indebted to Dr. Donald Hunter and Dr. Kenneth Perry for their advice and criticism. I also thank Mrs. E. Scott, chief dietitian to the hospital, for her help, as well as the many general practitioners who co-operated in this investigation.

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# TWO CASES OF COW'S-MILK ALLERGY

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Acute allergic reactions to cow's milk in infancy are uncommon enough to justify a description of two cases that presented problems in diagnosis and management. In particular, the occurrence of ascites in one case deserves mention as a sign not previously reported.

#### Case 1

The patient, a female infant, was delivered by caesarean section after a 38-weeks' pregnancy. She was the first child of healthy parents and there was no family history of allergy. The neonatal period was uneventful. She was fully breast-fed until 3 weeks of age, when she was given a bottle feed of dried milk ("ostermilk No. 2"). Immediately after this feed she vomited, and the next day developed diarrhoea with much mucus but no blood in the stools. Rapid deterioration with fever, intense irritability, and further vomiting led to her admission to the Children's Hospital, Birmingham, on July 26, 1956, within 48 hours of the first feed of cow's milk.

On admission she was shocked with peripheral cyanosis, a fever of 103° F. (39.4° C.), pulse rate of 160, and respiration rate of 50. Her cry suggested pain. The abdomen was distended and tympanitic, but no other signs were found.

Investigations.--Cerebrospinal fluid, normal. X-ray examination (Dr. R. Astley) of chest, normal; of abdomen: "The small and large intestines are fairly full of gas, with

a few small fluid levels. In addition there is some diffuse opacity, and the abdominal distension is not entirely due to intestinal gas. Consistent with peritonitis." Paracentesis abdominis : clear straw-coloured fluid obtained without difficulty; microscopy showed some red cells, a few endothelial cells, and lymphocytes; no organisms were seen or cultured. Blood count: haemoglobin, 100% (14.8 g. per 100 ml.); W.B.C., 6,600 per c.mm. (metamyelocytes 1%, myelocytes 3%, polymorphonuclears 35%, eosinophils 1%, lymphocytes 54%, monocytes 6%). Urine, normal. Blood urea, 19 mg. per 100 ml. Stool: many fat globules, no pathogens isolated. Blood culture: Staphylococcus albus (contaminant).

Before paracentesis a diagnosis of primary peritonitis had seemed likely, but the nature of the ascitic fluid ruled this out. In the absence of a diagnosis the patient, who presented the picture of an overwhelming infection with intense toxaemia, was treated with oxygen, subcutaneous fluids, penicillin, and streptomycin. Her condition improved quickly and within a few hours of admission she tolerated oral feeds of 5% dextrose in 0.18% saline. The following day the fever had settled and she had gained 11 oz. (340 g.), but was still passing loose green motions with much mucus. The improvement continued and on the second day after admission quarter-strength feeds of dried milk (half-cream national dried milk) were started. Within a few hours she became ill once more; bile-stained vomits and frequent watery stools led to a weight loss of 6 oz. (170 g.). The pyrexia recurred, the abdominal distension increased, and a fine erythema appeared on the trunk and face. At this point the diagnosis of cow's milk allergy was first suggested. Consequently streptomycin and penicillin were discontinued and the feed was changed to expressed breast milk. The resulting improvement was dramatic; the fever settled, vomiting ceased, the motions became normal, abdominal distension subsided, and she started to gain weight.

Tests were undertaken to confirm the diagnosis of cow's milk allergy and, if possible, find a substitute for cow's milk: (1) Scratch tests\* on Infant : breast milk, negative ; half-cream national dried milk, positive; evaporated milk, positive; goat's milk, positive; "soyolk" (soya-bean milk), negative; "nutramigen" (a synthetic food in which aminoacids and simple peptides have been obtained by enzymic hydrolysis of casein), negative; "allergilac" (dried milk from which most of the lactalbumin has been removed and acid added), negative. (2) Passive transfer test\* (Prausnitz-Küstner reaction): Serum taken from the infant was injected intradermally into the mother's forearm; 24 hours later a drop of milk to be tested was placed on the skin areas thus treated and a scratch made through each drop. Control tests were carried out in untreated areas on the opposite forearm :

	" Treated " Areas	Control Areas
Breast milk Half-cream national dried	D. J.L.	Negative
Evaporated milk	. "	
Soyolk	• • • •	**

These tests confirmed the diagnosis of cow's milk allergy. but, as will be seen, were of no help in choosing a substitute.

During the next three weeks she was fed on expressed breast milk and gained over a pound (450 g.) in weight : the stools remained normal and she did not vomit. Four weeks after admission she was given a 6-oz, (170-ml.) feed of breast milk containing approximately 0.5 g. of soyolk powder. Within an hour of the feed she vomited copiously. The following day a similar feed had the same effect. The next day she tolerated a feed containing nutramigen in the

<sup>\* &</sup>quot;Positive" signifies appearance within 10 minutes of a weal and surrounding area of erythema greater than 2 cm. in diameter. "Negative" signifies absence of weal and little or no erythema. (Separation of test results into these two categories presented no difficulty.)

same dilution; during the ensuing five days the amount of nutramigen was gradually increased, but when the concentration reached eight times the original one vomiting recurred. On returning to pure breast-milk feeds vomiting ceased. Our third, and successful, choice was allergilac, which was added to breast milk at first in a dilution of 1 fl. dr. (3.5 ml.) of full-strength milk to 6 oz. (170 ml.) of breast milk; during the next nine days the amount of allergilac was increased up to full strength. She made uneventful progress and was discharged at the age of 10 weeks in excellent condition, but with a small patch of eczema on the forehead.

When she was four months old one drop of boiled cow's milk was added to each allergilac feed without ill effect, and thereafter the quantity was slowly increased, until two months later she was on full-strength cow's milk. No vomiting occurred during this period. Solids were then introduced, and she tolerated a normal toddler's diet, including cereals, eggs, meat, fish, etc. At 6 months the scratch test with cow's milk was negative and the passive transfer test gave only a slightly positive reaction.

Further progress has been uneventful, though the small patch of eczema on the forehead persisted to the age of 7 months.

### Case 2

The patient, the fourth child in the family, was born normally at term. Birth weight, 8 lb. (3,630 g.). During the pregnancy, which had been complicated by excessive vomiting, the mother took between 1 and 2 pints (570 and 1,140 ml.) of milk daily. The three siblings were healthy, but the mother had always had eczema of the hands, and a paternal uncle suffered from asthma.

During the first few days of life two complementary feeds of cow's milk were given. A rash with "blisters" appeared on the buttocks at this time and took some weeks to fade. From the end of the first week until the age of 41 months she was entirely breast-fed and thrived. Introduction of cow's milk was then tried, but each attempt led to pronounced resistance, the baby spitting out the milk vigorously; "blisters" appeared wherever milk touched the skin, and an erythematous rash occurred on face, neck, and trunk. Boiled cow's milk, three different popular dried milks and allergilac produced the same result whether given by bottle, cup, or spoon. Though there was no vomiting, she lost weight during out-patient observation. At the age of 6 months the mother's milk was failing and the infant had to be admitted to hospital to find a substitute for breast milk or, if the search proved unsuccessful, to desensitize her to cow's milk.

On admission she was contented and not obviously wasted, though her weight was only 12 lb. 8 oz. (5,585 g.). The following sensitivity tests were carried out: (1) Scratch Tests on infant: Breast milk, negative; cow's milk, positive; half-cream national dried milk, positive; full-cream national dried milk, positive; allergilac, positive; goat's milk, positive; soyolk, negative. (2) Prausnitz-Küstner reaction (intradermal injection of patient's serum into her father's forearm and scratch testing 24 hours later): No reaction to half-cream national dried milk, full-cream national dried milk, unmodified cow's milk, allergilac, soyolk, breast milk.

Soyolk therefore seemed suitable for trial. For three days this feed was given with no ill effect, although her resistance to feeding by bottle, cup, or spoon was such that it had to be given by intragastric tube. Then vomiting started and, far from being relieved by chlorpromazine, was apparently aggravated by it. Consequently, after a short period of dextrose feeding, a slow intragastric drip of breast milk was started, and vomiting ceased. At this point a barium-meal x-ray examination showed no anatomical abnormality of the oesophagus, stomach, or duodenum, but the stomach emptied slowly.

Three weeks after admission we tried goat's milk, despite the positive skin test, as an adequate supply of breast milk could not be guaranteed. A feed of 1 fl. oz. (28 ml.) of goat's milk and  $5\frac{1}{2}$  fl. oz. (156 ml.) of expressed breast milk was given, but was immediately vomited. For the next 10 days her feed consisted of breast milk alone, with two notable exceptions: one feed contained a small amount of soyolk and the other consisted of a full-strength dried milk feed given in error. These two feeds were the only ones to cause vomiting. As all these feeds were given by intragastric tube, it seems unlikely that a different taste or smell was responsible for the vomiting.

A desensitization course of cow's milk was started at the end of the fifth hospital week, when she was  $7\frac{1}{2}$  months old. A feed containing one drop of cow's milk in 8 oz. (230 ml.) of breast milk was given without incident, but when on the following day two drops were added to the feed she vomited. On this, as on the five subsequent occasions when an increase led to vomiting, no further increase was made for two or three days. After five weeks she was tolerating full-strength cow's milk.

When, during the period of desensitization, occasional feeds were offered by bottle or spoon she still refused them; and after desensitization it took five weeks of patient persistence on the part of the nursing staff before she accepted feeds from cup or spoon. Chlorpromazine was given for part of the time and seemed to help. Mixed feeding was then introduced without difficulty.

At 10 months she was discharged home, where good progress continued. Her mother had no difficulty in feeding her with solids, but at 16 months she still resented milk if it was not disguised.

## Incidence

In British paediatric practice cow's-milk allergy is regarded as uncommon and in many of our standard textbooks is not mentioned, but Sheldon (1951) and Holzel (1955) give full descriptions. In other countries estimates of its incidence vary widely. Vest (1953) discovered only nine cases among 1,500 infants seen in a 25-year period (incidence 0.06%), and Collins-Williams (1956) found an incidence of only 0.3% in 3,000 infants and children. On the other hand, De Toni and Mitolo (1955), basing their opinion on the finding of positive intracutaneous skin tests in 14% of 132 healthy infants, regard cow's milk allergy as a very common condition during the first months of life, and stress its importance in the causation of many allergic conditions. Similarly, Clein (1951) found the high incidence of 1 in 15 infants (6.7%), but he attributes to cow's milk allergy such common symptoms as colic, "always chesty and snuffly," or "very unhappy all the time."

Loveless (1950) obtained information from a poll of specialists in allergy and paediatrics and estimated the incidence to be 1.5%. In our experience the condition is rare. One of us (O. H. W.) has seen approximately 2,000 infants and children during the period in which these two cases came under our care. All would agree that severe anaphylactoid reactions, such as were described by Cumming (1928) and Ashby (1929), are rare. In 1955 Collins-Williams reported another such case and stated that it was the 30th case of acute allergic shock due to milk in the English literature. In the milder reactions the diagnosis must often remain in doubt, at least to the sceptical observer.

## Symptoms and Signs

Onset of Symptoms.—Symptoms may occur, as in our first case, immediately after the first feed of cow's milk. Vest (1953) suggested that placental transfer of antigen may then be responsible for sensitization. Collins-Williams (1955) stressed that a high milk intake during the pregnancy may be dangerous, but Clein (1951) could find no connexion between maternal milk intake during the pregnancy and subsequent development of allergy in the infant. More commonly the first symptoms occur one to five weeks after starting cow's milk or when cow's milk is reintroduced after a period of breast-milk feeding. Symptoms usually appear during the first four months except when introduction of cow's milk has been delayed until the second six months, as it was in Cumming's (1928) and Ashby's (1929) cases.

Typical symptoms are acute shock with peripheral failure, wheezing, vomiting, diarrhoea, abdominal distension, fever, and the appearance of a rash where milk touches the skin. Ashby (1929) and Rubin (1940) described the presence of blood in the stools. Some writers attribute many common symptoms in infancy to milk allergy; but we, in agreement with Bachman and Dees (1957), regard as unconvincing the evidence for milk allergy being a cause of such conditions as colic, a constant runny nose, a cough, or persistent crying. Warren (1957) described a case which presented with marasmus. Ascites, a prominent feature in our first case, has to our knowledge not been previously reported and led to much diagnostic difficulty; another unusual feature was the high fever, so that the picture at first suggested a severe infection rather than allergy. The symptoms and signs in our second case were more typical; spikes of fever again accompanied reactions.

### Diagnosis

The diagnosis is usually made on clinical grounds and without inquiry into the diet is apt to be missed. Sometimes, as in our first case, the diagnosis is not made until the second attempt at introducing cow's milk has led to relapse. The diagnosis is confirmed by the rapid improvement that occurs when cow's milk is replaced by breast milk and the recurrence of symptoms when cow's milk is reintroduced. We agree with Vest (1953) that further tests are often unnecessary and at times their results are difficult to interpret.

Direct Skin Test.—Most writers (Hill, 1939; Loveless, 1950; Miller, 1950; Rosenblum and Rosenblum, 1952; Collins-Williams, 1955; Tudor, 1956; Bachman and Dees, 1957) find this test of little value; positive results are not conclusive, and negative results do not rule out the diagnosis. If the test is of limited value in diagnosis, it gives even less help in choosing a substitute for cow's milk. Despite negative skin tests, both our patients were unable to tolerate soyolk, and Case 1 reacted similarly to nutramigen.

Passive Transfer Test (Prausnitz-Küstner Reaction). This test is useful and when positive is proof of allergy (Miller, 1950), but a negative reaction does not rule out the diagnosis. Positive reactions may be commoner in patients with acute allergy. Thus in our first case the reaction was positive, while in our second case, with less severe manifestations, it was negative.

*Eosinophils in Stools.*—Rosenblum and Rosenblum (1952) and Bigler (1955) stressed the value of this test, but Bachman and Dees (1957) found it disappointing.

### Progress

Death from milk allergy undoubtedly occurs (Holzel, 1955), and possibly is not quite as rare as a search of the literature would suggest. The clinical picture in our first case made us realize how easily we might have arrived at a mistaken diagnosis of "overwhelming infection with intense toxaemia," and if the infant had died not even the necropsy examination would have given the correct diagnosis.

In the survivors the condition is commonly self-limited and cow's milk is tolerated during the second six months of the first year (Clein, 1951; Rosenblum and Rosenblum, 1952; Vest, 1953), but according to Clein 15% of cases remain sensitive to cow's milk. As both our cases were given desensitization courses we cannot comment on this point.

Sequelae.—Eczema and other allergic manifestations were regarded as common by Rubin (1940), but as uncommon by Vest (1953) and Collins-Williams (1955). Except for a small patch of eczema in our first case we noted no such manifestations, not even when during the later

months of infancy food substances other than milk were introduced into the diet. Cumming (1928) mentioned that in his case of extreme hypersensitivity weaning was very troublesome; in our second case we had the greatest difficulty in persuading the infant to take feeds from the bottle and for long periods had to resort to feeding by oesophageal tube. Even some time after desensitization an intense distaste for cow's milk persisted and presented a real problem in management.

#### Treatment

Immediate treatment consists of withdrawal of cow's milk and, in cases of acute reactions, treatment for shock. Breast milk is the feed of choice, but if it is not immediately available a clear fluid mixture—for example, 5% sugar in one-fifth normal saline—can be used to tide the infant over the immediate emergency. A breast-milk bank provides an invaluable service for these infants, but as they may remain intolerant of cow's milk for several months it is unwise to rely entirely on this service; therefore the search for a substitute should start as soon as possible. In this search, which may be difficult and at times, as in our second case, fruitless, one has little to guide one but trial and error.

1. Evaporated Milk.—Ratner and Gruehl (1935) and Collins-Williams (1955) suggested that evaporated milk is somewhat less allergenic than boiled, dried, pasteurized, or unmodified cow's milk, but Collins-Williams's (1955) case of allergic shock occurred after evaporated milk.

2. Goat's Milk.—According to the literature on severe cow's milk allergy, goat's milk is a valuable substitute (Hill, 1939). However, our patients gave strongly positive skin reactions with goat's milk and, more significant, the second patient vomited immediately after the first trial feed.

3. Soya-bean Milk.—Most writers have had good results with this preparation (Clein, 1951; Rosenblum and Rosenblum, 1952; Vest, 1953; Ratner *et al.*, 1955; Collins-Williams, 1956; Tudor, 1956); but cases of sensitivity to it are on record (Vest, 1953), and our two cases were sensitive.

4. Nutramigen.—Unlike Rosenblum and Rosenblum (1952) we found nutramigen of no value in the patient on whom it was tried.

5. Allergilac is prepared specially for use in infantile eczema; we have not seen a mention of its use in severe cow's milk allergy, and were surprised to find it so successful in our first case.

6. Other Substitutes.—Vest (1953) suggested the flour of various nuts or 10% oatmeal porridge and wheat germs, and Holzel (1955) described a pudding made with "farex" and eggs.

Desensitization.-Vest (1953) stated that cow's milk is best avoided until cure has occurred-that is, until the infant can tolerate cow's milk without desensitization. Collins-Williams (1955) described a case in which desensitization was not started until the age of  $7\frac{1}{2}$  months, and even at  $2\frac{1}{2}$  years only four teaspoonfuls of cow's milk could be given in a day. When, as in our second case, the infant has to be reared on expressed breast milk, desensitization is urgent, as supplies of breast milk are not inexhaustible. Even when a substitute has been found, it would still seem preferable to start desensitization early, because the nutritional adequacy of the substitute food will often be in doubt (Fries, 1957) and because weaning on to solid foods will be easier if the patient can already tolerate cow's milk. We suggest that desensitization is started when the infant has fully recovered from the acute allergic illness and is making a satisfactory gain in weight. In the first case this was three months after admission, at the age of 4 months, and in the second case five weeks after admission, at the age of  $7\frac{1}{2}$  months.

### Summary

Two cases of severe cow's-milk allergy are described. In one patient, in addition to the severe collapse produced by the first feed of cow's milk, ascites was a presenting feature and caused diagnostic difficulty. In the second patient gastro-intestinal symptoms and urticaria after feeding with cow's milk were followed by refusal of milk which persisted for some weeks after desensitization.

Diagnosis of cow's-milk allergy is mainly clinical. The passive transfer test is a useful aid, but the direct skin test is of little value. Treatment consists in withdrawal of cow's milk and substitution of a suitable alternative, the choice of which is a matter of trial and error. Alternatively, desensitization to the milk is carried out.

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# **DIABETIC COMA IN INFANCY\***

#### BY

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During infancy diabetes mellitus presents as an acute metabolic disturbance.

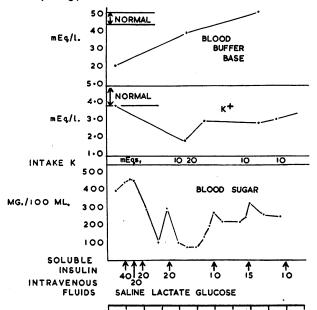
Both Gaisford and Lightwood (1954) and Paterson (1956) state that diabetes is very rarely seen under the age of 1 year, but Schwartzman et al. (1947) collected details of 57 cases in this age group, and Keidan (1955), reviewing the literature, added 22 cases, six of these being transient in the first month of life.

Since that time sporadic cases only have been reported, but details of the following two cases are presented "to augment the knowledge of this group" (Schwartzman et al., 1947). As guidance on the management of diabetic coma in small babies is difficult to obtain, certain aspects of treatment have been discussed. These comments are based on experience in these two cases, on a further two cases in patients under the age of 2 years (not reported here), and on the available literature. Recent experience in the treatment of problems in adult diabetic coma has been utilized and adapted.

## Case 1

A full-term female baby born on October 30, 1954 (Birth weight 2.6 kg.), progressed normally until she was first admitted to hospital on July 10, 1955, with irritability, cough, loose bowel motions, and temperature suggesting an infection of the upper respiratory tract. Various investigations were carried out with negative results, and the temperature slowly settled on penicillin therapy. At this time the urine showed a trace of reducing substance on one occasion, but not on four other occasions. The C.S.F. sugar was 80 mg./100 ml. She was discharged home five weeks later with a diagnosis of recurrent bronchitis.

She was readmitted on October 18, at the age of  $11\frac{1}{2}$ months, with a cough and rapid respiration and dehydration, the diagnosis being pneumonia. By next morning drowsiness had increased and a diagnosis of probable diabetic acidosis was made. Blood sugar was 400 mg./100 ml. and serum electrolytes showed a severe primary metabolic acidosis with pH 7.18; CO<sub>2</sub> tension, 22 mm. Hg; blood buffer base, 26 mEq/l.; bircarbonate 7.8 mEq/l.; sodium, 146 mEq/l.; potassium, 3.6 mEq/l.; chlorides, 120 mEq/l. Serum keto-acids were 180 mg./100 ml. Her weight was 18 lb. (8.1 kg.).



HOURS O 6 12 18 24 30 36 42 48 54 60 66 FIG. 1.-Details of treatment, showing blood-sugar levels, serum potassium levels, and improvement in acidosis in Case 1.

Soluble insulin was started at 1 p.m., and Fig. 1 shows that an initial insulin dosage of 80 units was required before some control of the blood sugar was obtained. The blood buffer base rose steadily with the correction of the acidosis and with 150 ml. of 1/6 molar sodium lactate solution given intravenously.

The initially rather low potassium fell to 1.7 mEq/l. within 24 hours of starting treatment. During this period calcium gluconate was given intravenously on two occasions for fits of a decerebrate nature with relief of twitchings. On these two occasions the blood sugar was 350 mg. and 110 mg. respectively. (The low serum potassium may have played some part in her slow recovery from drowsiness, but the irritability may have been related to the relative increase in alkalinity.) After the first 24 hours soluble insulin was given according to urine tests three times daily, the total daily dosage being 20-30 units.

Insulin zinc suspension was begun on the fourth day, when solid foods were again taken. The dosage was steadily increased, and she was finally discharged after a respiratory infection on 20 units of I.Z.S. and a 1,200 calorie diet. Before discharge the chest x-ray picture was clear and the ocular fundi were reported normal by the ophthalmologist.

Over the next year she was on a diet averaging 1,200 calories (distributed as protein 40 g., carbohydrate 160 g., and fat 40 g.) and gained 11 lb. (5 kg.), to weigh 29 lb. (13.2 kg.) and measure 34 in. (86 cm.). The height and weight are at the upper limit of normal for her age.

The insulin dosage for this age and weight was 16 units of I.Z.S., and the blood sugars two and a half and two hours after meals were 95 and 105 mg./100 ml.

<sup>\*</sup>Based on papers read before the Annual Meeting of the New Zealand Paediatric Association in 1956 and 1957.