FAMILIAL ASSOCIATION OF CROHN'S AND COELIAC DISEASES

SIR,—We have observed Crohn's disease and coeliac disease in 3 unrelated Sicilian families. We know of no other reports of such an association, although familial predisposition to both diseases is well documented[1,2] and inflammatory bowel disease (IBD) associated with coeliac disease has been described in at least 20 cases.

The relationship is parent-child in two cases and second degree in one. Crohn's disease was diagnosed on clinical, radiological, and histological (endoscopic or surgical) criteria, while coeliac disease was confirmed both histologically and by repeat biopsy with the patient on a gluten-free diet.

The cases were identified from among the 293 Crohn's disease patients being followed up in our department by a questionnaire which asked about IBD or coeliac disease in first and second degree relatives and in our spouses. Statistics on the prevalence of Crohn's and coeliac diseases are not available in Sicily, though Crohn's disease seems similar in prevalence to that seen in Western Europe and North America, being 2·7 per 100 000.[3] For prevalence rates of 30–50 cases of Crohn's disease per 100 000 population[4] and 50–100 cases of coeliac disease[5] 2 instances of coexistence of the diseases among first degree relatives are more than would be expected by chance (Poisson). The coincidence of the two diseases in 3 instances from the larger denominator of first degree and second degree relatives was not significant. However, since we have not been able to ask every patient with coeliac disease being followed up about IBD in their relatives, the 3 instances may be underestimated.

An association between Crohn's disease and coeliac disease, if valid and not merely fortuitous, might be explained by a genetic link, by a common defect in intestinal permeability to foreign antigens,[6,7] or immunologically since both diseases are associated with immunological disorders.[8,9]

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HANTAVIRUS NEPHROPATHY IN NETHERLANDS

SIR,—In 1984 we reported the first cases of hantavirus (HV) infection in the Netherlands.[1] HV-specific antibodies were demonstrated by immunofluorescence assay (IFA) in four laboratory workers at the National Institute of Public Health and Environmental Protection (RIVM), who had handled HV-infected Lou/M laboratory rats. One worker had severe transient nephropathy; the other three had only mild symptoms. No HV-specific antibodies were demonstrated by IFA in RIVM laboratory workers who had had no contact with these rats.

Using a newly developed ELISA, which permits the rapid screening of large numbers of sera,[2] we have now tested samples collected from people with different clinical histories in the Netherlands, who had not been in direct contact with laboratory animals (table). In a panel of 865 arbitrarily chosen samples of sera from patients with suspected leptospirosis who proved to be seronegative for leptospira, the samples being collected from all over the country between 1984 and 1988, 5 ELISA-positive sera were found. Testing by ELISA of recently collected samples from 10 individuals with a history of severe transient nephropathy admitted to hospital in the past 15 years, revealed that 7 had HV-specific antibodies. 1 had had nephropathy as early as 1974. The 12 ELISA-positive reactions (titres 100 to 20 000) found in these two groups were all confirmed by IFA and western blot.[2] 488 serum samples from farmers living in the northern, non-forested part of the country (Friesland)[3] and of 171 RIVM workers who had not been in contact with HV-infected laboratory animals, were also screened by ELISA. All these sera were negative.

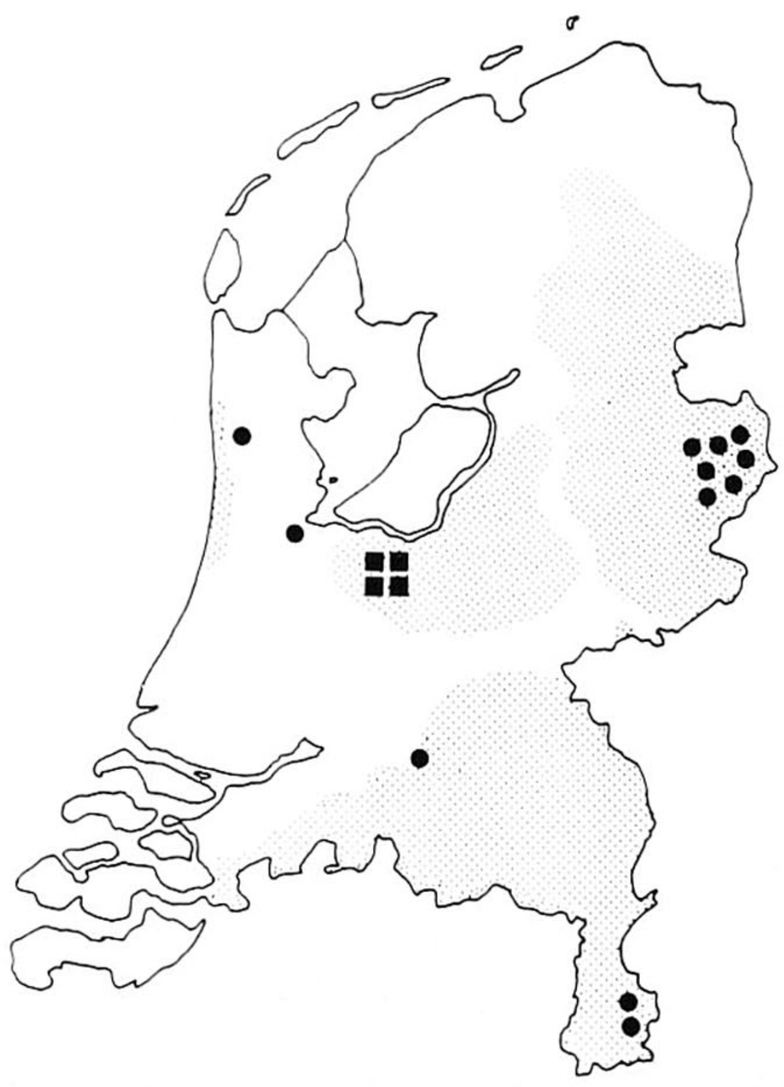
SAMPLES WITH HANTAVIRUS-SPECIFIC ANTIBODIES* IN NETHERLANDS (1974–89)

Origin	Years	Total	No positive
Laboratory workers in contact with infected rats*	1981–84	9	4
Workers not in contact with rats	1981–88	171	0
Suspected leptospirosis	1984–89	865	5
Farmers of 82 farms in Friesland	1986–87	488	0
History of severe transient nephropathy 1974–88	1989†	10	7

*ELISA confirmed by IFA and western blot.
†Time of serum collection.

Both by ELISA and IFA the 4 sera from the laboratory-associated HV-infected individuals consistently showed at least two-fold higher titres with the HV serotype I ("*Apodemus* associated") strain Hantaan virus 76.118, than with members of the other three proposed serotypes.[4,5] The serum samples of the 13 non-laboratory-associated cases of HV infection showed at least twofold higher antibody titres with serotype III ("*Chlethriominus* associated") strain Hälnäss, than with members of the other proposed serotypes.[6]

These data suggest that apart from laboratory-associated infections with HV serotype I, infections with HV serotype III associated with severe renal disease, have occurred in the Netherlands in the past 15 years. Since 10 out of 12 of these seropositive individuals lived in the eastern and southern forested



Map of The Netherlands, indicating location of patients with HV-specific antibodies: ■ laboratory associated cases, ● non-laboratory associated cases, ▒ forested areas.

areas of the country (figure) and since at least 1 of the other 2 visited one of these areas shortly before the symptoms developed, it is most likely that, as in neighbouring countries West Germany and Belgium,[7,8] wild rodents are the reservoir of the virus.

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SCHIZOPHRENIA INDUCED BY RESTITUTION OF THYROID FUNCTION IN A PREDISPOSED PATIENT

SIR,—Individuals predisposed to schizophrenia may have a lower threshold for a putative common stimulus.[1] In non-familial ("sporadic") schizophrenia, individuals may be predisposed as a result of severe obstetric complications,[2] and such patients may show a prodrome of soft neurological signs[3] and behavioural and cognitive disorders in childhood.[4] However, these reports have been based on liability models or retrospective statistical analysis of data from large population studies. We report a woman in whom schizophrenia developed after a subthreshold stimulus known to provoke psychotic symptoms.

A 29-year-old single black woman from Bermuda had a primary diagnosis of schizophrenia. After a previously uneventful school career and normal early development, she presented at age 15 with constant head banging, feelings of intense sensitivity, and truancy. Acute adolescent situational crisis was diagnosed. There is no psychiatric illness in any second or first degree relative. She was born at term, although there had been premature rupture of membranes before labour, which was recorded as being "greatly prolonged". Mental state examination on initial admissions revealed an uncommunicative aloof girl without features of schizophrenia. Neurological examination revealed non-purposeful grimacing and abnormal postures. At age 17 she proved to be hypothyroid: T_4 33 µg/l (normal range 45–115); T_3 26·3 U/l (35–45); free thyroxine index 0·86 (2·2–4·7); and thyroid stimulating hormone 650 mU/l (less than 10). Thyroid scan showed a non-functioning left thyroid lobe. Other investigations including electroencephalography were normal. Psychometric testing revealed a performance IQ of 83. She was treated with thyroxine 0·1 mg daily.

Seven months later she had clear evidence of schizophrenia. Thyroid hormone levels were normal (T_4 53, T_3 33·6). In the next two years she had several admissions for schizophrenia, when thyroid function tests were normal. In February, 1987, she no longer heard voices and she was hypothyroid (T_4 29, T_3 34). Her thyroxine was increased to 0·2 mg daily; two months later she was admitted following a violent incident. She had prominent psychotic symptoms and she was biochemically euthyroid. Thyroxine was stopped as a therapeutic trial. Two weeks later she was diffident and consistently denied any signs of schizophrenia; work and daily activities were persistently improved. She was hypothyroid (TSH 76·8, T_3 10·9, T_4 20). Since presentation with psychotic symptoms she has been continuously on conventional doses of flupenthixol decanoate depot (80–120 mg fortnightly) and trifluoperazine hydrochloride (15–30 mg daily).

Schizophrenia-like psychoses can be provoked by severe hyperthyroidism and the schizophreniform picture is closely linked to the course of the hyperthyroidism.[5] In this patient restitution of normal thyroid function was accompanied by expression of first rank symptoms of schizophrenia, and many features that have been postulated to accompany an increased risk of the disorder were displayed—ie, obstetric complication, childhood behavioural disorder, and soft neurological signs.[6] Although threshold theories were devised from genetic studies[7] the model can be applied to non-genetically predisposed patients.[8] Thus this patient's high sensitivity to thyroxine with respect to the development of schizophrenic symptoms not only suggests that the threshold theory[7] is valid, but also supports the notion that the putative risk factors may indeed be implicated in her schizophrenic illness. Our case supports theories about the liability to develop schizophrenia in predisposed individuals.[9]

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PSEUDOAUTOSOMAL LOCUS FOR THE CEREBRAL DOMINANCE GENE

SIR,—Asymmetry of function and structure of the cerebral hemispheres relates to man's capacity for speech and communication. Presumably such asymmetry depends upon a development of growth control mechanisms that is recent in primate evolution. The gene (the "cerebral dominance gene" or "right shift factor") involved may be transmitted according to a simple mendelian rule.[1]

Studies[2,3] on sex chromosomal aneuploidies suggest a possible genetic locus:

Syndrome		*Verbal IQ*	*Performance IQ*
Turner's[2] (XO)	(n = 35)	100	88
Klinefelter's[3] (XXY)	(n = 24)	83	100

In a collated sample of XXX girls a verbal-performance discrepancy similar to but of lesser magnitude than that in XXY males was seen.[4]

In Turner's syndrome verbal IQ is normal but performance IQ is reduced; in Klinefelter's syndrome the pattern of deficit is the reverse. It is implausible to attribute these impairments to environmental insults; presumably they result from developmental imbalance or arrest. The likely interpretation is that in Klinefelter's syndrome there is a lack of development of the left (dominant) hemisphere, whereas in Turner's syndrome there is right-sided impairment. The fact that these deficits complement each other,