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used to alter intestinal permeability in the laboratory animal is 250 mmol/l[8,9] whereas the quantity of ^{51}Cr-EDTA used in our tests is less than 1 μmol.

The physiological inertness of ^{51}Cr-EDTA has been well documented[10] as a consequence of its widespread use as a premeability marker and its routine use to measure glomerular filtration rate. The fact that we found a deficit even in patients who were histologically normal can be explained most simply by the greater precision and sensitivity of radioactivity measurements compared with chromatography of sugars; it does not seem necessary to seek a more elaborate explanation.

The convenience and practicability of a test depends on individual circumstances. We find no special difficulty in obtaining a 24 h urine collection, and a test which requires only a few minutes in the laboratory is welcomed by hard-pressed technical staff.

The importance of the finding of a persistent selective defect in permeability by the small intestine of gluten-sensitive patients with histologically normal mucosa is that, while explaining many features of this enigmatic disorder, it offers clear research leads, a situation lacking of late in coeliac disease.

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GLIADIN ANTIBODIES IN COELIAC DISEASE

SIR,—The letter from Dr Unsworth and colleagues (April 16, p 874) prompts us to report our data on gliadin and reticulin antibodies in the diagnosis of childhood coeliac disease (CCD).

IgA and IgG gliadin antibodies were detected by immunofluorescence (IFL-AGA[1]) and micro-ELISA (ELISA-AGA[2]) while IgA and IgG reticulin-R_1 antibodies (R_1-ARA) were sought by immunofluorescence.[3] Sera from 50 children with CCD aged 2–10 years at different stages of the disease, and diagnosed according to defined criteria,[4] were studied. As controls, sera from 166 patients with intestinal and non-intestinal conditions associated with immunological abnormalities were tested. 30 sera from healthy age-matched children were also studied. Results are reported in the table.

8. Tidball CS. Magnesium and calcium as regulators of intestinal permeability. *Am J Physiol* 1964; **206:** 243–46.
9 Ecknauer R, Buck B, Breitig I. An experimental model for measuring intestinal permeability *Digestion* 1983; **26:** 24–32.
10. Lokken P. Studies on ^{51}Cr EDTA and its evaluation as a reference substance in gastrointestinal research (*Norwegian monog Med Sci*) Oslo: Universitetsforlagett, 1970
1. Unsworth DJ, Manuel PD, Walker-Smith JA, Campbell CA, Johnson GD, Holborow EJ. New immunofluorescence blood test for gluten sensitivity. *Arch Dis Child* 1981; **56:** 864–68.
2. Savilahti E, Perkkiö M, Kalimo K, Viander M, Vainio E, Reunala T IgA antigliadin antibodies· a marker of mucosal damage in childhood coeliac disease *Lancet* 1983; i: 320–22
3 Rizzetto M, Donisch D Types of "reticulin antibodies" detected in human sera by immunofluorescence. *J Clin Pathol* 1973, **26:** 841–51.
4 Anon. Confirming the diagnosis of coeliac disease. *Br Med J* 1975; iv· 2.

FREQUENCY OF ANTIBODY POSITIVES

Antibody	CCD* A (n=22)	CCD* B (n=8)	CCD* C (n=20)	Disease controls† (n=166)	Healthy controls (n=30)
IFL-AGA IgA	15 *(68%)*	5	0	0	0
IFL-AGA IgG	13 *(59%)*	4	3	0	0
Either or both	22 *(100%)*	8	3	0	0
ELISA-AGA IgA	19 *(86%)*	6	1	0	0
ELISA-AGA IgG	22 *(100%)*	8	4	8 *(5%)*	*0*
Either or both	22 *(100%)*	8	4	8 *(5%)*	*0*
R_1-ARA IgA	7 *(31%)*	4	0	0	0
R_1-ARA IgG	5 *(23%)*	3	0	0	0
Either or both	12 *(54%)*	7	0	0	0

*A=newly diagnosed, untreated, unconfirmed; B=confirmed after gluten challenge C=after 1 year on gluten-free diet.
†Post-enteritis syndrome (15), ulcerative colitis (31), Crohn's disease (15), autoimmune chronic hepatitis (55), rheumatoid arthritis (50). The 8 ELISA-AGA IgG positives had post-enteritis syndrome (3), ulcerative colitis (3), and Crohn's disease (2).

Both IFL-AGA and ELISA-AGA were more sensitive than R_1-ARA ($p<0·01$). However, R_1-ARA were strictly confined to CCD, as was IFL-AGA, while ELISA-AGA were occasionally found in control patients. IFL-AGA and ELISA-AGA showed a very similar sensitivity, while IFL-AGA were slightly more specific than ELISA-AGA. Unlike Unsworth et al we could not find IFL-AGA in groups other than CCD. The low prevalences of IFL-AGA and ELISA-AGA and R_1-AGA found by us in the gluten-free diet CCD subgroup are probably due to the fact that our patients were tested after a longer period (1 year instead of 3 months). Both sensitivity and specificity of IgA and IgG antibodies were identical for IFL-AGA, while IgG ELISA-AGA were more sensitive than IgA ELISA-AGA ($p<0·01$) but less specific. On the whole, IFL-AGA and ELISA-AGA gave similar results in the diagnosis of CCD. The choice of test will depend on the facilities available in each laboratory.

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PRESENTATION OF COLORECTAL CARCINOMA

SIR,—Dr Houghton-Allen (May 7, p 1055) states that abdominal pain may be a common presenting symptom of carcinoma of the colon. We believe this to be especially true in elderly patients.

We and colleagues (D. L. Crosby and M. S. Pathy) have evaluated the presenting symptoms of 288 patients over the age of 65 years admitted with colorectal carcinoma to the acute geriatric or surgical ward at the University Hospital of Wales. Of the patients admitted to the geriatric ward with colonic carcinoma 39·8% complained of abdominal pain, whilst of those admitted to the surgical ward 60% complained of abdominal pain. Of patients with rectal carcinoma 25% of those admitted to the geriatric ward and 28% of those admitted to the surgical ward had abdominal pain. Abdominal pain seems to be more common in colonic than in rectal carcinoma, but 1 in 4 of those who had rectal carcinoma complained of this symptom.

Those patients admitted to the geriatric ward also appeared to present with more vague symptoms (eg, vomiting, anorexia, and general malaise). The classic triad of altered bowel habit, rectal bleeding, and tenesmus in rectal carcinoma was present in only 50% of the surgical patients. Tenesmus in particular was an uncommon symptom, being complained of by only 1 patient admitted to the geriatric department.

It is thus important to consider the diagnosis of colorectal carcinoma in elderly patients who present with ill-defined symptoms rather than rely on the classical presentation of these conditions.

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PARENTAL ORIGIN OF CHROMOSOME 15 DELETION IN PRADER-WILLI SYNDROME

SIR,—The Prader-Willi syndrome (PWS), generally sporadic in occurrence, is characterised by infantile hypotonia, early childhood obesity, mental deficiency, small hands and feet, short stature, and hypogonadism.[1–3] Recently, a deletion of chromosome 15 has been found in 50% of clinical diagnoses of PWS.[4]

In a clinical and cytogenetic survey of 37 PWS individuals, we have identified the interstitial deletion, based on blind studies of

1 Prader A, Labhart A, Willi H. Ein Syndrom von Adipositas, Kleinwuch, Kryptorchismus and Oligophrenic nach Myatonieratigam Zustad in Neugeborenenalter *Schweiz Med Wschr* 1956, **86:** 1260–61.
2. Zellweger H, Schneider HJ. Syndromes of hypotonia, hypomentia-hypogonadism—obesity (HHHO) or Prader-Willi syndrome *Am J Dis Child* 1968, **115:** 588–98.
3 Hall BD, Smith DW. Prader-Willi syndrome *J Pediatr* 1972; **52:** 286–93.
4. Ledbetter DH, Riccardi VM, Airhart SD, Strobel RJ, Kennan BS, Crawford JD. Deletions of chromosome 15 as a cause of the Prader-Willi syndrome. *N Engl J Med* 1981; **304:** 325–29

PARENTAL ORIGIN OF CHROMOSOME 15 DELETION

Proband sex	Age (yr)		Staining procedure									
			AgNOR			GTG			QFQ			
	Pat	Mat	Pat	Mat	Child	Pat	Mat	Child	Pat	Mat	Child	Origin
F	27	27	..	..	..	mp/mp	sp/lp	mp*/lp	..	..	..	Pat
F	36	34	M/M	L/S	L/M*	mp/mp	lp/mp	lp/mp*	4/1	3/2	2/1*	Pat
M	22	23	M/−	S/S	M*/S	$-p^+/sp$	−p/−p	sp*/−p	..	..	..	Pat
M	26	26	..	..	..	sp^-/sp^-	mp/mp^-	sp^-*/mp	2/2	3/2	3/2*	Pat
M	39	30	M/M	L/S	M*/S	mp/mp	lp/mp	mp/mp*	..	..	..	Pat
M	23	21	M/M	M/−	M*/−	lp/mp	lp/−p	mp*/−p	3/3	2/1	3*/1	Pat
M	40	40	..	..	..	mp/mp	lp/sp	1p/mp*	1/1	3/1	3/1*	Pat
F	22	21	..	..	..	lp/lp	$-p^+/mp$	lp*/mp	4/2	1/1	4*/1	Pat
M	36	21	..	..	..	mp/sp	lp/lp	lp/sp*	3/1	5/2	5/1*	Pat
M	32	31	..	..	..	mp/mp	mp/mp	mp/mp*	2/2	4/4	4/2*	Pat
M	24	21	L/L	M/S	L*/S	lp/lp	sp/sp	lp*/sp	4/2	1/1	4*/1	Pat

The code for heteromorphisms described by AgNOR is: L = large, M = medium, S = small, − = inactive. GTG stained slides were scored for satellite stalk and short arm length (l = long, m = medium, s = short, − = absent stalk, p^+ = long, p = normal, p^- = absent p arm). QFQ stained slides were scored for satellite intensity after Paris nomenclature (1 = negative, 2 = pale, 3 = medium, 4 = intense, 5 = brilliant).[9] The deleted chromosome in each case is identified by an asterisk.

chromosome 15 (breakpoints q11 and q13) in 21 patients and normal chromosomes in the remaining individuals. Clinical differences between the deletion and non-deletion chromosome groups have been identified.[5,6] The mean ages at conception for 11 affected individuals in the deletion group were 30 years for the father and 27 years for the mother. The mean age of the PWS child at time of examination was 11 years.

Parental studies to determine the origin of the chromosome deletion in eleven families utilised variants affecting the satellite region of chromosome 15.[7] Short arm regions of acrocentric chromosomes are considered stable and a reasonable number of variants permits parental origin determination. These regions at or near the centromere are useful for linkage analysis because of their position and constitutive heterochromatin composition both of which preclude crossing over. The variants were identified at high resolution by sequential staining with G-banding and silver of the nucleolar organising region (NOR) or G and Q banding. In all eleven families, the chromosome 15 donated by the father was identified as the chromosome in which the deletion had occurred (table). Both sets of parents' chromosomes were normal; thus all chromosome deletions were de novo. The probability that the father would donate the chromosome resulting in the deletion in all cases in our sample by chance was less than 1 in 1000 ($\frac{1}{2}$)[11].

Why should the deletion affect only the chromosome donated by the father? The continued proliferation of male gametogenesis makes this stage more vulnerable to environmental insult than is female meiosis, which is arrested for a long period. If chromosome 15 is sensitive to a particular environmental agent, there may be a greater chance for chromosomal breakage to occur. One possible agent is human coronavirus. One or more loci for sensitivity to human coronavirus 229E have been identified on the long arm (qll→qter) of chromosome 15 by cell hybridisation.[8]

This finding of paternal origin of deletions in PWS suggests that other deletion syndromes be investigated to establish whether paternal origin of de novo deletions is more widespread.

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5. Butler MG, Meaney FJ, Kaler SG, Yu PL, Palmer CG. Clinical differences between chromosome 15q deletion and nondeletion Prader-Willi individuals. *Am J Hum Genet* 1982; **34:** 119A.
6. Butler MG, Kaler SG, Yu PL, Meaney FJ. Metacarpophalangeal pattern profile analysis in Prader-Willi syndrome. *Clin Genet* 1982; **22:** 315–20.
7. Wachtler F, Musil R. On the structure and polymorphism of the human chromosome number 15. *Hum Genet* 1980; **56:** 115–18.
8. Berg K, Evans JH, Hamerton JL, Klinger H, eds. Human Gene Mapping 6. Oslo Conference (1981): Sixth International Workshop on Human Gene Mapping. *Birth Defects Orig Art Ser* 1982, **18:** 314.
9. Bergsma D, ed. Paris Conference (1971): Supplement (1975): Standardization in human cytogenetics. *Birth Defects Orig Art Ser* 1975; **11:** 6.

HLA TYPE AND ISLET CELL ANTIBODY STATUS IN FAMILY WITH (DIABETES INSIPIDUS AND MELLITUS, OPTIC ATROPHY, AND DEAFNESS) DIDMOAD SYNDROME

SIR,—The DIDMOAD syndrome is a recessively inherited disease (Diabetes Insipidus, Diabetes Mellitus of juvenile onset, Optic Atrophy, and sensorineural Deafness).[1] It may be associated with other degenerative diseases of the central nervous system, including ataxia and hypogonadism of presumed hypothalamic origin.[2] Because the recessively inherited syndrome includes insulin-dependent diabetes with no known precipitating factors the study of genetic and immunological factors is of considerable interest. We report the results of HLA typing and islet cell antibody status in a family in which two siblings are affected by the disorder.

Both the mother and the father are unaffected. There was no evidence of consanguinity but grandparents on both sides of the family had the same surname. Of their three children two (A and C) now have diabetes mellitus, partial cranial diabetes insipidus, and optic atrophy.

Sibling A presented at age 8 years with classical symptoms of diabetes mellitus. He is now well controlled with twice-daily 'Rapitard' insulin. Aged 10 he noted decreasing visual acuity and was found to have optic atrophy. Despite good blood glucose control he complained of persistent thirst and polyuria. Aged 15 he was found to have diabetes insipidus on water deprivation test (maximum urine osmolality 643 mosmol/kg, plasma osmolality rising from 295 to 302 mosmol/kg). An intranasal test dose of desmopressin produced a maximum urine osmolality of 790 mosmol/kg. Treatment with desmopressin 10 μg at night has resulted in complete resolution of thirst and polyuria. Now aged 16 he has early signs of pubertal development.

Sibling C presented with decreased visual acuity at age 10 and was found to have early optic atrophy. 1 year later she complained of excessive morning thirst, polyuria, and nocturia. A water deprivation test demonstrated a maximum urine osmolality of 344 mosmol/kg. Urine concentrated normally with intranasal desmopressin and an evening dose of 5 μg resulted in complete resolution of her symptoms. Fasting blood sugar at this time was 4·6 mmol/l. 1 year later recurrence of thirst and polyuria developed, associated with hyperglycaemia (21 mmol/l) and ketonuria. She is now controlled with twice daily insulin.

Sibling B (aged 15) has remained symptom-free with no ocular changes and normal glucose tolerance.

Fluorescence studies for islet cell antibodies[3] were negative in all family members. HLA typing is shown in the table.

1. Wolfram DJ, Wagener HP. Diabetes mellitus and optic atrophy amongst siblings. *Proc Mayo Clin* 1938; **13:** 715–17
2 Marquadt JL, Lorinaux DL Diabetes mellitus and optic atrophy. *Arch Intern Med* 1974; **134:** 32–37.
3. Bottazzo GF, Florin-Christensen A, Doniach D. Islet cell antibodies in diabetes mellitus with autoimmune polyendocrine deficiencies. *Lancet* 1974; ii: 1279–83.