4 Kazdin AE. *Conduct disorders in childhood and adolescence*. London: Sage, 1995.
5 Farrington DP. The development of offending and antisocial behaviour from childhood: key findings from the Cambridge study in delinquent development. *J Child Psychol Psychiatry* 1995;36:929-64.
6 Robins LN, Price RK. Adult disorders predicted by childhood conduct problems: results from the NIMH epidemiologic catchment area project. *Psychiatry* 1991;54:116-32.
7 Rutter M, Giller H. *Juvenile delinquency*. Harmondsworth: Penguin, 1983.
8 Bailey V, Graham P, Boniface D. How much child psychiatry does a general practitioner do? *J R Coll Gen Pract* 1978;28:621-6.
9 Scott S. Mental retardation. In: Rutter M, Taylor E, Hersov L, eds. *Child and adolescent psychiatry: modern approaches*. 3rd ed. Oxford: Blackwell Scientific, 1994.
10 Garralda E, Bailey D. Psychiatric disorders in general paediatric referrals. *Arch Dis Child* 1989;64:1727-33.
11 Goldsmith HH, Gottesman II. Heritable variability and variable heritability in developmental psychopathology. In: Lenzenweger MF, Haugaard JJ, eds. *Frontiers of developmental psychopathology*. Oxford: Oxford University Press, 1995.
12 Bohman M. Predisposition to criminality Swedish adoption studies in retrospect. In: Rutter M, ed. *Genetics of criminal and antisocial behavior*. Chichester: Wiley, 1996. (CIBA Foundation symposium 194.)
13 Rutter M. *Genetics of criminal and antisocial behaviour*. Chichester: Wiley and Sons, 1996.
14 Farrington DP. Early developmental prevention of juvenile delinquency. *Criminal Behaviour and Mental Health* 1994;4:209-27.
15 Patterson GR, Reid JB, Dishion JT. *Antisocial boys*. Eugene, OR: Castalia, 1992.
16 Gardner EM. Parent-child interaction and conduct disorder. *Educ Psychol Rev* 1992;2:135-63.
17 Lyons-Ruth, K. Attachment relationships among children with aggressive behavior problems: the role of disorganized attachment patterns. *J Consult Clin Psychol* 1996;64(1):64-73.
18 Fonagy P, Steele H, Steele M. Maternal representations of attachment during pregnancy predict the organization of infant-mother attachment at one year of age. *Child Dev* 1991;62:891-905.
19 Dodge KA, Lochman JE. Social-cognitive processes of severely violent, moderately aggressive and non-aggressive boys. *J Consult Clin Psychol* 1994;62:366-74.
20 Kupersmidt KB, Coie JD, Dodge KA. The role of poor peer relationships in the development of disorder. In: Asher SR, Coie JD, eds. *Peer rejection in childhood*. Cambridge: Cambridge University Press, 1990.
21 Hinshaw S. Externalizing behaviour problems and academic underachievement in childhood and adolescence: causal relationships and underlying mechanisms. *Psychol Bull* 1992;111:127-55.
22 Goodman R, Stevenson J. A twin study of hyperactivity: I. An examination of hyperactivity scores and categories derived from Rutter teacher and parent questionnaires. II. The aetiological role of genes, family relationships, and perinatal adversity. *J Child Psychol Psychiatry* 1989;30:671-710.
23 Taylor E, Chadwick O, Heptinstall E, Danckaerts M. Hyperactivity and conduct problems as risk factors for adolescent development. *J Am Acad Child Adolesc Psychiatry* 1996;35:1213-26.
24 Moffitt TE, Lynam D, Silva PA. Neuropsychological tests predict persistent male delinquency. *Criminology* 1994;32:101-24.
25 Quinton D, Pickles A, Maughan B, Rutter M. Partners, peers, and pathways: assortative pairing and continuities in conduct disorder. *Dev Psychopathol* 1993;5:763-83.
26 Scott S. Measuring oppositional and aggressive behaviour. *Child Psychol Psychiatry Review* 1996;1:104-9.
27 Loeber R. Antisocial behaviour: more enduring than changeable? *J Am Acad Child Adolesc Psychiatry* 1991;30:393-7.
28 Bank L, Marlowe JH, Reid JB, Patterson GR, Weinrott MR. A comparative evaluation of parent-training interventions for families of chronic delinquents. *J Abnorm Child Psychol* 1991;19:15-33.
29 Farrington P. *Understanding and preventing youth crime*. York: Joseph Rowntree Foundation, 1996.
30 Webster-Stratton C, Hollinsworth T, Kolpacoff M. The long-term effectiveness and clinical significance of three cost-effective training programs for families with conduct-problem children. *J Consult Clin Psychol* 1989;57:550-3.
31 Webster-Stratton C, Herbert M. *Troubled families—problem children. Working with parents: a collaborative process*. Chichester: Wiley, 1994.
32 McCord J. The Cambridge-Somerville study: a pioneering longitudinal experimental study of delinquency prevention. In: McCord J, Tremblay RE, eds. *Preventing antisocial behaviour—interventions from birth through adolescence*. New York: Guilford Press, 1992.
33 Dadds MR, McHugh TA. Social support and treatment outcome in behavioral family therapy for child conduct problems. *J Consult Clin Psychol* 1992;60:252-9.
34 Puckering C, Rogers J, Mills M, Cox D, Mattson-Graff M. Process and evaluation of a group intervention for mothers with parenting difficulties. *Child Abuse Rev* 1994;3:299-310.
35 Pfiffner LJ, Barkley RA. Educational placement and classroom management. In: Barkley R, ed. *Attention deficit hyperactivity disorder: a handbook for diagnosis and treatment*. New York: Guilford Press, 1991.
36 Hannon P. *Literacy, home and school: research and practice in teaching literacy with parents*. Falmer: Falmer Press, 1995.
37 Prinz RJ, Blechman EA, Dumas JE. An evaluation of peer coping-skills training for childhood aggression. *J Clin Child Psychol* 1994;23:193-203.
38 Levin DE. Making peace in violent times: a constructivist approach to conflict resolution. *Young Children* 1992:47;4-13.
39 Schweinhart LJ, Weikart DP. *A summary of significant benefits: the High Scope Perry pre-school study through age 27*. Ypsilanti, MI: High Scope, 1993.
40 McCord J, Tremblay RE, Vitaro F, Desmarais-Gervais L. Boys' disruptive behaviour, school adjustment, and delinquency: The Montreal prevention experiment. *Int J Behav Dev* 1994;17:739-52.


*Lesson of the week*

# Emergence of classic enteropathy after longstanding gluten sensitive oral ulceration

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**Patients with recurrent oral ulcers may have gluten sensitivity and subsequently develop coeliac enteropathy**

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continued over

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The mechanisms responsible for recurrent oral ulcers have yet to be defined. Oral ulcers occur in several conditions, including connective tissue disease, viral infections, and gastrointestinal disorders such as inflammatory bowel disease and gluten sensitive enteropathy or coeliac disease. Treatment of gluten sensitivity with a diet that is free of gluten results in resolution of small intestinal lesions and often also oral ulcers.[1] While some patients present with gluten sensitivity and recurrent oral ulcers without gastrointestinal abnormalities,[2] the possibility that some of these patients may subsequently develop enteropathy has not been confirmed. We report on a patient with gluten sensitivity and oral ulcers who developed abnormalities of the small intestine without gastrointestinal symptoms after many years of surveillance.

## Case report

A 14 year old boy presented to the coeliac outpatient clinic in St James's Hospital, Dublin, with a history of oral ulcers since 3 years of age. His mother had longstanding coeliac disease but had had no oral ulcers; there was no other family history of coeliac enteropathy or oral ulcers. When the patient was 13 years old investigations showed normal jejunal histology.

At presentation his antibody concentrations to gliadin were raised (31.0 arbitrary units/ml, normal range 0 to 3 arbitrary units/ml; reference range based on a protocol developed at St James's Hospital, Dublin). A duodenal biopsy at this time showed no abnormality. The patient's ulcers resolved after he was put on a diet free of gluten; the concentration of antibodies to gliadin fell to 14 arbitrary units/ml within six months. As the patient may have had latent coeliac disease he was challenged with a normal diet containing gluten for four months; the ulcers recurred and the concentration of antibodies to gliadin increased to 16 arbitrary units/ml. A duodenal biopsy at this time was normal (fig 1 (left)) and the patient had no gastrointestinal symptoms.

At 20 years of age the patient presented again with severe oral ulcers after he had followed a normal diet. During the intervening six years he had developed oral ulcers whenever he consumed a normal diet, but these had resolved when he reverted to a diet free of gluten. On presentation the patient had high concentrations of antibodies to gliadin (>32 arbitrary units/ml), and he was also positive for antibodies to endomysium, which were available for the first time. Antibodies to both gliadin and endomysium are increasingly tested to detect and monitor patients with gluten sensitive disorders, and provide a sensitive and non-invasive means of diagnosing and following such patients. Haematological investigations including full blood counts and folate concentration were normal throughout. The patient independently resumed a diet free of gluten to relieve his ulcers; a duodenal biopsy performed four weeks later showed features consistent with coeliac disease that had been partially treated–that is, fusion of villi, inflammatory cell infiltration of the lamina propria, and increased numbers of intraepithelial lymphocytes (fig 1 (right)). When the patient resumed a diet free of gluten, duodenal histology and the concentrations of endomysial and gliadin antibodies returned to normal.

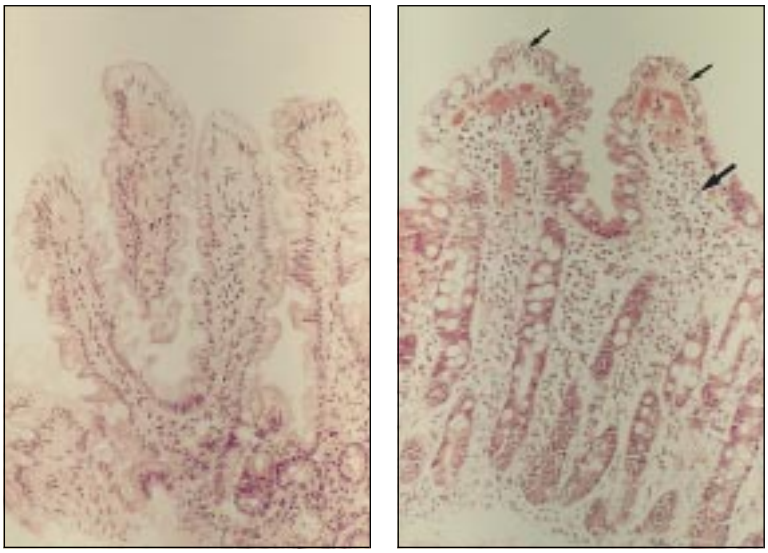

**Fig 1** (left) Normal villus morphology in patient with sensitivity to gluten and recurrent oral ulcers (×10). (right) Enteropathic changes including increased numbers of intraepithelial lymphocytes (small arrows) and inflammatory cell infiltration of lamina propria (large arrow) in patient with recurrent oral ulcers and sensitivity to gluten (×10)

## Discussion

Recurrent oral ulcers may be associated with gluten sensitivity both in people wih classic coeliac disease and in those with no intestinal abnormalities. About 4% of patients with recurrent oral ulcers have underlying gluten sensitive enteropathy.[1 3] Our patient developed gastrointestinal abnormalities consistent with coeliac disease after clinical manifestations of sensitivity to gluten were confined to the oral cavity for a prolonged time. Our group's previous study of 10 patients with sensitivity to gluten and recurrent oral ulcers showed clinical and serological relapse after challenge with gluten, although there was no histological or symptomatic evidence of gastrointestinal disease.[4] This patient also showed no abnormality in the three original biopsy specimens of small intestine taken when oral ulcers were present.

We suggest that all patients with recurrent oral ulceration should be tested for sensitivity to gluten by measuring endomysial and gliadin antibody concentrations and response to a diet free of gluten. Once this subgroup of patients has been identified they need close monitoring for villus atrophy as enteropathy may develop after several years. As ours seems to be the first case in which delayed onset enteropathy has been identified we do not know how often biopsies are needed. Biopsy surveillance every one to two years is probably sufficient, although any increase in antibody concentrations would necessitate more urgent investigation. Given the importance of keeping to a diet free of gluten to minimise the risk of complications, including malignancy, patients who are sensitive to gluten and develop recurrent oral ulcers need to be identified early if appropriate treatment is to be started.


1 Ferguson MM, Wray D, Carmichael HA, Russell RI, Lee FD. Coeliac disease associated with recurrent aphthae. *Gut* 1980;21:223-6.
2 Wray D. Gluten sensitive recurrent aphthous stomatitis. *Dig Dis Sci* 1981;26:737-40.
3 Wray D, Ferguson MM, Hutcheon AW, Dagg JH. Nutritional deficiencies in recurrent aphthae. *J Oral Pathol* 1978;7:418-23.
4 O'Farrelly C, O'Mahony C, Graeme-Cook F, Feighery C, McCartan B, Weir D. Gliadin antibodies identify gluten-sensitive oral ulceration in the absence of villous atrophy. *J Oral Pathol Med* 1991;20;476-8.


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### Correction

*General management of end stage renal disease*

An editorial error occurred in this Recent Advances by Robert Walker (29 November 1997, pp 1429-32). The legend of the figure should have said it was reprinted with permission from Parfrey PS, Harnett JD, Foley RN. Heart failure and ischaemic heart disease in chronic uraemia. *Curr Opin Nephrol Hypertens* 1995;4:105-10.

*One hundred years ago*

## The Queen's visit to the Riviera

The arrangements for the Queen's visit to Nice are now, we understand, quite complete, and we are able to confirm our previous statement that the sanitary matters which were in dispute at the beginning of the season have been arranged satisfactorily. Everything in the Regina Hotel, Cimiez, and in its neighbourhood is in excellent order from the sanitary point of view. Her Majesty will have the enjoyment of the same fine set of gardens, some sixty acres in extent, for her morning drives in her donkey carriage, as before. The winter in Nice has been very dry, and except that there has been an epidemic of influenza of a mild average type the health of the town has been good. The influenza epidemic now shows signs of diminishing. (*BMJ* 1898;i:648)