

Acute Urticarial Reactions to Cow's Milk in Infants Previously Fed Breast Milk or Soy Milk

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ABSTRACT

Twenty-nine breastfed or soy formula-fed infants with IgE-mediated sensitization to cow's milk (CM) were identified because they had acute urticarial reactions while being fed CM for the first time. One of these infants had a reaction to CM in the newborn nursery, suggesting in-utero sensitization. Sixteen other infants inadvertently had been fed CM in the newborn nursery without reaction, suggesting that this was their initial sensitizing event. The remaining 12 may have been sensitized by small amounts of CM antigens either in utero or via breast milk. The clinical condition is characterized by elevated serum IgE levels; positive RASTs to alpha-lactalbumin (AL), beta-lactoglobulin (BL) and casein (C) and a high frequency (16/29, or 55%) of recurrent wheezing. The important role of heredity in the development of this entity is demonstrated by its occurrence in identical twins and in HLA-identical siblings, and by the high frequency of allergy in 28 parent pairs (89%) and in 56 parents (70%). Although the condition appears to be clinically homogeneous, genetic homogeneity could not be demonstrated by HLA-typing. There was not increased frequency of any HLA-A, HLA-B, or HLA-DR phenotype either in the patient group or in the parent group.

INTRODUCTION

VIVID DESCRIPTIONS OF EXTREME SENSITIZATION to cow's milk (CM) were recorded by Schloss in 1920 ⁽¹⁾ and by Tisdall and Erb in 1924.⁽²⁾ Urticaria and other signs of anaphylaxis occur within minutes of the first ingestion of CM when attempting to wean the infant from breastfeeding.

Gerrard and Shenassa⁽³⁾ and Ford et al.⁽⁴⁾ have distinguished two types of CM allergy. The first type develops in breastfed babies; is triggered by trace amounts of CM antigen, tends to cause immediate cutaneous reactions, is IgE-mediated, and may persist for several years. The second type

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develops in CM formula-fed babies; is triggered by large amounts of CM antigen, tends to cause gastrointestinal symptoms of vomiting, diarrhea, and colic, is not associated with CM-specific IgE antibodies or with anaphylactic reactions, and often subsides spontaneously. Assigning milk-allergic children to one or other of these categories should increase the reliability of interpreting investigations and clinical findings.

We have identified 29 breastfed or soy formula-fed infants who exhibited the first type of allergy to CM proteins while being fed CM for the first time. Clinical observations on this group of infants provided an opportunity to address again questions concerning how and why sensitization occurs. Our observations support the notion that initial sensitization to CM may occur not only by CM protein exposure in utero or by CM protein exposure via human breast milk but also by small amounts of CM formula inapparently and inadvertently fed in the newborn nursery. These infants became immunized to alpha-lactalbumin (AL), beta-lactoglobulin (BL), and casein (C). By history, their parents had a high prevalence of allergy. For these types of parents, breastfeeding or soy formula-feeding is encouraged by many pediatricians and allergists as a prophylactic measure to attempt to avoid later development of atopic dermatitis, asthma, and allergic rhinitis in their infants.⁽⁵⁾ Our observations suggest that alternatives to CM formula feeding may accelerate rather than delay or abort the development of clinical atopy, such as acute urticaria and asthma. In order to assess the possibility that infants with this type of allergy represent a subset of children who are genetically homogeneous with respect to extreme sensitization to CM proteins, we studied the frequency of HLA phenotypes and haplotypes in 17 of the families.

MATERIALS AND METHODS

Subject selection

Twenty-nine Caucasian children (17 boys, 12 girls), born between 1975 and 1985, were referred to us because of a history of anaphylactic symptoms while drinking CM. According to the referral information and histories obtained from mothers, before their first known CM feeding, all had been exclusively breastfed or soybean formula-fed. When available, newborn nursery records were reviewed (21 patients). Parents were interviewed for a history of atopic dermatitis, asthma, seasonal allergic rhinitis, urticaria, and hypersensitivity to food, drugs, and stinging insects.

Seventeen families participated in a study that examined the association of HLA phenotypes and haplotypes with CM allergy. These subjects included 34 parents, 18 affected children (one set of female identical twins), and 14 siblings. For this purpose, blood was obtained from each subject.

Total and specific serum IgE

Total serum IgE was determined by the Phadebas PRIST method (Pharmacia Diagnostics, Piscataway, NJ). Cow's milk-specific IgE antibodies were determined by the RAST method (Pharmacia Diagnostics). Whole CM was tested in 28 of 29 infants (1 other had a 3+ scratch test to CM: Hollister Stier, Spokane, Washington). RASTs to AL, BL, and C were determined on serum from 24 of 29 CM-allergic children (including one set of identical twins) and on serum from 4 other HLA-identical siblings.

HLA typing

HLA typing for A, B, and DR loci was performed on isolated peripheral blood lymphocytes by standard microcytotoxicity assays using the eosin exclusion technique.⁽⁶⁾ Typing for HLA-DR was done with enriched B cell preparations obtained from peripheral blood lymphocytes using the T cell rosetting separation technique with neuraminidase-treated sheep erythrocytes. HLA-A and HLA-B testing was done on Accugenix (Cooper Biomedical, Inc., Garden Grove, CA) complementary trays (LT 3-E3 and LT 4-A5), which include all of the presently known A loci and all of the broad specificity

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B loci. For HLA-DR typing, UCLA DRW trays (Lots 15 and 16) were used. They typed for the known 10 DR loci. All typing was done in the tissue typing laboratory at Strong Memorial Hospital. Normal HLA phenotype frequencies at the A and B loci for the Rochester population were obtained from the Rochester Area blood donor pool (1000 donors). Normal HLA-DR phenotype frequencies were derived from the current literature.⁽⁷⁾ Terasaki HLA tables⁽⁸⁾ were used for control Caucasian HLA haplotype frequencies (per 10,000 haplotypes).

Statistical analysis

Differences of HLA antigen frequencies between patient and control groups were analyzed for statistical significance using the Chi-square test, incorporating the Yates correction factor. The resulting *p*-values again were corrected by multiplication with a factor representing the number of antigens tested. Antigen frequencies were considered statistically different when the computed *p* value was equal to or less than 0.05.⁽⁹⁾

RESULTS

Infant histories

Twenty-nine infants had been breastfed and/or soybean formula-fed (patient 23 was breastfed and soyfed) since birth according to the histories obtained from their mothers and from the referring physicians (Table I). We were able to review the delivery room and nursing records from the newborn nursery for 21 of these infants. Their birth weights ranged from 2900 g to 4370 g. Two infants were delivered by cesarean section (patients 5 and 26). Sixteen of these 21 newborns inadvertently received CM formula (casein-predominant), either Enfamil or Similac, during the first 72 h of life. Amounts ranged between 10 ml and 685 ml per infant. Infants were fed CM formula when mothers elected not to feed their own babies because of the time of day or night, other personal reason, or when the nursing staff introduced CM feedings without the mothers' awareness but according to the usual and customary nursery procedures in effect at the time. One mother fed her infant soybean formula after her infant (patient 2) had a reaction to a CM formula in the newborn nursery. The remaining 8 infants were exclusively breastfed (7) or soyfed (1) until the time of their initial reactions when they received CM for the first known time. Their newborn nursery records were not available for review. Their mothers did not know if their infants had been inadvertently fed CM in the newborn nursery. None of the mothers restricted CM from their diets during pregnancy or during lactation.

Twenty-nine infants had acute urticarial reactions within 30 min of their first known feeding of CM. One acute episode, accompanied by projectile vomiting, occurred in the newborn nursery and was not thought to be erythema toxicum. This infant (patient 2) was subsequently fed soy formula. The next attempt to introduce CM resulted in vomiting, the appearance of contact urticaria where milk touched the skin, and wheezing. The rest of the infants had their first reactions between the ages of 1 and 10 months (mean, 5.2 months). These reactions ranged in severity from urticaria alone, usually around the mouth and where CM came in contact with the skin, to generalized urticaria, angioedema, and wheezing. Two infants were seen in emergency rooms and were found to be hypotensive. All reactions subsided spontaneously or responded to antihistamines and/or epinephrine. All infants had reactions to CM on two or more occasions. Because of the acute onset of signs and symptoms with CM exposure, both parents and the infants' physicians were convinced that the reactions were due to CM allergy. Twenty (69%) infants had generalized urticaria, 17 (59%) had contact urticaria, 19 (66%) had angioedema, and 14 (48%) had wheezing. Sixteen (8 males, 8 females) of 29 (55%) now have recurrent asthma.

Parent histories

Allergy histories were obtained from 28 sets of parents (two infants were identical female twins) (Table II). They were considered to be allergic if they had a history of asthma, hayfever, recurrent

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TABLE I
TWENTY-NINE INFANTS WITH EXTREME SENSITIZATION TO COW'S MILK

PATIENT SEX			BIRTH DATE	AGE ONSET	FEEDING BM SM CM			INITIAL REACTION 6-U C-U A-E WHZ				DEVELOPED ASTH ECZM	
1	BD	M	23-Apr-75	7	+	-	-*	+	-	+	+	YES	NO
2	JWB	M	07-Sep-75	1 da	-	+	-*	-	+	-	+	YES	NO
3	H8	F	09-Dec-75	3	-	+	-*	+	-	+	+	YES	NO
4	MI	M	22-Feb-78	4.5	-	+	-	+	-	+	+	YES	NO
5	CW	M	24-May-78	4	+	-	-*	+	-	+	-	NO	NO
6	TB	M	14-Sep-78	4.5	+	-	-*	+	+	-	-	NO	NO
7	JF	F	20-Feb-79	6	+	-	-	-	+	+	-	YES	NO
8	AF	F	20-Feb-79	6	+	-	-	-	+	+	-	YES	NO
9	BL	M	07-Apr-79	5	-	+	-*	+	+	-	+	YES	NO
10	MS	M	13-Nov-80	3	+	-	-	-	+	-	-	NO	YES
11	AS ^{ch}	F	15-Nov-80	5.5	+	-	-	+	-	-	+	YES	NO
12	SP	F	24-Sep-81	6	+	-	-	+	-	+	+	YES	NO
13	JK	M	09-Oct-81	8.5	+	-	-*	+	-	+	-	NO	NO
14	JB	M	15-Nov-81	1	+	-	-*	+	-	+	-	NO	NO
15	MW	F	24-Nov-81	7	+	-	-*	+	+	+	-	NO	NO
16	JW	M	29-Jan-82	5	+	-	-	+	-	-	-	YES	YES
17	MC	M	03-Mar-82	4	+	-	-*	-	+	-	+	YES	NO
18	AS	F	13-Mar-82	8	-	+	-*	+	-	+	-	YES	NO
19	SK	F	16-Nov-82	5	+	-	-*	+	+	+	-	NO	YES
20	RG	F	19-Nov-82	5.5	+	-	-	-	+	+	+	NO	NO
21	DP	M	22-Nov-82	10	-	+	-*	-	+	-	-	NO	NO
22	JS	M	27-Feb-83	6	+	-	-*	-	+	-	-	YES	NO
23	TF	M	11-Apr-83	6	+	+	-*	+	-	+	-	NO	NO
24	LS	F	25-Dec-83	4	-	+	-*	+	-	+	+	NO	NO
25	MR	F	05-Jun-84	5.5	+	-	-*	+	+	+	-	YES	NO
26	AR	F	25-Dec-83	5	+	-	-*	+	+	+	+	YES	YES
27	DH	M	26-Dec-83	8	+	-	-*	+	+	+	+	NO	NO
28	NH	M	22-Dec-83	10	+	-	-*	+	+	-	+	NO	NO
29	ML	M	09-Mar-85	4	+	-	-*	-	+	+	+	YES	YES
MALES		17	MEAN AGE = 5.2		22	8	0	20	17	19	14	16	5
FEMALES		12	ONSET(mos)					69%	59%	66%	48%	55%	17%

AGE ONSET: Age(in months) of reaction to "first" feeding of cow's milk

FEEDING: BM = Breast Milk
SM = Soy Milk Formula
CM = Cow's Milk
+ = known to have received CM in newborn nursery
= did not receive CM in newborn nursery

REACTION: G-U = Generalized Urticaria
C-U = Contact Urticaria
A-E = Angioedema
WHZ = Wheezing

DEVELOPED: ASTH = Asthma; ECZM = Eczema (atopic dermatitis)

urticaria due to foods, or generalized reactions to drugs or to stinging insects. Twenty-five of the 28 infants (89%) had at least one parent with significant allergies. Both parents were allergic in 14 (50%) families, mothers alone in 4 (14%), fathers alone in 7 (25%), and neither in 3 (10%). Of the 56 parents, 25 (45%) had seasonal allergic rhinitis, 12 (21%) had asthma, 3 (5%) had stinging insect hypersensitivity, 7 (13%) had urticaria, 4 (7%) had drug allergy (pencillin), and 7 (13%) had food allergy. Historical evidence for allergy was present in 39 of the 56 (70%) parents.

Total and specific IgE

Twenty-eight children had positive RASTs to CM (Table III). Another child has a 3-plus positive scratch test to CM. The RAST classes ranged from class I to class IV, with 23 of 28 (82%) being of class III or IV. Corresponding values expressed as PRU (Phadebas RAST units) ranged from 0.38 to more than 17.5. RASTs were also positive to AL, BL, and C. Class III or IV RASTs were found for AL in 17 of 24 (71%), for BL in 13 of 24 (54%), and for C in 12 of 26 (46%) patient sera tested.

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TABLE II
ALLERGY HISTORIES : TWENTY-EIGHT PARENT PAIRS

PATIENT	MOTHER	FATHER
1	U	SAR
2	A, SAR, U, S	U
3	A, SAR	SAR
4	A	-
5	A, D	SAR
6	-	SAR
7&8	A, F	A
9	SAR	SAR
10	-	A
11	-	SAR
12	SAR	-
13	SAR	-
14	-	-
15	SAR, E, U	S
16	-	-
17	A, SAR, D	-
18	F, D	SAR, E
19	-	SAR
20	A	E, F
21	A, F	F
22	SAR	S
23	D	E, U
24	-	-
25	SAR, U, F	-
26	SAR, E, U, F	A, SAR
27	-	SAR
28	SAR	SAR
29	-	A, SAR

Bilateral = 14/28 (50%)
 Unilateral = 11/28 (39%)
 Mothers = 4/28 (14%)
 Fathers = 7/28 (25%)
 Neither = 3/28 (10%)

Asthma (A) = 12/56 (21%)
 Seasonal Allergic Rhinitis (SAR) = 25/56 (45%)
 Urticaria (U) = 7/56 (13%)
 Drug (D) = 4/56 (7%)
 Food (F) = 7/56 (13%)
 Sting (S) = 3/56 (5%)
 Eczema (E) = 5/56 (9%)

The lowest RAST values were found for C, and 6 of 26 (23%) had negative C RASTs. Twenty-nine children has serum IgE determinations. Twenty-six of 29 (90%) had elevated ($> +1$ SD) serum IgE (range, 21–2000 IgE U/ml). Two children had normally low IgE (CW had 4 U/ml; LS had 3 U/ml).

HLA-A and HLA-B phenotypes

Eighteen Caucasian patients were typed for 19 antigens at the HLA-A locus and 40 antigens at the HLA-B locus. (Table IV). Patients 7(JF) and 8(AF) were HLA-identical female twins. Therefore, HLA frequencies were calculated on the basis of 17 patients from 17 unrelated families. There was no significant increased frequency of any A or B type when the patient group was compared to 1000 donors from the Rochester Area blood donor pool.

HLA-DR phenotypes

Eighteen patients were typed for 10 antigens at the DR locus (Table V). Seventeen patients from 17 unrelated families were used in the analysis. There was no increased frequency of any HLA-DR phenotype in the patient group when compared to the frequencies in 399 Caucasoids reported in the recent literature.⁽⁷⁾

TABLE III
SERUM RAST VALUES AND IgE CONCENTRATIONS

PATIENT		SERUM RAST VALUES (PRU)				SERUM IgE
		MILK	ALPHA	BETA	CASEIN	
1	*	>17.50	4.21	>17.50	9.36	72
2	*	7.50	1.41	1.82	0.95	35
3	*	>17.50	>17.50	12.13	>17.50	682
4		(III)	ND	ND	ND	400
5	*	(IV)	ND	ND	(IV)	3
6	*	(IV)	ND	ND	(IV)	48
7		>17.50	>17.50	11.02	7.39	2000
8		13.99	9.77	6.62	4.49	1700
9	#	>17.50	>17.50	>17.50	>17.50	229
10		@ST=4+	ND	ND	ND	146
11		>17.50	>17.50	13.25	3.75	1000
12		>17.50	9.34	6.03	2.59	21
13	#	4.43	0.44	1.67	0.15	508
14	#	(III)	ND	ND	ND	182
15	#	0.38	< 0.12	< 0.12	0.37	300
16		8.16	6.02	4.8	4.67	264
17	*	>17.50	>17.50	12.88	4.1	320
18	*	>17.50	>17.50	>17.50	4.43	98
19	*	17.50	12.47	1.67	0.69	102
20		3.97	3.69	1.53	< 0.12	64
21	*	12.66	8.20	0.15	0.45	56
22	*	2.13	0.99	1.50	< 0.12	39
23	*	2.17	0.71	0.56	< 0.12	50
24	*	1.65	1.68	1.67	< 0.12	4
25	*	12.66	3.84	6.09	2.46	181
26	*	>17.50	>17.50	>17.50	>17.50	366
27	*	>17.50	11.61	2.98	< 0.12	22
28	*	3.38	1.97	0.59	< 0.12	10
29	*	(IV)	(IV)	(IV)	(IV)	54
POSITIVE %		29/29 100	24/24 100	23/24 96	20/26 77	26/29 90

PRU = Phadebas Rast Units

() = RAST Class

RAST Class: 0 = <0.12 PRU II = 0.71-3.4
 I/0 = 0.12-0.34 III = 3.5-17.5
 I = 0.35-0.70 IV = >17.5

IgE = Units/ml

@ ST = Scratch Test

* = known to have received CM in newborn nursery

= did not receive CM in the newborn nursery

ND = Not Done

HLA-DR phenotyping was done on 34 parents. As with their children, there was no increased frequency of any HLA-DR phenotype.

No association was observed with other HLA-D region antigens, DQ (previously known as MB), and DRw52/53 (previously known as MT). We did not determine the DP (previously known as SB) antigens.

HLA haplotypes

Since 34 parents were also typed, haplotypes of parents and patients could be determined (Table VI). There was no increased frequency of any one HLA-A, B haplotype in the group of 68 parent-haplotypes or 34 patient-haplotypes when compared to frequency data obtained from the Terasaki HLA tables (updated August 1983) of the haplotype frequencies per 10,000 haplotypes ($n = 5559$ whites).⁽⁸⁾ The most frequent haplotype was A1BB, which occurred in 6 of 68 (8.8%) parent-haplotypes and in 5 of 34 (14.7%) patient-haplotypes. None of the patients was homozygous for A1B8.

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TABLE IV

OCCURRENCE AND FREQUENCY OF HLA-A AND HLA-B PHENOTYPES
SEVENTEEN PATIENTS* WITH EXTREME SENSITIZATION TO COW'S MILK

ANTIGEN	OCCURRENCES 1000 DONORS	FREQUENCY %	OCCURRENCES 17 PATIENTS	FREQUENCY %	p-VALUE
A1	301	30	5	29	N.S.
A2	473	47	11	64	P>0.10
A3	310	31	6	35	N.S.
A9	176	18	5	29	P>0.30
A11	110	11	1	5	N.S.
A26	61	6	1	5	N.S.
A28	59	6	1	5	N.S.
A29	70	7	1	5	N.S.
Aw30	58	6	1	5	N.S.
Aw31	58	6	1	5	N.S.
B5	92	9	2	12	N.S.
B7	293	29	6	35	N.S.
B8	216	22	6	35	P>0.25
B12	218	22	4	23	N.S.
B13	56	6	2	11	N.S.
B14	75	8	2	11	N.S.
B15	103	10	1	5	N.S.
Bw16	59	6	1	5	N.S.
B17	89	9	2	11	N.S.
B18	96	10	1	5	N.S.
Bw35	175	18	1	5	N.S.
Bw38	28	3	1	5	N.S.
B40	115	12	2	11	N.S.

* = patients from unrelated families; HLA-identical twins counted once.

1000 DONORS = donors from the Rochester Area Blood Donor Pool.

p-VALUE = Chi Square analysis. N.S. = not significant

Others are not significant. p-Values indicated as examples

TABLE V

OCCURRENCE AND FREQUENCY OF HLA-DR PHENOTYPES

ANTIGEN	OCCURRENCES (FREQUENCY %) MILWAUKEE CAUCASOIDS ⁷		OCCURRENCES (FREQUENCY %) 17 PATIENTS 34 PARENTS	
DR1	70	(17.5)	0(0)	2(6.3)
DR2	114	(28.6)	5(29.4)	12(35.3)
DR3	96	(24.1)	6(35.3)	12(35.3)
DR4	116	(29.1)	4(23.5)	5(14.7)
DR5	82	(20.6)	4(23.5)	12(35.3)
DRw6	79	(19.1)	0(0)	1(2.9)
DR7	92	(23.1)	4(23.5)	11(32.4)
DRw8	23	(5.8)	1(5.9)	1(2.9)
DRw9	6	(1.5)	1(5.9)	2(5.9)
DRw10	3	(0.8)	0(0)	0(0)
DR-"blank"	**	(2.0)	0(0)	0(0)

Patients from unrelated families; HLA-identical twins counted once.

** = personal communication (Dr. Jawahar Tiwari, UCLA HLA Tissue Typing Laboratory) - 400 donors.

"blank" typing implies the antigen present at the DR locus on each chromosome is presently undefined. Antigen or antigens, for which no alloantisera exist, may be present.

TABLE VI
HLA HAPLOTYPES
EIGHTEEN PATIENTS* WITH EXTREME SENSITIZATION TO COW'S MILK

PATIENT NUMBER	MATERNAL HAPLOTYPE			PATERNAL HAPLOTYPE		
	A	B	DR	A	B	DR
1	3	7	2	2	5	5
2	2	8	7	9	13	-
3	1	8	3	3	12	4
5	1	8	3	3	8	3
6	2	5	5	1	8	3
7 & 8	28	7	2	9	14	3
9	2	12	2	1	8	3
12	1	8	4	10	w16	w8
13	11	7	2	3	7	-
14	26	13	7	2	12	7
15	2	17	7	w31	7	3
16	2	40	w9	9	14	4
18	9	40	5	2	15	5
19	2	w38	7	2	7	-
20	w30	18	-	28	-	5
21	2	17	7	3	w35	7
24	9	12	4	3	7	2

* = patients from unrelated families; 7 & 8 = HLA identical twins

- = HLA-DR"blank"

Eight of the 17 (47%) patients who were typed have asthma. Three of these have A1B8. There was no association of the development of asthma in patients with extreme sensitivity to CM and the A1B8 haplotype ($p > 0.08$).

HLA-identical siblings

Five patients (7, 9, 13, 14, 18) have HLA-identical siblings. Two of these (siblings of patients 7 and 14), including the identical female twin (patient 8), were breastfed and developed acute generalized urticaria while being fed CM for the first time. They have positive RASTs to CM proteins and have developed asthma. Their mothers did not avoid CM during pregnancy or during lactation. Three others are RAST negative, not CM-allergic, and have not developed asthma. One (sibling of patient 13) was breastfed for 9 months. His mother avoided dietary CM during the last trimester of pregnancy and during lactation. The second (sibling of patient 9) was fed CM from birth, and the third (sibling of patient 18) was fed soy. The breastfed and the soyfed infants did not receive CM in the newborn nursery. None of the 10 HLA-nonidentical siblings are milk allergic.

DISCUSSION

The 29 infants in this study fit the clinical description of extreme sensitization to CM given by Schloss in 1920⁽¹⁾ and by Tisdall and Erb in 1924.⁽²⁾ The typical reaction occurs directly after the first known ingestion of CM and is generally noted initially when an attempt is made to wean the infant. The diagnosis usually is made by the parents. After ingesting a small amount of CM, the infant refuses to take more and cries as if in pain, and in 2-5 min, there is swelling of the lips, tongue, and mucous membranes of the mouth and throat. Laryngeal edema and wheezing may occur. Cow's milk spilled on the skin results in contact urticaria; in some instances, huge urticarial wheals appear over the entire body. The infant may pass into a condition of shock. After 15-60 min, the symptoms disappear and the child returns to his former condition, although some signs of exhaustion remain. Scratch tests to CM are positive. Potentially, this type of reaction could be lethal, although we are unaware of any infant deaths. Our group of patients had some or all of the signs and symptoms

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of anaphylaxis. They had acute generalized and/or contact urticaria and markedly elevated levels of serum IgE antibodies to CM proteins, including AL, BL, and C.

How and why does this type of sensitization occur to CM? Our observations support the notions that sensitization can occur in utero, in newborn nursery, in breastfed infants, and in genetically predisposed infants.

That sensitization can occur in utero is supported by the observations that one newborn (patient 2) had a reaction to CM on the first day of life and that one infant (patient 9) who was exclusively fed soy formula had a reaction at age 5 months during the time of his first CM feeding.

That sensitization can occur in the newborn nursery when nurses supplement breastfeeding with CM is supported by our chart review findings that 16 newborns were inadvertently fed CM in the newborn nursery and did not have a reaction at that time. Four of these (patients 3, 18, 21, 24) were subsequently fed only soy formula and then had a reaction with their first feeding of CM.

That sensitization can occur through CM allergens in mother's breast is supported by the observations that 3 breastfed infants (patients 13, 14, 15) who had not been fed CM in the newborn nursery had reactions on their first CM feeding. These infants, however, may have been sensitized in utero.

That heredity plays an important role in the development of extreme sensitization to CM is evidenced by the observation that 89% of the parent pairs had a history of clinically significant allergy. In addition, we have observed this clinical entity in one set of HLA-identical twins and in one pair of HLA-identical siblings.

Atopy plays a significant role in this condition, as evidenced by high serum total IgE levels, IgE antibodies to multiple CM allergens, and a high risk of subsequently developing asthma.

Except for the method of patient selection, the 29 patients in the present study resemble the group of children reported by Kaplan and Solli in 1979.⁽¹⁰⁾ Our patients were referred to us because of their reactions to CM. Fifty-five percent (16/29) have subsequently developed asthma. Kaplan and Solli's patients (ages 10 months to 5 years) were new allergy clinic patients with a diagnosis of bronchial asthma, a strong family history of atopy, and evidence of IgE to multiple common inhalant allergens. Subsequently, they were discovered to have IgE antibodies to CM protein (CMP). Of the 18 patients, 13 of 14 who had been breastfed, 1 of 2 who had been CM-fed, and 1 of 2 who had been soy formula-fed had a history of developing immediate reactions within 40 min after the ingestion of CM. Urticaria or urticaria accompanied by angioedema or wheezing had occurred in 12 or 14 infants who had been breastfed (2 others had abdominal pain and vomiting; 1 of these also had diarrhea) and in 1 of 2 who had been soyfed. The first urticarial reactions were noted between age 4 1/2 and 10 months, although 1 CM-fed infant had urticaria at 2 weeks of age. No attempt was made to obtain a newborn nursery feeding history. At least 17 patients in our study received CM feedings in the newborn nursery. Only 1 had an allergic reaction at that time. Later, at the time of the infants' initial urticarial reactions (age 1–10 months), the 16 other mothers said that their infants had never received CM formula. Thus, without newborn nursery feeding history, it might have been assumed that CM protein sensitization could have occurred only in utero, via dietary CM proteins in breast milk, or by other inadvertent and unrecognized CM exposure.

Observations on the present series of infants are consistent with those of Firer, et al.⁽¹¹⁾ They found that children allergic to CM who had been breastfed and had minimal exposure to CM had vastly increased total IgE and CM-specific IgE antibodies compared with CM-fed infants. Their observations led them to suggest that initial sensitization to CM protein may have occurred in utero, in the neonatal nursery, or by passage of bovine antigens in their mother's milk. In a later study, Ford et al.⁽⁴⁾ reported that reactions were experienced at what seemed to be the first exposure to CM in 31% of children with CM sensitivity. Cow's milk was introduced at a later stage in this group than in the group of children who did not react at their first exposure. These data seemed to support the notion that children with reactions at their first exposure may have been sensitized via breast milk. However, no detailed history of feeding in the neonatal nursery was available in either of these studies.

That atopic sensitizations can sometimes occur in utero is supported by a number of earlier publications.⁽¹²⁻¹⁴⁾ The human fetus is capable of making IgE from the 11th week of gestation.⁽¹⁵⁾ Other

supportive observations are found in the fact that four infants in the Firer et al. study and one infant (patient 2) in the present study has signs consistent with allergy to CM within the first 72 h of life when they were given CM in the newborn nursery. In another study by Hill et al.⁽¹⁶⁾ 7 of 17 children with CM allergy had immediate urticarial reactions and were skin test-positive to CM. One of these children developed angioedema when fed CM on the first day of life. In addition, one infant (patient 9) in the present study did not receive CM in the newborn nursery. He was fed soy formula exclusively from the time of birth and had a reaction to the first CM feeding at 5 months of age.

There are other reports of reactions occurring in infants upon the first known exposure to CM.^(17, 18) Van Asperen et al.⁽¹⁸⁾ have pointed out that food, particularly CM, might have been given in the neonatal period. In their prospective study of 80 infants of atopic parents, 5 developed hyperacute reactions (3 of 5 to milk; 4 of 5 to egg). Because all infants were seen initially in the neonatal period and were followed every 4 months until they were 16 months of age, these authors believed that the most likely route of sensitization was via breast milk. However, it was not explicitly stated that these authors reviewed feeding histories from the time of birth. Future studies must be controlled for feeding in the newborn nursery.

It is a fairly common practice to give infant formulas occasionally in the newborn nursery.⁽¹⁹⁾ This probably occurs because the staff is uncertain whether the mothers will have enough breast milk initially and because they want to induce rapid weight gain. In 1935, Ratner⁽²⁰⁾ recommended that isolated feedings of CM to breastfed infants during the newborn period should be avoided. In 1955, Collins-Williams⁽²¹⁾ stated, "It should be a rule in all newborn nurseries that, if an infant is to be breast-fed, any necessary supplement given before the flow of breast milk is well established should consist only of lactose or glucose water." In 1979, Stintzing and Zetterstrom⁽²²⁾ reported that 16 of 25 infants with gastrointestinal ($n=21$), cutaneous ($n=10$), respiratory ($n=4$) symptoms from CM, proven by provocative challenge, had received a CM formula in the newborn nursery. Today, these recommendations should be reconsidered seriously. This is especially important since the decision to breastfeed is becoming the rule rather than the exception (61% of mothers in the United States in 1983 vs 25% in 1971).⁽²³⁾

In her discussion of perinatal influences on IgE responses, Jarrett⁽²⁴⁾ has proposed that an IgE response would occur only when the amount of antigen absorbed across mucous membranes was below a threshold required to stimulate IgE-suppressor T cells. This threshold would be very low in normal people but much higher in atopic subjects who have a variety of immunological abnormalities. Feedback regulation by IgG antibody is one such mechanism that could restrain the production of IgE antibodies. In support of this idea are the additional findings of Firer et al.⁽¹¹⁾ Infants allergic to CM had higher CM-specific IgE antibodies than nonallergic controls ($p<0.002$). Nonallergic controls had higher CM-specific IgG antibodies than the milk-allergic infant group ($p<0.002$).

Several interactive factors are operative in the scenario that results in extreme sensitization to CM, including early exposure to CM either in utero or in the newborn period, initial small doses of CM antigen, and the genetic substrate of the infant. These factors appear to be more important than the immunological specificity of the antigen, since the infants in the present study made significant IgE responses to immunologically distinct CM proteins, including AL, BL, and C. Casein constitutes about 80% of milk proteins, and the whey proteins collectively (including AL and BL) account for 20% of milk proteins in casein-predominant formulas.⁽²⁵⁾ RAST values of AL and BL were higher than values of C, and several infants (6 of 26 tested) had negative RAST values to C. Perhaps larger amounts of C were immunosuppressive for the production of specific IgE despite the early inadvertent feeding of CM. Whether or not similar sensitization will occur in infants inadvertently fed the newer whey-predominant formulas (whey:casein = 60:40 or 70:30) remains to be observed.

Provocative double-blind challenges were not done on the 29 infants in the present study. Their histories were clear-cut: the reactions were acute and occurred while being fed CM, and all of the infants had two or more reactions to CM. Their serum total IgE concentrations and RAST values

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were elevated, similar to those reported by Bjorksten et al.,⁽²⁶⁾ who found a sensitivity of 94% and a specificity of 80% for the total IgE assay ($> +1$ SD) and sensitivity of 79% and specificity of 80% for the RAST assay (RAST score 1–4) using commercially available CM discs (Pharmacia Diagnostics).

Dannaeus and Johansson⁽¹⁹⁾ reported that children like ours with low antibody levels developed tolerance more rapidly than those with high levels. Under close observation in a hospital office setting, we gradually fed small quantities of CM (1 drop in a quart of water—5 ml increments at 15 min intervals until 60 ml consumed, the remainder being consumed over the following week with the same procedure repeated weekly with 5, 10, and 50 drops) to the two children with the lowest RAST scores (LS:RAST = 1.65; IgE = 3, and MW:RAST = 0.38; IgE = 300). One (MW) still had positive prick tests to whole CM, and the other (LS) had negative tests. Both had negative provocation tests and can tolerate CM without systemic reactions. The child with the elevated serum total IgE and positive skin tests continues to have contact urticaria. In each case, parents had requested provocative challenge testing because milk avoidance had become burdensome. Neither child has asthma nor do their parents. We do not recommend this potentially dangerous procedure in a general office setting.

It is well recognized that heredity plays an important role in the development of atopy. Eighty-nine percent of the parent pairs of 29 infants had a history of atopic conditions, including asthma, hayfever, atopic dermatitis, and food, drug, and stinging insect hypersensitivity. Their infants were breastfed or soyfed in an attempt to avoid their future development of similar allergies. Instead, the opposite occurred. Fifty-five percent (16 of 29) currently have asthma. The number of patients in this report is small compared to the large bulk of breastfed and soy formula-fed infants of allergic and nonallergic parents in Rochester, New York, who do not develop extreme sensitization to CM proteins. These observations suggest that this relatively homogenous subgroup of patients with CM allergy (acute urticarial reactions and IgE antibodies to CM proteins) might have special hereditary characteristics. Identical twins with this condition also supported this concept. For these reasons, we studied HLA types.

Studies in humans have suggested that disease susceptibility genes are linked to the major histocompatibility complex (MHC) located on the short arm of chromosome 6. Most of these diseases are characterized by abnormal immune reactions.⁽⁹⁾ The strong association between HLA-B27 and ankylosing spondylitis has been helpful in the early diagnosis of this entity. The MHC contains four polymorphic loci (HLA-A, -B, -C, and -D), which determine the expression of class I (HLA-A, -B, -C) and class II (HLA-D) antigens on cell surfaces. Class I antigens are detected with anti-HLA-A, -B, -C alloantisera using microcytotoxicity assays. Class II antigens are responsible for, and detected by, the mixed lymphocyte response (MLR). Their detection has been facilitated by the availability of HLA-DR alloantisera. Class I and class II antigens serve as receptors in immune recognition and response, the balance of their interaction resulting in T cell help or suppression.⁽²⁷⁾

Verkasalo et al.⁽²⁸⁾ and others^(29–31) have reported an association of celiac disease with the HLA antigens B8, DR3, and DR7. However, in a study of 100 patients with intestinal CM allergy, no association with any HLA types was found.⁽³²⁾ The frequencies of HLA antigens have not been reported in studies of children with IgE-mediated allergy to CM.

In our study of 17 children with extreme IgE-mediated sensitivity to CM, we have not been able to find any strong associations with HLA-A, HLA-B, or HLA-DR phenotypes or with HLA-A/HLA-B haplotypes. No association was observed with other HLA-D region antigens, such as DQ (previously known as MB) and DRw52/53 (previously known as MT). Under the conditions of this study, HLA typing cannot identify infants at risk for CM atopy. However, we did not determine the DP (previously known as SB) antigens in patients. Therefore, we cannot exclude the possible association of the disease with DP, the HLA-D region that is located between DR and GLO (centromeric to DR on chromosome 6).⁽³³⁾

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