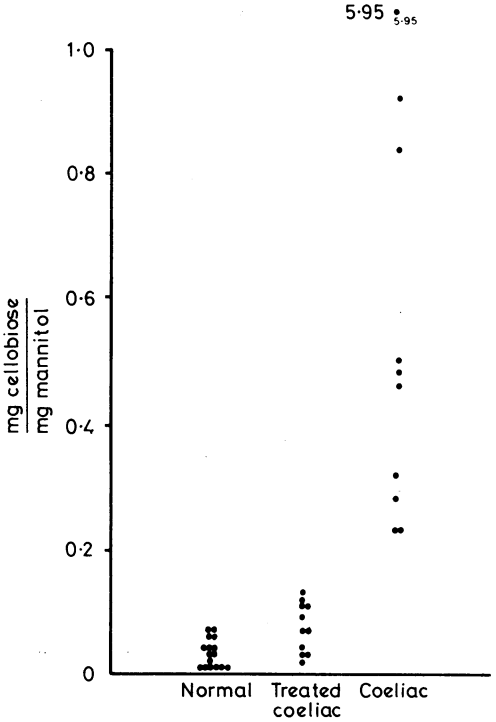
In this patient it merged into what, in retrospect, was the first symptom of the shoulder-hand syndrome. Whether the pain itself or the resulting immobility with impairment of the venous and lymphatic pumping mechanism[4] triggers the development of the syndrome is unknown, but in any event it seems that laparoscopic sterilisation can be added to the long list of potential precipitating factors.[1] The history of psychiatric illness in this patient may also be relevant.[5] As this case shows, the illness can be lengthy, disabling, and resistant to treatment, particularly when diagnosis is delayed.[2 3] The syndrome is uncommon, particularly in young people,[2] and early diagnosis will depend on being alert to the possibility.

We thank Dr W D Alexander for permission to report this case.

[1] Steinbrocher, O, and Argyros, T S, *Medical Clinics of North America*, 1958, **42**, 1533.
[2] *Lancet*, 1974, **1**, 850.
[3] Woolf, D, *Practitioner*, 1974, **213**, 176.
[4] Moberg, B, *Surgical Clinics of North America*, 1960, **40**, 367.
[5] Fleming, A, *et al*, *Annals of the Rheumatic Diseases*, 1976, **35**, 456.

(*Accepted 1 August 1978*)

Department of Medicine, Gardiner Institute, Western Infirmary, Glasgow G11 6NT
L C K LOW, BSC, MRCP, medical registrar
D C McCRUDEN, BSC, MRCP, medical registrar
L E RAMSAY, MB, MRCP, lecturer in medicine



Ratio of cellobiose to mannitol in five-hour urinary collections. Values in all three groups differed significantly from each other ($P<0.01$ Mann-Whitney test).

Intestinal permeability assessed by excretion ratios of two molecules: results in coeliac disease

The small intestinal mucosa in coeliac disease is abnormally permeable to large molecules—for example, intact proteins,[1] and disaccharides[2] —but relatively impermeable to small molecules, such as xylose. We have studied the simultaneous absorption of two molecules one of which should be absorbed in increased and the other in decreased amounts by patients with coeliac disease.

Method and results

The molecules were cellobiose, a disaccharide of molecular radius 5 Å, and mannitol, a polyhydric alcohol of radius 4 Å. The test solution comprised 5 g cellobiose and 2 g mannitol in 100 ml, to which was added 20 g sucrose and 20 g lactose to make it hypertonic (1500 mmol (mosmol)), a compromise dictated by problems of palatability and solubility. This was drunk after fasting overnight and emptying the bladder on rising. All urine passed was collected over the subsequent five hours. Mannitol was assayed by a modification of the method of Corcoran and Page.[3] Cellobiose was assayed by quantitative paper chromatography.[4] Three groups of subjects carried out the test, both inpatients and outpatients: 10 untreated adults with villous atrophy, 11 treated patients with coeliac disease, and 16 patients with normal jejunal histological appearances.

Control patients excreted about 20% (range 10·0-51·1) of ingested mannitol in five hours, and 0·5% (range 0·02-0·62) of cellobiose. Patients with villous atrophy excreted significantly less mannitol (range 1·2-9·7% $P<0.01$ Mann-Whitney test) and more cellobiose (range 0·34-2·76% $P<0.01$) than controls. Patients with treated coeliac disease had intermediate values. The ratios of cellobiose to mannitol excretion (see figure) clearly separate untreated patients with coeliac disease from the other groups.

Comment

Menzies[2] showed that after an oral load patients with coeliac disease excreted more lactulose than controls. This effect was enhanced when the test solution was hypertonic. We used cellobiose in preference to lactulose because it is cheaper in pure form. Although there is some cellobiase activity in human intestinal mucosa, we have shown no significant difference from lactulose in its excretion in normal subjects or in patients with coeliac disease ($P>0.2$), under the conditions of this test. We preferred mannitol to xylose, as the latter is partly actively absorbed.

The reason for the contrasting behaviour of the two molecules is speculative. The intestinal barrier has been regarded as a lipid membrane perforated by water-filled pores of a finite radius, which some workers[5] have estimated to be about 4 Å. This may account for the relative ease with which mannitol passes compared with cellobiose, both molecules being highly water soluble.

In coeliac disease loss of intestinal surface area may result in there being fewer pores through which the mannitol can diffuse. The increased permeability to cellobiose probably reflects mucosal damage. Alternatively, the increased cell turnover which occurs in the disease implies that there may be more extrusion zones, through which large molecules might pass.

Measuring simultaneous absorption of these water-soluble molecules shows two aspects of intestinal permeability which are abnormal in coeliac disease. When expressed as a ratio it results in excellent discrimination of untreated patients from treated ones or normal subjects. It should also minimise errors due to non-mucosal factors (such as renal function). Preliminary data confirm this and we would expect fewer false-positive results than with the xylose test. We have found it useful both for screening and for following the response to treatment.

We thank the professorial medical unit for laboratory space and use of equipment, and the staff of the hospital pharmacy for help in preparing the solutions. IC is in receipt of a grant from the West Riding Research Fund.

[1] Kivel, R M, Kearns, D H, and Liebowitz, D, *New England Journal of Medicine*, 1964, **271**, 769.
[2] Menzies, I S, *Gut*, 1972, **13**, 847.
[3] Corcoran, A C, and Page, I H, *Journal of Biological Chemistry*, 1947, **170**, 165.
[4] Menzies, I S, *Journal of Chromatography*, 1973, **81**, 109.
[5] Lindemann, B, and Solomons, A K, *Journal of General Physiology*, 1962, **45**, 801.

(*Accepted 18 July 1978*)

Gastroenterology Unit, The General Infirmary, Leeds LS1 3EX
I COBDEN, MB, MRCP, research registrar
R J DICKINSON, BSC, MRCP, registrar
J ROTHWELL, technician
A T R AXON, MD, MRCP, consultant physician