The Genetics of Coeliac Disease

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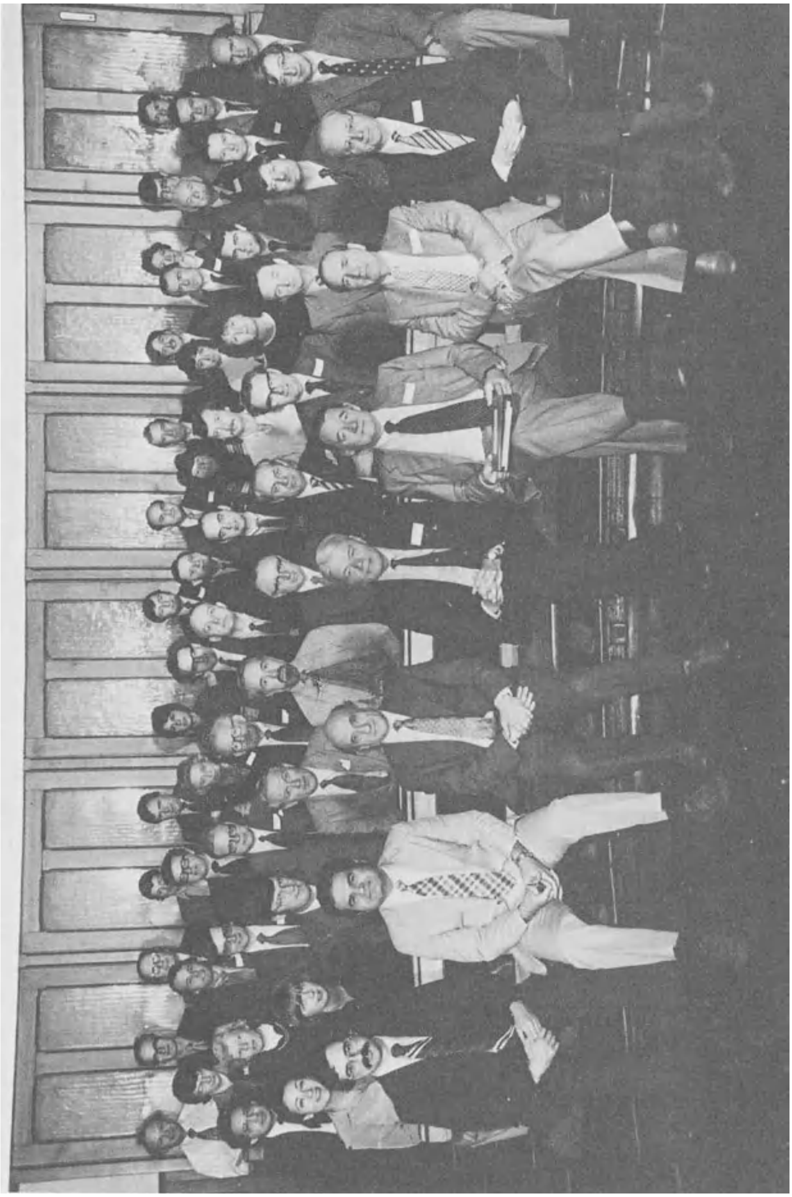

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Introduction

R. B. McConnell

During the past 10 years three international symposia on coeliac disease have been held. The first was in London in 1969, the second in Leiden in 1973 and the third in Galway in 1977. At each there were contributions on the familial, hereditary or genetic aspects of the disease but because all features of the condition were being considered at the symposia there was not the time for detailed discussion of the genetic aspects. These three international symposia were sponsored by Mr Jeremiah Milner and Welfare Foods (Stockport) Limited.

During 1978 Mr Milner and I were aware of intensive studies being made at various centres in Europe and America on the genetics of coeliac disease, and we decided that to bring these teams together and let the members spend a whole day discussing the genetics of coeliac disease might well result in a valuable exchange of data and ideas; the discussions could also point to the most potentially fruitful avenues for further research. Professor Charlotte Anderson, Dr C. C. Booth and Professor Ciaron McCarthy joined Mr Milner and me in forming a Steering Committee, and the International Symposium on the Genetics of Coeliac Disease was held in the Liverpool Medical Institution on 28 and 29 November 1979.

Even though the study of genetics uses mainly intra-familial techniques, the differences between population incidences must also be noted. They are likely to be due to different environmental conditions but they may, in some instances, be due to variations in the genetic make-up of the populations. Thus in coeliac disease a study of its epidemiology is very much part of the study of its genetics. For this reason the letters, inviting people to participate in the Symposium, asked them if they would like to present data on the epidemiology of the condition as well as on its genetic aspects. When the replies started

coming in it became apparent that more than a single day was needed and eventually it was decided to spend the first half-day discussing its epidemiology, the second half-day its immunogenetics and the final half-day the familial distribution of the condition.

We invited to the Symposium, not only people actively engaged in research on the genetics of coeliac disease but also a number of distinguished medical geneticists and gastroenterologists. We were fortunate that the majority of those invited were able to accept the invitation and at the symposium an important contribution was made to the discussions by these expert geneticists and clinicians. A highlight of the Symposium was a lecture given by Sir Cyril Clarke who honoured us by starting the second day with a personal view of the future of medical genetics. It was the lively and thought-provoking kind of talk which we expect from this doyen of clinical genetics and I am grateful that he has allowed me to present it in print as the Introductory Lecture of this volume.

OBJECTIVES OF GENETIC RESEARCH

It is to be hoped that elucidation of the genetic basis of a condition will also throw light on the environmental factors involved. One of the great puzzles about coeliac disease is why the condition is so much less common in the United States than in Europe. This is almost certainly not due to under-diagnosis by American physicians, nor is it likely to be due to the Americans eating less gluten than people in Britain. Is there some other environmental factor as well as wheat which causes the onset of coeliac disease in an Irishman in Galway but not in his cousin in Boston?

There does not seem to be much more hope in the future of spotting the potential coeliacs amongst the people of the general population who have no family history of the condition. On the other hand their identification might well be possible in a family which already contains a coeliac. There are several benefits which would follow elucidation of the genetic basis of gluten sensitivity:

(1) It could enable the liable family members to be identified by testing genetic markers. This might mean that the disease could be diagnosed in near relatives of a coeliac without doing jejunal biopsies.
(2) Such early identification of the genetically predisposed relatives would result in their diagnosis without delay soon after the development of symptoms.
(3) It may be useful to identify the genetically prone in the first months of life. If it becomes established that early gluten feeding or excess gluten, or some other environmental precipitating factors, are concerned in its aetiology, the onset of the disease might be avoided. The development of cancer might also be avoided if it

should be shown that the cancer risk in coeliacs is lessened by the avoidance of gluten from an early age.

DEFINING THE HEALTH OF COELIAC RELATIVES

In the study of the genetics of relatively common conditions which do not have a simple Mendelian pattern of heredity, there is usually difficulty in deciding who has the condition and who is healthy. Such conditions are often graded in severity and there may be no clear-cut dividing line between health and disease. Coeliac disease is no exception. The age at onset of symptoms ranges from the first year of life to the late 70s and symptoms can range from none to life-endangering anaemia or diarrhoea. We are uncertain about the state of the jejunal mucosa in the young adult years of those coeliacs who first develop symptoms and are diagnosed in middle and old age. At one time I thought that villous atrophy had probably been present throughout gluten-eating life, but now I think this is unlikely. Is it possible that a relative whose jejunal biopsy shows a normal mucosa may present with full-blown coeliac disease in later life? If so such a person should have the same genetic predisposition and its markers as a relative who has already developed coeliac disease.

Because of the importance of scoring relatives as correctly as possible as affected or unaffected there was considerable discussion at the Symposium of the criteria for the diagnosis of coeliac disease. Considering its great clinical diversity it is not surprising that opinions differed. There was no disagreement with the opinion that the diagnosis of coeliac disease for research purposes should be based on the finding of total or subtotal villous atrophy in the jejunum which changes towards normal morphology on exclusion of the gluten from the diet with return towards atrophy if gluten is re-introduced. For instance, in the propositi of families studied to elucidate the genetics of the condition the diagnosis should have been established according to this criterion.

There was considerable agreement that this criterion is too restrictive for use in scoring relatives of a coeliac as affected or unaffected, and if applied rigorously would lead to erroneously low estimates of the numbers of affected relatives to the extent of rendering the data of limited value in genetic analysis. Several of the participants had seen patients who presented initially with normal or near-normal jejunal biopsies and yet subsequently were shown to be coeliacs with total villous atrophy which responded to gluten withdrawal. Therefore a single normal or near-normal biopsy does not exclude coeliac disease.

Several surveys have shown an incidence of relatives with subtotal villous atrophy of between 5 and 10%. Thus the known probability of a first-degree relative also being a coeliac starts at about 1 in 10 or 20. In the individual relative this probability gradually increases as more abnormalities of absorption are found. One can only be absolutely sure that a relative is a coeliac if total or subtotal villous atrophy is

demonstrated, but if partial villous atrophy and malabsorption are found, the probability of the relative also being a coeliac is very high.

In genetic research it is rarely possible to persuade every first-degree relative to undergo jejunal biopsy, and if one is to obtain as accurate a measurement as possible of the number and distribution of affected relatives other criteria must be used to assess probability and possibility.

EPIDEMIOLOGICAL DATA

A striking feature of the Epidemiology papers was that they were nearly all offered by paediatricians. These specialists tend to cover a circumscribed area or a definite population and are therefore likely to have total ascertainment of the children being diagnosed as coeliac in their area. This enables an accurate annual childhood incidence to be calculated, either in relation to live births or to population figures.

The adult gastroenterologists had little idea of incidence as new coeliacs are diagnosed by the numerous general physicians and by a variety of specialists. In addition they were aware that many adult coeliacs go undiagnosed for years and possibly are never diagnosed because they are under the care of general practitioners or specialists who do not know the many ways in which the condition can present in adult life.

In the discussion it became apparent that even in this expert audience there was considerable uncertainty about the proportion of coeliacs who are diagnosed in childhood and some lack of appreciation of the frequency with which it presents in the sixth and seventh decades. I have therefore added data on the membership of the Coeliac Society of the United Kingdom which were not presented at the Symposium but which give a partial answer to some of the questions raised in the discussion and contribute to the value of the epidemiological section of this book. I am grateful to Miss Kay Leighton and Mr John Andrew of the Coeliac Society for their help in producing these data.

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transcribing the discussions from tapes, as well as much assistance in the secretarial work, and to Mrs Vera Jones who was responsible for the bulk of the secretarial work concerned with the organization of the Symposium and the production of this volume. My thanks also go to Mr David Bloomer and Mr Martin Lister of MTP Press Limited for publishing these proceedings with such efficiency. I feel sure that the book will be found useful both by gastrointestinal clinicians and those involved in all aspects of coeliac research, as well as by all clinical geneticists.

R. B. McConnell

INTRODUCTORY LECTURE

Clinical Genetics: The Wider Horizon

Sir Cyril Clarke

If I were young again – which God forbid – had been trained as a general physician and later on developed an interest in genetics (which is what happened to me about 30 years ago) what aspects of clinical genetics, particularly those relevant to improving the lot of patients, would I now plump for?

It is easier first of all to say what I would not do, and I have no difficulty in deciding my non-priority number one. I personally would not become involved in studying further the association of HLA types with disease. I do not deny that this research has great academic interest, particularly with regard to linkage, but it has been on the go now for ten years or so and what I have against it is that as far as I can see no patient has benefited from the knowledge that, for instance, B27 is associated with ankylosing spondylitis – in fact rather the reverse. I know a very distinguished clinical geneticist who suffers from ankylosing spondylitis but he is *not* B27, and he is regarded as a traitor – but how disreputable is this at present? Again, there is a medical man who *is* B27, and every time he gets 'my back' or a stiff neck he rushes off for an ESR and an X-ray. It seems to me that there is no particular point in knowing one is 'at risk' for ankylosing spondylitis, because there is no specific treatment.

An additional reason for my scepticism is that in Liverpool we were in on the ABO and duodenal ulcer association 20 years ago[1], but nothing useful ever really came of that, and I have a great sense of *déjà vu* over HLA.

I quite appreciate that the associations between blood groups and duodenal ulcer were not nearly so impressive as many of those with