Cow's milk protein intolerance

Transient food intolerance of infancy

In the past most reports of cow's milk protein intolerance or cow's milk allergy have centred upon immunological investigations. Anderson and Schloss in 1923 found antibodies to cow's milk protein in the sera of infants exposed to cow's milk, but the presence in the serum of cow's milk antibodies cannot *per se* be equated with clinical intolerance to this protein. While it is true that clinical cow's milk protein intolerance is often associated with high titres of such antibodies, these levels may also be found in some children with coeliac disease who clinically do not have intolerance to cow's milk. Skin tests may on occasion be a useful diagnostic test, but in one report only 59% of children with cow's milk protein intolerance had positive tests (Goldman *et al.*, 1963). Matthews and Soothill (1970) have reported interesting work on the effect of milk feeding on complement activation in children with cow's milk protein intolerance, but there is at present no single immunological investigation generally available which is invariably positive in children with cow's milk allergy, and the diagnosis is usually based on clinical criteria. It indeed seems probable that several different types of immune response may be involved in this syndrome: IgE antibodies giving positive skin tests, IgG and IgM antibodies giving raised titres for serum antibodies, and abnormalities of cell-mediated immunity leading to abnormal lymphocyte transformation tests (Fontaine and Navarro, 1975).

Paediatric gastroenterologists are now paying increasing attention to diseases causing abnormality of the small intestinal mucosa, i.e. small intestinal enteropathies, other than coeliac disease. Notable among these is cow's milk protein intolerance. It now appears that typically the proximal small intestinal mucosa in this disorder is abnormal when biopsied, as described in this issue of the *Archives* by workers in Helsinki (Kuitunen *et al.*, 1975) and in Paris (Fontaine and Navarro, 1975). Although the severity of this mucosal abnormality on biopsy, unlike coeliac disease, is clearly very variable from child to child, Kuitunen and his

colleagues found about half their children had a flat small intestinal mucosa indistinguishable from that observed in coeliac disease, whereas Fontaine and Navarro found *partial* villous atrophy to be the most common finding on small intestinal biopsy. Some of the children they have reported had only minor mucosal abnormalities on biopsy. Occasionally a normal small intestinal mucosa has been described in this disorder.

Diagnostic criteria

Many paediatricians have been sceptical in the past about making the diagnosis of cow's milk allergy. This has often been due to difficulty in fulfilling the diagnostic criteria for cow's milk protein intolerance as described by Goldman and his colleagues in 1963, and widely quoted subsequently. These criteria are as follows.

- (1) Symptoms subside after dietary elimination of milk.
- (2) Symptoms recur within 48 hours after milk challenge.
- (3) Reactions to three such challenges must be positive and have a similar onset duration and clinical features.

It is now clear that these criteria, while basically sound, are too rigid and lead to underdiagnosis of this disorder. It is often impractical, and indeed unacceptable to some mothers, for repeated milk challenges at short intervals to be undertaken. Most clinicians now would accept one positive challenge as strong evidence in favour of this diagnosis. Further, the Helsinki workers have produced evidence that it may take up to a month after re-exposure to milk for some infants to have a recurrence of symptoms. Clinicians will also agree it is sometimes difficult to interpret the results of a challenge, e.g. the return of vomiting or diarrhoea after a milk challenge may be due to an intercurrent illness.

There is also often the difficulty in differentiating this disorder from the other major cause of milk

intolerance in infancy, i.e. lactose intolerance. It now appears that lactose intolerance may accompany cow's milk protein intolerance and it may be difficult to unravel the two disorders by a response to milk elimination diets alone (McNeish, 1974).

Elimination of cow's milk protein from the diet of an infant is usually effected by putting the child on a substitute milk. The Table indicates some of the commercial substitute formulae readily available in Britain at present. The first three formulae are based on soy protein. Pregestimil

TABLE
Commercial milk substitutes

Milk substitute	Manufacturer	Sugar
Velactin	Wander	Sucrose
Prosobee	Mead Johnson	Sucrose
(liquid)		
Sobee	"	Sucrose
(powder)		
Pregestimil	"	Glucose

contains charcoal-treated, enzyme-hydrolysed casein, and so may not be effective in all cases of milk allergy. With knowledge of the sugar content of these feeds it is clear that they are all effective in the management of lactose intolerance, as well as cow's milk protein intolerance. So a clinical response after starting one of these substitutes will not differentiate the two disorders. Nutramigen (Mead Johnson), which is often used in the management of lactose intolerance, contains hydrolysed casein and therefore may also be equally effective in many infants with cow's milk protein intolerance.

Sometimes infants also cannot tolerate these milks, in which case comminuted chicken meat, with additions of monosaccharide and minerals as appropriate, may be useful. Goat's milk is not usually recommended as there often is cross-reactivity with cow's milk protein.

In addition to these special milks, care must be taken to ensure that the infant's solids are free of cow's milk. Many proprietary foods sold in tins and jars do contain some milk products.

A further difficulty in making the diagnosis of cow's milk protein intolerance stems from its very transience. If challenges are delayed after the age of one year no intolerance may then be present. The importance of making this diagnosis is firstly to manage infants effectively with appropriate feeds, and secondly to differentiate this syndrome from other disorders of the small intestinal mucosa in infancy, in particular coeliac disease, giardiasis, and the postgastroenteritis syndrome.

Many infants at present in whom the diagnosis of cow's milk protein intolerance is eventually made will have a small intestinal biopsy performed in the initial assessment, as these infants often present in a gastrointestinal manner with many clinical features resembling coeliac disease or the postgastroenteritis syndrome. Whenever an abnormal small intestinal mucosa is found on biopsy in an infant under the age of one year the diagnosis of cow's milk protein intolerance must be considered if the infant is having cow's milk feed. It must now be realized that even when the mucosa is flat in this age group, cow's milk allergy as well as coeliac disease is a diagnostic possibility. The two disorders may occur together (Kuitunen *et al.*, 1975). If this diagnosis is considered possible, then a trial of a milk-free diet should be undertaken. Once clinical recovery has occurred, and before a clinical challenge with milk, a further small intestinal biopsy may be of value to show improvement in the mucosa after milk elimination. Once clinical relapse appears to have occurred, and this, as mentioned before, may be equivocal or unequivocal, it may be of particular value to perform yet another biopsy to show histological deterioration. Thus, by using serial biopsies in addition to a single clinical challenge it may be clearly shown that the infant's small intestinal mucosa is sensitive to milk (Kuitunen *et al.*, 1973) (see Fig.). The wider use of small intestinal biopsy in this way for such children may lead to the recognition and effective management of hitherto undiagnosed cases. Examination of such serial biopsies should include assessment of crypt length, epithelial cell height, lymphocyte infiltrate, etc., as well as overall morphology.

Pathogenesis

Why does this state of transient intolerance to cow's milk protein occur? It is probable that this group of infants has excessive antigen entry across the small intestinal epithelium. This could be due to a transient immunodeficiency state as described by Taylor *et al.*, (1973) who suggested that transient IgA deficiency in infancy may predispose to the development of atopy including cow's milk protein intolerance. It could also be due to small intestinal mucosal damage from any cause. Both factors could operate together.

There are other syndromes of transient food protein intolerance in infancy, and as Kuitunen and his colleagues make clear, these may coexist. They include intolerance to soy protein (Mendoza, Meyers, and Snyder, 1970; Ament and Rubin, 1972) and wheat protein; the latter is often known as transient gluten intolerance (Dicke, 1952; Visa-

FIG.—(a) Small intestinal biopsy at diagnosis in an infant with cow's milk protein intolerance. (b) Second biopsy after milk-free diet. (c) Third biopsy 48 hours after milk challenge. (With acknowledgements to Dr. N. France, Queen Elizabeth Hospital for Children.)

korpi and Immonen, 1967; Walker-Smith, 1970). It is now becoming clear that in all these forms of transient food protein intolerance there is usually an abnormality of the small intestinal mucosa, i.e. an enteropathy present, though the mucosal abnormality may often not be as severe as that found in children with coeliac disease.

The cause of this mucosal damage is uncertain. It could be due to the food protein itself associated with some altered immunological reactivity of the mucosa, or else it could be a secondary phenomenon. Harrison (1974) has provided some evidence that acute gastroenteritis may be followed not only by lactose intolerance but also by cow's milk protein intolerance, which may be longer lasting than the state of lactose intolerance.

This could be due to altered immunological reactivity via one of the allergic reactions as classified by Gell and Coombs (1968) namely type I, i.e. anaphylactic reaction, IgE-mediated; type II, i.e. antigen-antibody reaction with complement activation and immune complex formation; and type IV, i.e. delayed hypersensitivity with cell-mediated immune reaction. All are possible and may be variously involved in individual children. Evidence that these three types of reaction may occur in children with cow's milk protein intolerance was cited earlier. Doe, Henry and Booth (1974) have produced evidence that immune complex formation occurs in another enteropathy (coeliac disease), and Ferguson (1974) has shown in experimental animals that cell-mediated immunity may be important in the genesis of an abnormal small intestinal mucosa. The involvement of IgE in the immunological response of the lamina propria to milk challenge in children with cow's milk protein intolerance has recently been shown by Shiner and her colleagues (Shiner, Ballard, and Smith, 1975) and also by Kilby and her co-workers (Kilby, Walker-Smith, and Wood, 1975). The type of abnormal immune reaction in any given child with this disorder is likely to influence the type of clinical response to a cow's milk challenge.

It is clear that detailed study of the small intestinal mucosa and its immune mechanisms

offer an important way of increasing our understanding of cow's milk protein intolerance in infancy.

REFERENCES

- Ament, M. E., and Rubin, C. E. (1972). Soy protein—another cause of the flat intestinal lesion. *Gastroenterology*, **62**, 227.
- Anderson, A. F., and Schloss, O. M. (1923). Allergy to cow's milk in infants with nutritional disorders. *American Journal of Diseases of Children*, **26**, 451.
- Dicke, W. K. (1952). De subacute chronische en recidiverende darmstoornis van de kleuter. *Nederlandsch Tijdschrift voor Geneeskunde*, **96**, 1860.
- Doe, W. F., Henry, K., and Booth, C. C. (1974). Complement in coeliac disease. *Coeliac disease. Proceedings of the Second International Symposium*. Stenfort Kroese, Leiden.
- Ferguson, A. (1974). Thymus-dependence of experimental villous atrophy. *Coeliac Disease. Proceedings of the Second International Coeliac Symposium*. Stenfort Kroese, Leiden.
- Fontaine, J. L., and Navarro, J. (1975). Small intestinal biopsy in cow's milk protein allergy in infancy. *Archives of Disease in Childhood*, **50**, 357.
- Gell, P. G. J., and Coombs, R. R. A. (1968). *Clinical Aspects of Immunology*, 2nd ed. Blackwell Scientific Publications, Oxford.
- Goldman, A. S., Anderson, D. W., Sellers, W. A., Saperstein, S., Kniker, W. T., and Halpern, S. R. (1963). Milk allergy. *Pediatrics*, **32**, 425.
- Harrison, M. (1974). Sugar malabsorption in cow's milk protein intolerance. *Lancet*, **1**, 360.
- Kilby, A., Walker-Smith, J. A., and Wood, C. B. S. (1975). Small-intestinal mucosa in cow's milk allergy. *Lancet*, **1**, 531.
- Kuitunen, P., Rapola, J., Savilahti, E., and Visakorpi, J. P. (1973). Response of the jejunal mucosa to cow's milk in the malabsorption syndrome with cow's milk intolerance: a light and electron microscope study. *Acta Paediatrica Scandinavica*, **62**, 585.
- Kuitunen, P., Visakorpi, J. K., Savilahti, E., and Pelkonen, P. (1975). Malabsorption syndrome with cow's milk intolerance: clinical findings and course in 54 cases. *Archives of Disease in Childhood*, **50**, 351.
- McNeish, A. S. (1974). The role of lactose in cow's milk intolerance. *Acta Paediatrica Scandinavica*, **63**, 652.
- Matthews, T. S., and Soothill, J. F. (1970). Complement activation after milk feeding in children with cow's milk allergy. *Lancet*, **2**, 893.
- Mendoza, J., Meyers, J., and Snyder, R. (1970). Soy bean sensitivity case report. *Pediatrics*, **46**, 774.
- Shiner, M., Ballard, J., and Smith, M. E. (1975). The small-intestinal mucosa in cow's milk allergy. *Lancet*, **1**, 136.
- Taylor, B., Norman, A. P., Orgel, H. A., Stokes, C. R., Turner, M. W., and Soothill, J. F. (1973). Transient IgA deficiency and pathogenesis of infantile atopy. *Lancet*, **2**, 111.
- Walker-Smith, J. (1970). Transient gluten intolerance. *Archives of Disease in Childhood*, **45**, 523.
- Visakorpi, J. K., and Immonen, P. (1967). Intolerance to cow's milk and wheat gluten in the primary malabsorption syndrome in infancy. *Acta Paediatrica Scandinavica*, **56**, 49.

JOHN WALKER-SMITH

Department of Child Health, Royal Hospital of St. Bartholomew, West Smithfield, London EC1A 7BE.