Inheritance of Coeliac Disease

W. M. McCRAE

From the Department of Child Life and Health, The University of Edinburgh, Edinburgh

Coeliac disease has been for many years a familiar diagnosis to those interested in the diseases of children. The signs and symptoms (Buchan, 1786; Gee, 1888) are those that might be expected in any extensive disturbance of absorption. As fibrocystic disease (Andersen, 1938) and other well-defined causes of malabsorption have been recognized, there has been a resulting change in the scope of 'coeliac disease'. It may be that even now 'coeliac disease' is not a single disorder, but present experience seems to indicate that if coeliac disease is defined as a malabsorptive disorder associated with villous atrophy of the jejunum and responding to withdrawal of gluten from the diet, it becomes a sufficiently well-defined entity to make study of its aetiology possible.

Environmental Aetiology

Response to gluten in the diet is not the only environmental factor involved in the aetiology of coeliac disease. It is known that, though on the same diet, only one of a pair of identical twins may be affected (D. Gairdner, 1968, personal communication). There is no recognizable relation in time between the introduction of gluten into the diet and the onset of the disease. A condition that, by our definition, must be accepted as coeliac disease has followed the stress of gastric surgery (Hedberg, Melnyk, and Johnson, 1966), and there is evidence to suggest that other environmental factors may be involved (Roufail and Ruffin, 1966). Since the recognized precipitating environmental factors are common, it is of interest to consider the possibility that they operate only in the presence of an inherited predisposition to coeliac disease.

Genetic Aetiology

Previous studies of the inheritance of 'coeliac disease' (Thompson, 1951; Boyer and Andersen, 1956; Carter, Sheldon, and Walker, 1959) indicate an increased incidence in the relatives of known

cases. These studies preceded the use of jejunal biopsy, and therefore the index cases would not satisfy present diagnostic criteria. It is of interest, therefore, to carry out further studies in which the index cases fit the present definition of 'coeliac disease'.

The previous studies (including that of MacDonald, Dobbins, and Rubin, 1964) do not prove simple inheritance of coeliac disease as a single gene effect. It is, therefore, possible that the genetic component in coeliac disease is an underlying genetic susceptibility of multifactorial inheritance of the type demonstrated in the aetiology of peptic ulcer (Falconer, 1960).

Present Study

This investigation was designed to estimate the incidence of coeliac disease in the population served by the Royal Hospital for Sick Children, Glasgow, and to calculate the heritability of coeliac disease, assuming the genetic component to be multifactorial.

Material and Method

The index cases were 100 patients with coeliac disease, diagnosed and treated at the Royal Hospital for Sick Children, Glasgow. All had clinical features in keeping with the diagnosis; all had characteristic findings on jejunal biopsy; and all had a satisfactory response to withdrawal of gluten from the diet, as observed during a period of at least 6 months' 'catch-up growth'. These patients were seen regularly at a follow-up clinic so that it was easy to explain the purpose of the investigation. The parents were asked to inquire about the health of other members of their families. After this preparation each family was visited at home so that the family history could be discussed at leisure and in detail away from the usual rush of the out-patient clinic.

Every reported illness in the family was investigated if it was at all suggestive of coeliac disease or malabsorption. With the co-operation of the general practitioners and the hospitals concerned it was possible to examine the records of all of these illnesses, so that there was no need to accept reports of coeliac disease without supporting evidence. In a number of cases the diagnosis of

coeliac disease was suggested by the parents but disproved on examination of the hospital records. The usual cause of these false claims was gastro-enteritis in infancy. In all, histories were obtained for 2790 relatives.

The remaining part of the investigation was to discover the incidence of coeliac disease in the general population. This estimate was made by a method suggested by Carter (1961). The calculation of heritability was performed by the method introduced by Falconer (1960), which assumes that liability to the disease is a graded characteristic inherited multifactorially.

Results

Estimation of Size of Population Served by Hospital. During the years 1952-62 the mean annual incidence of congenital hypertrophic pyloric stenosis at the Royal Hospital for Sick Children was 113.7. Assuming an incidence of 3 per 1000 (Carter, 1961), this indicates that the population served by the hospital has a birth rate of 37,900 per annum.

Since it seemed possible that the Hospital might serve different populations for acute surgery and general medicine, the calculation was repeated using fibrocystic disease as marker. The incidence of fibrocystic disease during the same years was 17.8, and the assumed frequency of fibrocystic disease was 1 in 2000. This indicated a population with birth rate of 35,700 per annum.

From the mean of two estimations the birth rate of the population served by the hospital was taken as 36,800.

Estimation of Frequency of Coeliac Disease in General Population. During the years 1952-62 the mean incidence of coeliac disease was 19.9. This incidence was derived from a population with a birth rate of 36,800 per annum. The prevalence of coeliac disease was therefore estimated as in Table I.

TABLE I

	Mean Incidence	Estimated Birth Rate of Population
Pyloric stenosis	113.7	37,900
Fibrocystic disease	17.8	35,700
Coeliac disease	19.9	mean 36,800

Estimated incidence of coeliac disease, 1:1850.

Incidence of Coeliac Disease in Relatives. Medical histories were obtained for 2790 relatives. In all, 12 cases of coeliac disease were reported during the interviews. On examination of the case records of these 12 cases, reports were found to be false in 6 cases (Table II).

TABLE II

Relation	No.	Affected
Sibs	317	2
Parents	198	0
Aunts and uncles	902	1
Cousins	1373	3
Total	2790	6

Calculation of Heritability. The calculation was based on the estimation of incidence of coeliac disease in the general population, in sibs, and in all relatives (Table III).

TABLE III

Heritability	% $\pm$ standard error
Sibs	44% $\pm$ 15
All relatives	45% $\pm$ 13

Trial of Hypothesis that Genetic Component is Graded Characteristic

If the concept of degree of genetic determination being a graded character is true, it should be expected perhaps that positive family history should occur more often in those whose genetic determination is greater. To test this two small groups of patients have been compared.

The first group may be supposed to have a high degree of determination, since the disease appeared and was diagnosed within 6 months of the introduction of gluten.

This group has been compared with a group of late onset. These may be supposed to be patients in whom environmental factors played a greater part. These patients were over 4 years of age. None had symptoms lasting for more than 6 months. None was so retarded in growth as to be outside the normal distribution of height for age.

TABLE IV
FAMILY INCIDENCE OF COELIAC DISEASE

	No.	No. of Relatives	No. of Cases of Coeliac Disease
Early onset	7	193	3
Late onset	8	257	0

Conclusions and Summary

The survey of the familial incidence of coeliac disease indicates that there is some genetic basis for

the condition as indicated by a heritability of approximately 44%. The findings are in keeping with the concept that susceptibility to the disease is inherited as a graded character. Environmental factors, other than the gluten of the normal diet, are probably of predominant importance in aetiology.

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