical, as opposed to overt, rheumatic carditis. This line of reasoning, however, does not explain why patients with AW19 antigens differ clinically from those other patients with no rheumatic history (group 2) who are also assumed to have had subclinical rheumatic carditis.

The aetiology of these cases of valvular heart disease, if not rheumatic, is unknown. It has, however, been suggested that viruses may sometimes be implicated. In animals viruses can produce valve lesions with many of the characteristics of chronic rheumatic heart disease in man.[3] There is also evidence in man that viruses[4,5] and similar organisms[6] may cause valvular damage. Other suggestions have been made which postulate a link between HLA antigens and some virus infections. For example, the neurotropism of polio virus appears to be partly dependent on the presence of HLA antigens A3 or B7.[7] In more general terms it has been suggested that these particular antigens might govern the response of the central nervous system to a common product of different viruses. Possibly the cardiotropism of viruses, such as those of Coxsackie group B, which is currently unexplained, has an analogous basis. This in turn could account for the association we have described between valvular disease and the HLA antigens A29 and AW30/31—that is, these HLA antigens might act as a conditioning factor[8] which occasionally transforms a mild viral myocarditis—a common occurrence[9]—into a severe pancarditis.

Our study does not directly implicate viruses as a cause of acquired valvular heart disease. It does, however, provide further evidence which is inconsistent with the traditional "rheumatic" explanation. It also indicates a possible line of research into the aetiology of obscure heart disease which has not yet been explored.

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Cows' milk protein intolerance: a possible association with gastroenteritis, lactose intolerance, and IgA deficiency

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Summary

Twenty-five children with cows' milk protein intolerance were studied. Twenty had presented with an illness clinically indistinguishable from infantile gastroenteritis; an enteropathogenic Escherichia coli was isolated from the stools in two children, and in six another member of the family simultaneously developed acute diarrhoea and vomiting. Twenty-three children had lactose intolerance secondary to cows' milk protein intolerance. Eight out of 20 children were found to be partially IgA deficient. An acute attack of gastroenteritis, in damaging the small mucosa, may act as a triggering mechanism in cows' milk protein intolerance, and a deficiency in IgA may be a predisposing factor in so far as it allows the patient to become sensitised to foreign protein.

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Introduction

Cows' milk protein intolerance is the clinical syndrome due to sensitisation to cows' milk protein antigens. The resulting immunological reaction causes symptoms that may be predominantly gastrointestinal, respiratory, or dermatological.[1]

Our purpose here is to report the possible role of gastroenteritis in the aetiology of cows' milk protein intolerance, describe the clinical and laboratory features of a group of children diagnosed as having the condition, and offer a hypothesis about the possible relationship between cows' milk protein intolerance, gastroenteritis, and lactose intolerance.

Patients and methods

We studied 25 children with cows' milk protein intolerance who were admitted to the academic unit at the Queen Elizabeth Hospital for Children, London, in the three years from October 1972.

The diagnosis of cows' milk protein intolerance was based on: (*a*) the presence of symptoms on a diet containing cows' milk, (*b*) the disappearance of symptoms on withdrawal of cows' milk, and (*c*) one or more positive reactions to milk challenges, with return of symptoms and the appearance of various associated phenomena (see tables II-VII). Twenty-three of the children had been fed on a cows' milk preparation from birth, while two had been breast-fed initially but received cows' milk after an acute episode of diarrhoea and vomiting.

Lactose tolerance test—An oral load of 2 g lactose/kg body weight was given before a milk challenge to 22 children. All stools passed for 24 hours afterwards were observed and tested for reducing substances. Most patients were continued on feeds of 7% lactose for 24 hours after the oral load.

Milk challenge—Challenges were performed after periods of milk withdrawal varying from one week to 12 months (mean 3·5 months)—that is, six weeks to 13 months after the initial episode of gastroenteritis (mean 6·5 months).

Blood samples were taken before and 24 hours after the challenge for eosinophil counts. 5 ml of fresh pasteurised cows' milk or a dried milk preparation were given, followed by a further 10 ml one hour later if there had been no reaction. No further cows' milk was given for 24 hours. Cows' milk was then reintroduced, starting at a dilution of 1/5 and increasing by 1/5 a day. All stools were tested for reducing substances using Clinitest tablets and for occult blood using Occultest tablets. Temperature was recorded every four hours and weight every 12.

Small intestinal biopsy—This was performed on one or more occasions in 18 children using a paediatric modification of the Crosby Capsule. The specimen was taken from close to the duodenojejunal junction. It was examined and photographed under the dissecting microscope, and subsequently by light microscopy, the pathologist being unaware of the clinical details. The findings were graded as follows: N = normal; ± = minimal or doubtful lesion; + = short wide villi, usually with some normal surface epithelium, increased cells in lamina propria, and rather longer crypts (parital villous atrophy); ++ = thickened ridges, usually with normal surface epithelium, moderate increase of cells in lamina propria, elongated crypts (moderate villous atrophy); and +++ = flat surface covered by abnormal epithelium with excess cells in lamina propria and elongated crypts (subtotal villous atrophy).

Immunofluorescent staining was performed on 13 biopsy specimens from five children. Mucosal disaccharidase activities were measured by the method of Burgess *et al.*[2] Duodenal juice was examined for *Giardia lamblia*. If the initial biopsy was abnormal it was repeated with disaccharidase assay before the milk challenge.

Other investigations—These included serial estimations of serum immunoglobulins by single radial immunodiffusion technique, estimation of milk precipitins by gel diffusion, and prick tests using whole cows' milk, α-lactalbumin, and cows' milk casein antigens (Bencard). A family history of atopy or cows' milk protein intolerance in a first-degree relative was sought.

Results

There were 18 boys and seven girls in the study. A positive family history of atopy was obtained in all the 19 families in whom it was asked for. Three of the fathers had required a special diet in infancy for cows' milk protein intolerance. The age of onset of symptoms is shown in table I; 19 children were aged 6 weeks or under.

Twenty children presented with the classical features of infantile gastroenteritis—that is, with an acute illness characterised by the sudden onset of profuse diarrhoea and vomiting. An enteropathogenic *Escherichia coli* was isolated from the stool at the time of the acute episode in two children and five weeks later in another. No other stool pathogens were isolated at any time. There was circumstantial evidence of infective diarrhoea in six children, another member of the family having developed diarrhoea and vomiting at the same time.

TABLE I—*Age at onset of symptoms*

Age (weeks):	1	2	3	4	5	6	7	8	9	10	11	12	45	60	64
No of children:	5	3	8		2	1	1	1				1	1	1	1

Three children who had been fed on cows' milk from birth presented with gastroenteritis at 9, 10, and 15 months. Within a month they developed cows' milk protein intolerance and two developed urticaria on drinking milk. Five children presented with chronic diarrhoea or vomiting, or both, of three to seven months' duration with failure to thrive, the weight being below the 3rd percentile in three and between the 3rd and the 10th percentile in two. In one of these a diagnosis of coeliac disease was possible.

Immunological results—Serum IgA levels were below the lower limit of normal for age on first testing in eight of the 20 tested. In only one child was the serum IgA level raised at any time (tables II and III).

Association with lactose intolerance—After rehydration with intravenous fluids or an oral glucose and electrolyte mixture all 20 children who presented with acute gastroenteritis failed to tolerate cows' milk feeds; diarrhoea, vomiting, and failure to gain weight recurred. Sixteen of these children developed 0·5-2% reducing substances in the stools, and paper chromatography of the stools confirmed lactose malabsorption in the 13 tested (table IV). Disaccharidase activities were depressed in three out of seven of these children. After an interval of lactose and milk withdrawal varying from two to nine months (mean 3·8 months) lactose tolerance tests were performed. All 20 children showed a rise in blood glucose above the fasting level of greater than 1·12 mmol/l (20 mg/100 ml). Seven per cent lactose feeds were tolerated, and no child developed diarrhoea. Disaccharidase activities were normal in all but one child (case 12) (table V). Thus there was no clinical evidence of lactose intolerance before milk

TABLE II—*Immunological results*

	Prick tests			Cows' milk precipitins	Serum IgA below normal
	Milk	Casein	Lactal-bumin		
No tested ..	16	16	16	23	20
No positive ..	13	9	10	12	8

TABLE III—*Details of children with low serum IgA levels*

Case No	Age (months)	IgA		
		Serum IgA (IU/ml)	Mean for age (IU/ml)	Range for age ±2 SD (IU/ml)
5	3	3·5	11	4-28
	9	8·5	21	11-49
	25	15	49	21-92
6	7	10·6	21	11-49
	20	21	49	21-92
	28	52·8	60	25-99
7	3	0	11	4-28
	17	31	49	21-92
14	26	0	60	25-99
	35	17·6	60	25-99
17	2	5	11	4-28
	11	14	28	18-53
22	2	4·2	11	4-28
	17	0	49	21-92
23	2	0	11	4-28
	4	13	18	7-42
	17	28	49	21-92
25	6	7	21	11-49
	9	15	28	18-53

TABLE IV—*Features of sugar malabsorption in 20 children presenting with gastroenteritis*

	No tested	No positive
Stool reducing substances of 0·5-2% on initial change from clear fluids to cows' milk ..	17	16
Presence of lactose and lactic acid on initial stool chromatography	13	13
Lactose tolerance test; rise in blood glucose of >1·12 mmol/l	20	20 (1·18-4·59; mean 2·13)
Stool reducing substances during lactose tolerance test	20	0
Stool reducing substances with 7% lactose feeds	15	0
Stool reducing substances before milk challenge	20	0
Stool reducing substances after milk challenge	20	20

challenge. Nevertheless, within hours of a milk challenge diarrhoea with abnormal amounts of reducing substances occurred in all 20 children and in a further three of the total studied. Loss of disaccharidase activity was shown in five children who underwent biopsy after challenge. Thus in 72% there was evidence of sugar malabsorption after a positive milk challenge.

TABLE V—*Lactase activities in small intestinal mucosa. Normal range (given in parentheses) varies according to site of small bowel biopsy*

Case No	Initial level (and normal range) (μm/min/g)	Level before positive milk challenge (and normal range) (μm/min/g)	Level after positive milk challenge (and normal range) (μm/min/g)
2		4·5 (2·7-9·3)	2·6 (2·7-9·3)
5	0·8 (2·7-9·3)	2·6 (2·0-16·2)	
6*		2·9 (2·7-9·3)	
7		0·5 (0·2-3·5)	
9		0·5 (0·2-3·5)	
11	2·2 (2·0-16·2)	6·6 (0·2-3·5)	0·1 (0·2-3·5)
12	1·6 (2·9-9·3)	1·1 (2·0-16·2)	
13	3·0 (0·2-3·5)	3·0 (0·2-3·5)	6·2 (2·8-18·7)
14		2·9 (2·7-9·3)	
15*		6·4 (2·0-16·2)	
19	5·0 (2·7-9·3)	2·4 (0·2-3·5)	0·1 (2·8-18·7)
20		5·0 (2·7-9·3)	
21		3·7 (2·0-16·2)	
22	0·9 (2·7-9·3)	2·1 (2·0-16·2)	
23	5·1 (2·0-16·2)	2·3 (2·0-16·2)	0·8 (2·0-16·2)
24*	0·6 (2·7-9·3)	2·1 (0·2-3·5)	

*Presented with chronic diarrhoea and failure to thrive.
Maltase and sucrase activities were measured, and in all cases reflected the lactase activities.
Conversion: SI to traditional units—Lactose: 1 μmol/min/g ≈ 0·36 mg/min/g.

TABLE VI—*Results of small intestinal biopsies*

Case No	Initial biopsy (months since gastroenteritis)	Months of milk before challenge (months since gastroenteritis)	Biopsy before challenge	Result of milk challenge	Biopsy after challenge
2		4·75 (7·75)	±/+	Positive	+ +
3		15 (16·75)	+ +/N	ND	
		20 (21·5)	N	Positive	
5	+ +/+ + + (1·25)	4 GF (5·25)	±	ND	
		7 GF (8)	+	ND	
		9 GF (10)	N	Positive	
		+2 M, GF (12)	+ +	ND	
		+4 M, GF (14)	N		
		+10 M, (24)	N		
6*		13	+	Positive	
		16·5	±/N	Negative	N
7	+/+ + (7·5)	19 (19·5)	N	Negative	
9		4 (4·5)	N	Positive	
11	+ + (2)	4 (6)	N	Positive	+ +
12	+ + (8)	5 (13)	N	Negative	
13		2 (4)	+	Positive	+ +/+ + +
		10 (11)	±	Positive	+ +
14		2 (12)	N	Positive	
15*	±				
18	+ + (3·5)	5 (12·5)	N	Negative	
19	+ + + (4)	3 GF (7)	+ +	Positive	+ +/+ + +
20*		2	N	Positive	
		31	N	Negative	
21		0·5 (1)	+/+ +	Positive	
		8 (11)	N/+	Positive	
22	+ + (0·75)	4 (5·5)	N	Positive	
		13 (14·5)	N	Positive	
23		0·5 (3)	±	Positive	
		3 (4·75)	N	Positive	
24*	+ + +	9 GF	N	Negative	

*Patient did not have gastroenteritis.
GF = On gluten-free diet. M = On milk-containing diet. ND = Not tested.

Small intestinal biopsy—Of the nine children who underwent biopsy before milk withdrawal none had a normal small intestinal mucosa (table VI). Two had subtotal villous atrophy (+ + +) (cases 19 and 24) and one (case 5) had a patchy lesion of moderate to subtotal villous atrophy (+ +/+ + +). These three children may have had coeliac disease. One patient (case 5) presented with sudden onset of diarrhoea and vomiting at three weeks of age, having had only one teaspoonful of cereal. Another (case 19) was well until he had *E coli* gastroenteritis at nine months of age, gluten having been introduced at six weeks; after the infection he could not tolerate milk. Another child (case 24) presented with chronic diarrhoea and vomiting, which preceded the introduction of gluten by four weeks. A pronounced increase in mucosal damage was seen in all five children who underwent biopsy after a positive milk challenge (table VI). This was accompanied by a rise in the number of immunoglobulin-containing cells in the lamina propria.

Milk challenge—The features of positive milk challenges are shown in table VII. In most younger children the reaction was rapid with onset of symptoms within 24 hours. In four older children it occurred over two to three weeks.

Age of recovery—The mean age of recovery was 18·4 months (range seven to 45 months). Four children were still intolerant to cows' milk protein, and 10 suffered from asthma and four from eczema at the time of writing.

Discussion

Gastroenteritis precipitating cows' milk protein intolerance has not been reported. Circulating levels of unaltered foreign protein are higher after feeding protein to infants recovering from infantile diarrhoea than after protein administration to normal infants. This is thought to be due to increased absorption from the damaged gastrointestinal tract.[3]

In this study two children were shown to have had an enteropathogenic *E coli* infection, and there was strong clinical evidence of acute gastroenteritis preceding the development of cows' milk protein intolerance in a further 18 of the 25 children. Proof of the diagnosis of gastroenteritis must wait until the technique of virus identification in stools becomes readily available. On the basis of our findings, however, we suggest that an acute attack of gastroenteritis may act as a triggering mechanism in the pathogenesis of cows' milk protein intolerance, sensitisation to cows' milk protein occurring when the gastrointestinal tract is damaged by infection, resulting in the absorption of cows' milk protein antigens.

Since the work of Burke *et al* in 1965,[4] it has been widely accepted that milk intolerance after gastroenteritis in infancy is due to lactase deficiency secondary to the small intestinal damage produced by infection, yet some workers have shown that sugar malabsorption may occur in association with cows' milk protein intolerance[5 6] and have even suggested that lactose intolerance occurs secondary to cows' milk protein intolerance.[7 8] We saw infants who had clear evidence of lactose intolerance at diagnosis with an abnormal small intestinal mucosa and depressed lactase activity. This state of lactose intolerance disappeared after a period on a hypoallergenic lactose-free diet, with mucosal healing and rise of lactase levels to normal, only to recur after a milk challenge, with evidence of recurrence of mucosal damage and fall of lactase levels in those studied. An abnormal immunological reaction may have occurred within the small intestinal mucosa of these children in response to ingestion of cows' milk, causing damage to mucosal cells and depression of disaccharidase

TABLE VII—*Results of milk challenge*

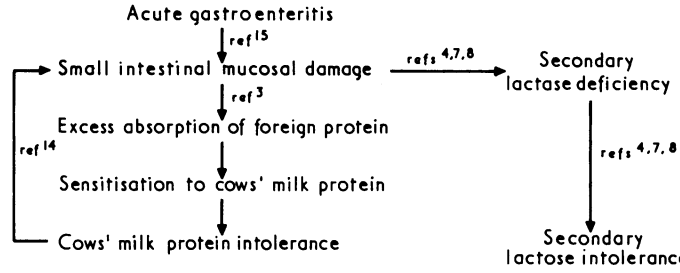
	Rise in eosinophil count >0·45 × 10⁹/l	Diarrhoea	Occult blood in stools	Vomiting	Weight loss >300 g in 24 h	Rise in temperature to >38°C	Reducing substances in stools of 0·5-2%	Rash	Urticaria	Wheezing	Anaphylaxis
No tested	25	25	23	25	25	24	25	25	25	25	25
No positive	16	25	22	24	22	19	23	4	3	3	2

activities resulting in lactose intolerance secondary to cows' milk protein intolerance. The rise seen in the number of immunoglobulin-containing cells of the lamina propria after a positive milk challenge supports this suggestion, details of which will be given in another paper.[9]

Insufficient attention has been paid to this relation between lactose intolerance and cows' milk protein intolerance, resulting in underdiagnosis of the protein intolerance. This also explains why breast milk with its lactose content of 194 mmol/l (7 g/100 ml) may fail in treatment. A lactose-free preparation is recommended in the treatment of cows' milk protein intolerance.

The association between coeliac disease and cows' milk protein intolerance is well known.[10,11] Three children with possible coeliac disease were included in this study. They illustrate the difficulty of distinguishing between the two conditions and the need for serial small intestinal biopsies coupled with accurate dietary information. They probably had cows' milk protein intolerance, but it is essential that a final biopsy is performed two years after the reintroduction of gluten to exclude coeliac disease, as cows' milk protein intolerance may be a precursor of coeliac disease.[11]

Why did sensitisation to cows' milk occur in these few children, when most recover uneventfully from gastroenteritis? A partial explanation may come from the observation that 40% of the 20 infants tested had a serum IgA level below the lower limit of normal for age at the time of diagnosis and that clinical recovery tended to coincide with a return of the IgA level to normal. Gerrard *et al*[12] postulated that sensitisation to foreign protein would be apt to occur in the newborn when the infant's rate of synthesis of serum and secretory IgA is low. Taylor *et al*[13] reported that IgA deficiency at three months is associated with the development of atopy and cows' milk protein intolerance in the offspring of reaginic parents. A family history of atopy was a notable feature in this study, although a control group was not included, and probably IgA deficiency may be a predisposing factor in the development of cows' milk protein intolerance.



Hypothesis on possible association of gastroenteritis and lactose intolerance with cows' milk protein intolerance.

A hypothesis based on the findings in this study, concerning the possible association of gastroenteritis and lactose intolerance with cows' milk protein intolerance, is indicated in the figure.

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Explanations for weight loss after ileojejunal bypass in gross obesity

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Summary

Twenty grossly obese patients underwent ileojejunal bypass operations. Measurements of calories lost in faeces showed that the malabsorption could not account for the weight loss. Furthermore, the malabsorption was not decreased two years after bypass, when weight was no longer being lost. Dietary restriction is therefore largely responsible for the weight loss and increased food intake for weight maintenance.

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Introduction

Payne and De Wind[1] in 1969 pioneered ileojejunal bypass for the treatment of gross obesity, a condition which can only rarely be treated by other means. After this operation about 40 kg of weight is lost over two years and the resulting lower weight is then easily maintained. It has usually been assumed that the weight loss is due to the malabsorption of fat and protein.[2] This explanation, however, has never been checked quantitatively. We report here the measurement of faecal calories before and after bypass.

Patients and methods

Seventeen women with a mean weight (± SD) of 117·71 ± 14·77 kg and three men weighing 142·33 ± 30·54 kg had a bypass operation in which 4 in (10·2 cm) of the proximal jejunum was anastomosed to 10 in (25·4 cm) of terminal ileum.[3] Before operation the patients were admitted for metabolic study. The women were given diets supplying 9·489 MJ (2270 kcal) and the men diets supplying 11·620 MJ (2780 kcal) on each of five days. The energy content of the diet was verified by calorimetry and the metabolisable energy derived by the equation