Morbidity and Mortality in Coeliac Disease

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Abstract

Celiac disease is a small intestinal immune-mediated enteropathy precipitated by exposure to gluten, a protein complex in the cereals wheat, barley and rye, in genetically susceptible people. Once considered an uncommon disorder restricted to children of European descent, it is now known to be one of the most common chronic diseases encountered in the Western world, with a serological prevalence of 1% that can be diagnosed at any age. Since it is so common much co-morbidity comprising malignant and non-malignant conditions will occur in association.

Malignant complications particularly lymphoma were first described over 50 years ago but the natural history and how commonly these occurred were unknown until relatively recently. Similarly, many non-malignant conditions were known to occur but initially the risks were unclear. It was not until the frequency of coeliac disease could be determined accurately in the community and population-based studies of morbidity and mortality in coeliac disease patients carried out in defined cohorts that these questions could be answered.

My research into these aspects of coeliac disease began in 1971 and a body of 35 of my publications spanning the years 1974 to 2018 on the morbidity and mortality of the disorder are presented in this thesis. I have introduced my research findings at many international and national meetings and these data have been influential in shaping the research agenda of other workers. One of my papers (Publication 9) published in Gut in 1989, was the most cited of all papers which appeared in the journal for that year. To date it has been cited 1122 times. Information exists for 24 papers presented here and for these the total number of citations stands at 3,887. This excludes references to book chapters. Anecdotal evidence indicates frequent mentions in lectures and clinical practice.

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Morbidity and mortality in coeliac disease

A critical appraisal of 35 published works

Introduction

Through the years I have researched many aspects of coeliac disease clinically and in the laboratory. I have selected a series of 35 publications that I have authored or co-authored on the morbidity and mortality of coeliac disease written between 1974 and 2018. Disorders contributing to morbidity and mortality in coeliac disease can be divided into malignant and non-malignant. Those due to malignancy particularly lymphoma, are the most serious. Fourteen of the publications are concerned primarily with this aspect while 21 are devoted to non-malignant associations. This is a personal journey that highlights my own research but also reflects the evolution of thinking on these subjects over the last 45 years.

Malignant associations

In 1936, an association between idiopathic steatorrhoea (now regarded as coeliac disease) and lymphoma was recognised (1) and subsequently in numerous reports. In each instance it was assumed that steatorrhoea occurred secondarily to lymphoma. However, in 1962 workers from Bristol (2) suggested that lymphoma was a complication of coeliac disease and that the mucosal lesion in the upper small bowel was a premalignant condition. This concept was strengthened in further publications from Bristol (3) and Birmingham (4), both appearing in 1967.

Malignant potential of coeliac disease (5)

Because of the paucity of information available, I decided to review the original series created by Harries and his colleagues (4) consisting of 202 patients with coeliac disease diagnosed at the General and Queen Elizabeth Hospitals Birmingham, between 1941 and 1965, to determine how many further malignant tumours had arisen after a further 10 years had elapsed (5). A criticism of the series of Harris is that only 136 patients were confirmed as

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having coeliac disease by small bowel biopsy while 66 were labelled as idiopathic steatorrhoea. It is likely that this latter group did have coeliac disease because subsequently 10 had a biopsy which confirmed the diagnosis by histology. For the statistical analysis expected figures for malignant tumours were obtained by Harries and his colleagues from the Birmingham Cancer Registry, with over 95% registrations for a population in the area of 4.5 million people. In total, 77 patients had died and 31 malignancies occurred in 29 patients of whom 14 had developed lymphoma and 6 carcinoma of the oesophagus. These were regarded as statistically significant results. It was not possible to decide the effect of a gluten free diet on the risk of malignancy because the data was inadequate. A criticism of this work is that patients were attending a secondary or even tertiary referral centre that would attract those patients with complications thus skewing the results. Also at that time it was not appreciated how many undiagnosed patients with coeliac disease there were in the community so the malignant risks were greatly overstated. Nevertheless, the high number of lymphomas arising in a relatively small number of patients indicated this was indeed a complication of coeliac disease. This suspicion was strengthened when I reviewed the series 10 years later (5). Another 20 patients had died (Table 1) and 4 more had developed lymphoma (Table 2).

At this time, I identified another series of 210 patients diagnosed by small bowel mucosal biopsy in Birmingham up to the end of 1972 and followed up to the end of 1974 (5). When deaths from all malignancies were analysed, a significant increase occurred in all deaths from cancer in the whole series and in men and women separately. An increase was noted in deaths from lymphoma in men and women and in oesophageal and pharyngeal cancer in men (5) [Table 7]. A gluten free diet was not shown to reduce the prevalence of lymphoma. This series did take matters a step further because only biopsy diagnosed patients were included but there was still the issue that these were a selected group seen in a referral centre and many undiagnosed cases now known to be in the community did not come into the risk calculations because at that time these were not known about. Also, it was perhaps optimistic to expect to demonstrate any effect of a gluten free diet in patients who had already been exposed to an oncogenic stimulus, gluten, for many years,

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probably since birth. This cohort of 210 patients was kept under careful review with the aim of a further analysis in future years (this was undertaken at the end of 1985 as detailed below).

Clinical features of malignancy in coeliac disease (6)

In the 1970s very little was known about the clinical manifestations of malignancy in coeliac disease particularly with regard to presentation, diagnosis and prognosis. Therefore at this time, we reviewed 55 patients with coeliac disease and malignancy, 27 with lymphoma and 28 with other cancers, who had been seen at the General Hospital Birmingham (6). That a lymphoma might have developed was suggested by deterioration in a patient previously stable on gluten free diet or who had not responded to diet from the outset. Weight loss, abdominal pain, diarrhoea, profound muscle weakness and fever, associated with anaemia, raised inflammatory markers, hypoalbuminaemia and steatorrhoea were important clinical features. The presentations of malignancies other than lymphoma were no different from those in non-coeliac patients and their development did not provoke a relapse of coeliac disease. There were no features that allowed an early diagnosis of lymphoma to be made and investigations available at that time were largely unhelpful. Only two thirds of lymphomas were diagnosed during life. The prognosis for lymphoma was extremely poor with life expectancy measured in a few months. There was no effective treatment. How common these complications were was unknown because reliable epidemiological studies could not be carried out at this time.

Malignancy in coeliac disease and the effect of a gluten free diet (7)

The series of 210 patients was again reviewed at the end of 1985 after a further 11 years of follow up (7). During this time 12 new cancers occurred of which 2 were lymphomas, a significant increase and 1 a carcinoma of the oesophagus (7) [Table 2]. This was further evidence that lymphoma does complicate coeliac disease. A two-fold risk of cancer was found and the excess was because of increased risk of cancers of the mouth, pharynx, oesophagus and non-Hodgkin's lymphoma. A 42.7-fold increased risk was found for non-Hodgkin's lymphoma [Table 1). In order to explore any influence of diet on

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cancer risk, the patients were grouped according to their adherence to a gluten free diet. Group 1 included those who had kept the diet strictly for 5 or more consecutive years. The 5-year period was an arbitrary time decided on before the analysis was carried out. This criterion was satisfied by 108 patients. Group 2 consisted of 46 patients who had not taken a gluten free diet and Group 3 was formed of 56 patients who had taken a gluten free diet for less than 5 years and 39 who had only taken the diet sporadically. Because of the small numbers in Groups 2 and 3 these were combined for most of the analyses and designated Group 2. The risk of cancer over all sites was not significantly increased for those taking a strict gluten free diet (Group 1) but increased for those having a reduced gluten or normal diet (Group 2) [Table 3]. The occurrence of the two lymphomas accounted mainly for the small excess in Group 1. Patients in Group 2 showed an excess of cancers of the mouth, pharynx and oesophagus and also of lymphoma. Although no differences between the groups could be detected for individual sites, on combining them the differences between the relative risks, 6.7 (Group 1) and 38.6 (Group 2) was significant ($p<0.05$). When the results were distributed into the three original diet groups, a significantly decreasing trend in excess morbidity rates over increasing use of the gluten free diet was observed [Table 4].

These results supported a protective role for a gluten free diet in guarding against lymphoma developing in coeliac disease. This was the first time that this had been demonstrated and the assertion has now been supported in at least 9 other studies so the proposition seems secure. This paper has been very influential and in the year of publication in 1989 in Gut, the Journal of the British Society of Gastroenterology, was the most quoted paper and was reproduced in a special edition of Gut to mark the Diamond Jubilee of the Society in 1997. It has since been cited on some 1118 occasions.

This paper can be criticised in that the risk of malignancy and particularly lymphoma, is overstated, because the work was done in an era when the prevalence of coeliac disease in the population was thought to be much less than it was later shown to be, following the advent of reliable serological screening tests.

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More accurate estimates of malignancy in coeliac disease (8)

In order to minimise the hazards of selection bias, a 24-year prospective, population-based cohort study of malignancy in diagnosed patients with coeliac disease was undertaken (8). For this investigation, data from the Derby coeliac disease register that I had compiled was utilised. All patients with coeliac disease diagnosed by small bowel biopsy and followed prospectively from 1978 to the end of 2001 were included in the study. This cohort of patients from a single centre in Southern Derbyshire was unique in studies of malignancy in coeliac disease, as it represented all cases occurring in a well-defined geographical area and follow-up was 99% complete. Referral bias is unlikely to have affected the results because Derby is not a tertiary referral centre for gastrointestinal diseases and patients in the study all derived from Southern Derbyshire. In addition, to avoid case ascertainment only malignancies occurring 2 or more years after the diagnosis of coeliac disease were considered in the main analysis. This was termed the post-diagnosis period. There were 637 patients with time to contribute to the analysis amounting to 5684 patient years of follow up (8) [Table 1]. Thirty-one malignancies (excluding non-melanoma skin cancer) were found when 30.30 were expected, so there was no increase in the overall cancer risk (SIR 1.02 95% CI 0.70-1.45). The risk for non-Hodgkin's lymphoma was elevated (SIR 5.80 95% CI 1.58-14.86). One lymphoma originated in the small bowel (SIR 40.51 95% CI 1.03-225.68) [Table 4]. This was the first time that an estimate for small bowel lymphoma in coeliac disease compared with the general population had been arrived at, presumably because other groups had no relevant population data to make the comparison. We used estimates generated by the West Midlands Cancer Intelligence Unit, which are likely to be robust because of validation of each registered case of lymphoma by reference to original case notes. This study also drew attention to the rarity of enteropathy-associated T-cell lymphoma, a tumour particularly linked to coeliac disease. Of 5 non-Hodgkin's lymphomas occurring in the period within 2 years of the diagnosis of coeliac disease, the peri-diagnosis period, only 3 were enteropathy-associated T-cell lymphomas [Table 4]. Small intestinal carcinoma was also shown to be a rare association, with only 1 occurrence.

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This overall risk for lymphoma is lower than previous estimates because of improved study design and reflects results from other investigations carried out at about the same time. In a study from Italy a relative risk for all non-Hodgkin's lymphoma was found to be 3.1, 16.9 for gut lymphoma and 19.2 for T-cell lymphoma (9). Only one patient with enteropathy-associated T-cell lymphoma was encountered.

European study of non-Hodgkin lymphoma in coeliac disease (10)

A large series of patients was required to confirm these findings and in order to achieve this a prospective, multicentre case-control study involving 12 working groups in 10 European countries was set up (10). This was supported by a grant from the Biomed-2 programme of the European Union. I travelled to Brussels with a colleague from the Netherlands to present the case to the Health Commissioner for carrying out the study which was accepted.

A total of 1446 patients with non-Hodgkin's lymphoma and 9655 controls recruited between May 1998 and April 2001 were screened for endomysial antibodies to detect coeliac disease and those found positive were offered a small bowel biopsy to confirm the diagnosis (10) [Figure 2]. It was found that patients with coeliac disease had a significantly increased risk of developing non-Hodgkin's lymphoma (OR 2.6 95% CI 1.4-4.9) [Table 2]. This risk was only present in those diagnosed clinically (OR 3.3 95% CI 1.4-7.9) but not in those with silent coeliac disease (OR 1.3 95% CI 0.6-2.7). Only 8 patients with enteropathy-associated T-cell lymphoma were identified which again highlighted the rarity of this tumour [Table 4]. This study emphasised the value of collaborative working because individual centres may not be able to recruit enough cases to draw valid conclusions. It was favourably reviewed by an expert in coeliac disease research and the finding that those detected by screening do not have an increased risk of lymphoma was particularly commented on (11). It was all regarded as good news and reassuring for patients.

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Non-lymphoma malignant complications of coeliac disease (12)

It was evident in early studies of coeliac disease that associated malignancy was not confined to lymphoma although this was given prominence. Certain gastrointestinal carcinomas, notably those of the oesophagus, pharynx and small intestine have also been linked (4, 5). We encountered 4 patients with adenocarcinoma of the upper small bowel in patients with coeliac disease and a review of the literature in 1980 revealed that only 14 others had been reported at that time (12). It was surprising that there were so few reports as this part of the bowel is characteristically abnormal in untreated coeliac disease with histological features of premalignancy (13). It was not possible from the study to say what the risk was of developing this tumour. Nearly all patients come to surgery and if the tumour is diagnosed early before it has metastasised, cure may be possible with long survival.

In the early 1980s a survey of coeliac disease and malignancy was undertaken (14). Twenty centres in the UK with an interest in coeliac disease were asked to report their experience. Overall, 133 lymphomas, 19 adenocarcinomas and 10 oesophageal carcinomas were encountered. The average number of tumours seen at each centre equates to 6.7, 0.95, and 0.5, respectively. These figures illustrate how rare these are, a fact curiously largely overlooked at that time.

Primary small bowel malignancy associated with coeliac disease (15)

Under the auspices of the British Society of Gastroenterology, I along with 3 other colleagues undertook a survey of small bowel malignancy in the UK and its association with coeliac disease (15). Clinicians in the UK registered with the British Society of Gastroenterology were asked using cards mailed out every month, to report newly diagnosed cases of primary small-bowel malignancy that they had encountered between June 1988 and May 2000. Following notification of a case further details were requested including demographic, clinical and pathological information and in particular whether coeliac disease was present or not. Telephone contact was made with clinicians to clarify details if deemed necessary. This was a very successful venture, for 395 cases including 175 adenocarcinomas, 107 lymphomas and 79 carcinoid tumours were reported. In 13% (23 of 175) of adenocarcinoma cases and 39% (42 of

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107) of lymphomas there was a diagnosis of coeliac disease [Table 1]. Adenocarcinomas (94%) and lymphomas (80%) associated with coeliac disease were in the proximal small bowel as might be expected because this is the part of the small intestine damaged in untreated coeliac disease. As expected most of the lymphomas (89%) were enteropathy-associated T-cell type, an entity first described in 1986 (16). About half of patients with these tumours presented acutely with features such as intestinal obstruction, haemorrhage or perforation. At the time of diagnosis about a half of patients with adenocarcinomas and a third with lymphomas had widespread metastatic disease resulting in a poor prognosis. The overall survival for those with adenocarcinomas was 58% at 30 months but for those with widespread disease was only 35% [Figure 1]. There was no evidence that having coeliac disease worsened the outlook. For patients with lymphoma the overall survival was 45% at 30 months but for those with advanced disease it was only 30%. The prognosis for those with coeliac disease was particularly poor with a 30 month survival of only 13 % compared with 52% for those without [Figure 3].

This national survey was one of the first such to be carried under the auspices of the British Society of Gastroenterology and resulted in the largest number of small intestinal malignancies reported in one series. It showed that there are clearly advantages in ascertaining cases of a rare disease through a central data base. Individual departments specialising in the diagnosis and management of coeliac disease, even large ones, do not encounter small bowel malignant tumours in sufficient numbers to draw any valid conclusions regarding their frequency and natural history. In this study over a 2 year period, 395 events, a commendably large number, were recorded for analysis. Such a scheme does have potential disadvantages. There may be under reporting but the number of tumours actually reported, accorded with the numbers predicted by data from the Derby coeliac clinic. Using the data from Derby, 55 lymphomas and 22 adenocarcinomas of the small bowel would be expected to occur in the UK during the 2 years of the survey. Given that 42 lymphomas and 23 adenocarcinomas were ascertained, suggested that reporting reflected the national expected incidence rate of small bowel malignancy associated with coeliac disease. The survey provided evidence that small bowel tumours are rare in the UK and in particular that the risk to coeliac

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patients developing malignancy is very low. These data were reassuring for patients and their carers.

Reviews of malignant complications

I have authored or co-authored several publications in journals or books that have reviewed knowledge of the malignant complications of coeliac disease as it has become available. These were often commissioned and spanned the years 1974-2014.

The earliest one on malignant complications published in 1974 was an attempt to summarise the sparse research that had been carried out to that date. It was recognised that the development of malignancy was a very serious problem with a poor prognosis, which was difficult to diagnose and for which there was no effective treatment. In particular, whether giving a gluten free diet to patients would reduce the lymphoma risk was not known (17).

A second article was published in 1978, based on a lecture that I gave to the Third International Symposium on Coeliac Disease held in Galway, Ireland in 1977. The clinical features of 27 patients with lymphoma who had attended the Department of Gastroenterology at the General Hospital Birmingham, were reviewed. Two thirds were diagnosed at laparotomy or autopsy. The appalling prognosis of patients who developed lymphoma was evident and measured in months. There was no effective treatment and still no evidence that a gluten free diet protected against the development of lymphoma (18).

A chapter that I co-authored in 1992 was a comprehensive account of the subject up to that time and covered clinical, diagnostic and pathological aspects (19). It contained many illustrations of the gross appearance of tumours and histological findings. The intriguing connection, not fully worked out then, between bowel lymphoma and chronic ulceration of the small intestine was also highlighted. The protective role of a gluten free diet in preventing the development of lymphoma was becoming apparent and was emphasised.

Two further reviews in the 1990s were constructed along similar lines and designed to keep readers up to date (20, 21). There was growing interest in the

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cellular origins of lymphoma, the role of intraepithelial lymphocytes in the development of enteropathy-associated T-cell lymphoma (the characteristic lymphoma that complicates coeliac disease) and genetic markers in coeliac disease and enteropathy-associated T-cell lymphoma and these were summarised in a later review that also included a discussion of non-responsive coeliac disease and its relationship to lymphoma which was becoming better defined (22).

In 2005, I co-authored a major review of malignancy in coeliac disease commissioned by the American journal, Gastroenterology, which is the most prestigious gastroenterology journal in the world (23) . By this time, important epidemiological studies had been published which showed that while coeliac disease is significantly associated with an increased risk of non-Hodgkin lymphoma, especially of the T-cell type and primarily located in the bowel, the link is less common than previously supposed with a relative risk of about 3. In addition, much evidence was accumulating to show that a gluten free diet was beneficial in reducing the risk of lymphoma from developing.

Non malignant associations

Coeliac disease is common so that other disorders will occur in association from time to time. Some of these will occur only by chance but others will have a statistically valid relationship. Those caring for coeliac patients need to aware of these links so that patients receive optimum treatment. Twenty-one publications that I have authored or co-authored are included in this section.

Autoimmune disorders

Early reports including small numbers of patients drew attention to coexistent disorders with known or suspected immunological aetiology. It was speculated that circulating immune complexes originating in the damaged mucosa or the passage of antigens across the permeable small bowel mucosa might trigger the development of these associations. We decided to analyse a large number of biopsy proven patients with coeliac disease diagnosed between 1958 and 1977 at the General Hospital Birmingham, with regard to immunological disorders (24). Of 314 patients considered, 63 had associated disorders of

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known or suspected immunological cause. The most common disorders encountered were diabetes mellitus, thyroid disease and ulcerative colitis [Table 1]. Other disorders found were connective tissue disease, chronic liver disease and diffuse lung disease. Twenty three atopic disorders were found in 22 patients. One women had eczema and one asthma. A gluten free diet and near normal jejunal biopsy did not prevent the development of these associations and had no effect on their course. Weaknesses are easy to identify in this survey. Information was obtained from direct interview with patients and by review of hospital notes when this was not possible. Only when there was a definite diagnosis of a disorder was this counted, although it is likely that there was an underestimation if information had not reached the notes or patients had failed to mention or forgotten about a diagnosed association. No firm conclusions could be drawn from these data regarding the frequency of the associations because the incidence of coeliac disease in the community was not known and that of immune disorders even less so. Nevertheless, interesting data were gleaned from this study and it pointed the way to future research.

Inflammatory bowel disease

There was an indication in the previous study that ulcerative colitis was commonly associated with coeliac disease with numbers possible greater than expected (24). From the Gastrointestinal Unit at the General Hospital Birmingham, 4 patients were reported having associated coeliac disease and inflammatory bowel disease, 3 with ulcerative colitis and 1 with Crohn's disease (25). Taking into account the prevalence of inflammatory bowel disease in the community at 96-190 cases per 100,000 and that 420 patients in the unit were surveyed, the observed prevalence in the series would be 5-10 times than expected. However, the patients were derived from a referral centre for inflammatory bowel disease and coeliac disease so were from a selected group. The main reason for reporting these cases was to encourage others to identify additional examples and so perhaps clarify better the nature of the association.

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Diabetes mellitus

It appeared that diabetes mellitus was the disorder most commonly associated with coeliac disease and worthy of further research. In 1984, I undertook a search for relevant publications for a chapter in a book on coeliac disease that I co-authored and was able to find 28. Nineteen of these included jejunal biopsy proven cases and in 14 patients had shown clinical and/or biopsy improvement on gluten free diet (26). This was the most commonly reported disorder associated with coeliac disease. At that time there was not enough evidence to state whether the association was more than could be accounted for by chance.

Because of the paucity of information in adults, we set up a study to determine the prevalence of coeliac disease in an unselected hospital-based adult diabetic population using IgA-antigliadin antibody (AGA) screening followed by endoscopic duodenal biopsy. In addition, whether those with coeliac disease had compatible symptoms of malabsorption was assessed and their acceptance of and response to a gluten free diet documented (27). A total of 1785 diabetic patients were screened between April 1st 1992 and March 31st 1993. 43% had insulin dependent diabetes mellitus (IDDM) and 57% non-insulin dependent diabetes mellitus (NIDDM). Of those screened, 73 had raised IgA-AGA and 8 selective IgA deficiency. Duodenal biopsies were performed in 49 patients with raised IgA-AGA of whom 10 with IDDM and 3 with NIDDM had small bowel histology compatible with coeliac disease. Twenty-four patients for various reasons did not have endoscopy. One of those with selective IgA deficiency also had coeliac disease so in total 14 new patients with coeliac disease were identified [Figure 1]. Of these, 4 had microcytic anaemia, 9 low serum ferritin and 4 low albumin-corrected calcium. Eight had gastrointestinal symptoms or chronic fatigue that improved on gluten free diet and 6 were asymptomatic. In addition during the study we encountered 4 patients, all IDDM, with known coeliac disease. The overall prevalence of coeliac disease in diabetes was 1:100 (18 in 1789). In adult IDDM it was 1:50 compared with 1:340 for NIDDM. Coeliac disease is common in IDDM and may cause malabsorption and ill-health that is corrected by gluten free diet. These figures may be underestimates of the true prevalence because it was assumed that

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patients who were not endoscoped did not have coeliac disease. Overall diabetic control did not change with the adoption of gluten free diet, although our patients did not experience hypoglycaemia and their diabetes was stable.

Based on these figures, our data suggested that at that time 2500 in England and Wales would have coexistent coeliac disease with about 1800 not diagnosed. It was emphasised that symptoms in these patients may be wrongly attributed to diabetes, so the diagnosis of coeliac disease may not be considered which is unfortunate because a gluten free diet can restore full health. It was shown that screening for coeliac disease is possible and may be worthwhile. Our results began a debate on this aspect of management for these patients.

Reviews of the association between coeliac disease and diabetes

Based on my interest in coeliac disease with co-existing diabetes mellitus I was asked to write three reviews. The first summarised what was known about the relationship between coeliac disease and Type 1 diabetes mellitus with emphasis on the prevalence of coeliac disease in diabetes in adults and children, possible reasons for the association, clinical presentations, the value of gluten free diet, implications for the control of diabetes and implications of screening programmes (28). Twenty papers exploring the prevalence of coeliac disease by serological screening of Type 1 diabetes in children, 8 in adults and 2 including both groups were found. An additional 48 publications were included and were related to serological screening for coeliac disease, expressions and complications of coeliac disease, the value of gluten free diet and the genetics of the two conditions. It was evident that more recent studies were now employing the more sensitive and specific screening tests looking for endomysial and anti-tissue transglutaminase antibodies.

Unless screening of patients with diabetes is undertaken coeliac disease will be missed, because patients often have atypical symptoms or none and even in those with classical symptoms the diagnosis may be overlooked and attributed wrongly to diabetes. Based on biopsy proven coeliac disease the prevalence of Type 1 diabetes in children in these publications was 1:6 to 1:103 and in adults 1:16 to 1:76. So the association occurs commonly. Following the institution of

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gluten free diet, patients may improve in terms of symptoms, growth in children, serum antibody levels, haematological and biochemical indices, morphology of the small bowel mucosa and control of diabetes. It was recommended that screening for coeliac disease should be undertaken and was cost effective. It was clear from the various series that a single screening is not enough because tests previously negative can become positive. In the absence of firm evidence, it was suggested that it would be prudent to screen at the diagnosis of diabetes and annually for 3 years, then at 5 years and then 5 yearly thereafter, or at any time if there are clinical indications.

The second invited review came from a paediatric journal (29). The average prevalence of coeliac disease among children with diabetes mellitus in 26 reports then available was 4.5%. There were a number of questions to consider. Will health benefits accrue in children in terms of resolution of symptoms, a reduction in complications associated with coeliac disease and improved control of diabetes if given a gluten free diet? Is one test enough and if not, when should subsequent tests be carried out? Is a screening programme cost effective when compared with other screening programmes, for example, for congenital hypothyroidism, cystic fibrosis and phenylketonuria? All these issues were discussed in the review. It was easy to make a case for screening given the high frequency of the association, the availability of high performing screening tests, on economic grounds and that intervention with gluten free diet can improve health and avoid complications. Indeed, many paediatricians were already screening and this practice was subsequently endorsed in guidelines published by the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) published in 2012 (30). A helpful algorithm was presented that set out a strategy that should be followed. Our work was referenced in these guidelines and contributed to a reconsideration of the diagnostic criteria for diagnosing coeliac disease.

The last commissioned review published in 2015 on this association, was aimed at nurses (31). It was concluded that although there is still much to unravel on this subject, enough is already known to guide health care workers in the diagnosis and management of people with associated coeliac disease and type

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1 diabetes and that it was incumbent on practitioners to be aware of this link so that patients receive optimal care and enjoy good health.

Neurological and psychiatric disorders

Neurological disorders associated with coeliac disease was a special interest of the Gastroenterology Department at the General Hospital, Birmingham and in 1966, 2 influential papers were published that documented 16 patients encountered, 9 of whom had autopsies. Clinical details and pathological findings were described in detail. The aetiology of the association was unknown and the outlook for these patients was very poor (32, 33). I continued with this interest and co-authored a report of 4 patients with coeliac disease who had developed neurological complications (34). Unfortunately, there had been no advances in understanding of this condition since the original paper nearly 30 years previously.

In 1997, I was invited to speak at a symposium on Epilepsy and other Neurological Disorders in Coeliac Disease held in San Marino. My title was neurological and psychiatric complications in coeliac disease and the contribution appeared in a book of the proceedings that same year (35). For this occasion, I reviewed these problems in 388 unselected patients with coeliac disease in my own clinic in Derby. In total 106 patients (26%) developed 132 neurological or psychiatric problems; several patients had more than one disturbance [Table 1]. Since patients were unselected and drawn from the local area, these data were likely to reflect the numbers and types of neuro-psychiatric disorders that occur in the community. Many of the disorders were only encountered as single cases but depression, epilepsy and migraine were well represented and the three commonest problems recorded. Depression affected 10% of the group and while it is an important feature in some instances, it is not certain whether it is more common in coeliac disease than the general population. Epilepsy did seem more common in coeliac disease at 3.6% for a prevalence in the population of about 0.5%. The prevalence of migraine at 3.1% was the same as in the community. Although care was taken only to include disorders for which there was good evidence, caution has to exercised in interpreting these results because it can be difficult to define

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these conditions with certainty and an added problem is that the prevalence in the population is difficult to determine.

We prepared a review for the Postgraduate Medical Journal on the neurological complications of coeliac disease which was published in 2002 (36). For this the experience of the Derby coeliac clinic was brought up to date. We found 263 neurological and psychiatric conditions in 189 (30%) patients out of 620 with coeliac disease (some patients had more than one condition) [Table 1]. This was a similar proportion to that found in the earlier study and again the commonest associated conditions were depression (11.5%), epilepsy (4.0%) and migraine (3.2%). Whether a specific neurological disorder occurs in coeliac disease remained unproven. Malabsorption did not satisfactorily explain the pathophysiology and it was considered that autoimmunity, heredity and gluten toxicity might have a role. In 2004 this review was reproduced in a book along with others that the editor referred to as outstanding (37). We looked in more detail at the prevalence of epilepsy in a large group of 801 unselected coeliac patients attending my clinic in 2004 and the condition did not appear to be significantly more common among these than in the population (38). Some other studies did find an association but conclusions were based on small numbers of patients.

Osteoporosis and bone metabolism

Coeliac disease has long been known to cause metabolic bone disease both osteomalacia secondary to calcium and vitamin D malabsorption and osteoporosis (39). Osteoporosis as determined by non-invasive dual-energy X-ray absorptiometry (DEXA) is common in coeliac disease affecting about half of patients and predisposing to fracture. However, because the magnitude of the risk was unknown we surveyed a population of patients recruited from Derby and Nottingham with coeliac disease (244 patients and 161 controls) to assess this. No overall increased fracture risk was found in this study, the largest to that date (40). A later meta-analysis found only a moderate fracture risk (41). The results indicated that surveillance by DEXA scanning was not warranted in general for osteoporosis, although subpopulations such as elderly women, those with a family history of osteoporosis, previous fractures and poor adherence to gluten free diet should be checked (42).

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Mesenteric lymph node cavitation syndrome

I first encountered a patient with this condition in 1982. Coeliac disease had been diagnosed in childhood in 1944. In 1982, he was referred to me very ill. Masses could be felt in the abdomen. It was feared that he had developed malignant lymphoma but at laparotomy large, multiple, tense cysts were found in the intestinal mesentery, the largest being 8 cm in diameter. The cysts were decompressed and after a stormy postoperative period he made a full recovery and was re-established on a strict gluten free. This very rare syndrome had previously been reported in the French literature but only in a handful of patients. My paper was the first to report this in English (43). The importance of the syndrome is that it may be mistaken for lymphoma or other cancerous growths in the abdomen although it is a benign condition and amenable to treatment.

Reviews of non-malignant complications

With regard to long-term health risks and non-malignant complications, I have authored or co-authored 8 invited reviews which have appeared in journals or as book chapters. The first was published in 1992 and drew attention to problems associated with fertility and pregnancy, disturbances of bone and calcium metabolism and neurological and psychiatric disturbances, all of which were increasingly being recognised around that time (44). A further review was commissioned 4 years later when I was able to report in much more detail on all these and other aspects. It was emphasised that the diagnosis of coeliac disease was crucial because a gluten free diet not only improves the general health of patients but may positively influence the development and progress of these associations (45). Other reviews have already been mentioned and contained new information from my Derby coeliac disease clinic as outlined above (36, 37, 46).

On the strength of our interest in the neurology of gastrointestinal disorders we were invited to contribute an editorial to the Journal of Neurology, Neurosurgery and Psychiatry which was published in 2006. This editorial had a wider remit than just coeliac disease and covered neurological complications of gastrointestinal, hepatic and pancreatic disease in adult patients (47). The

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role of liver failure in the development of neuropathology was well established but for other enteric diseases, whether any specific disorders occur remained unproven.

In 2010 and 2014, a colleague and I published major reviews of the risk of morbidity in contemporary coeliac disease, one in a journal (48) and the other as a book chapter running to 34 pages and 263 references (49). Many good studies were available of disorders occurring with coeliac disease that gave accurate estimates of the risk of the associations. It was concluded that those who care for coeliac patients need to be aware of these associations so that optimal management can be given. These are probably the most comprehensive accounts to date.

Malignant and non-malignant deaths in the serology era

The introduction of serological tests to aid the diagnosis of coeliac disease in the early 1990s led to more and more diagnoses being made (50, 51). Many, perhaps even most of these would not have been diagnosed in the pre-serology era because of so-called atypical or mild symptoms that may not have indicated coeliac disease as a potential diagnosis. An unanswered question was whether patients diagnosed in the serology era with less severe disease, experienced excess mortality and if so what was the magnitude of the risk. Most studies that had been carried out contained relatively small numbers of patients and gave contradictory results.

In order to address this issue Derby coeliac patients were stratified according to the year of diagnosis; (i) before 1990, (ii) between 1990 and 1999, and (iii) from 2000 onwards (50). These periods reflected the increasing use of serological tests to detect the condition. For this exercise only incident cases were considered i.e. those diagnosed after January 1978. There were 987 such individuals contributing 7,431 person-years beyond 2 years after the diagnosis of coeliac disease (post-diagnosis period) [Table 4]. Over the time of the study there was an exponential year-on-year increase in the number of diagnoses being made in the Derby Hospitals [Figure 1]. The number of diagnoses was eight-fold higher in 2001-2005 compared with 1981-1985. Patients diagnosed

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solely by serology were not considered. Overall, there was no trend towards increased or reduced mortality with a more recent diagnosis [Table 4].

To the end of 2006, 1,285 individuals were diagnosed with coeliac disease in Derby of whom 1,092 had follow-up beyond 2 years after the diagnosis of coeliac disease (post-diagnosis period) and were available for analysis. In this group were 142 deaths which represented a statistically significant increase from all causes compared with the general population of England and Wales (SMR=1.37; 95% CI 1.16-1.62) [Tables 1 and 2]. Raised risks were found for respiratory (not significant) and gastrointestinal disease (significant). When the risks were compared with those in the peri-diagnosis period (within 2 years of the diagnosis of coeliac disease), the increase in mortality was similar (SMR=1.31; 95% CI 0.89-1-84), significantly increased for men (SMR=1.86 95% CI 45-2.34) but not for women. Deaths from cancer and gastrointestinal disease were more pronounced than in the post-diagnosis period. [Table 2]. Overall there was a marked increase in deaths from non-Hodgkin's lymphoma (SMR=7.06; 95% CI 2.59-15.4) [Table 3]. Over half of the deaths due to respiratory causes (11 of 21) were due to pneumonia although the risk of death was not statistically significant [Table 3].

The results showed no evidence of a reduction in mortality associated with coeliac disease diagnosed in the most recent decade, and the magnitude of the overall increased risk was only modest. It might have been expected that the risk would have decreased, because in the serology era milder cases of coeliac disease would be diagnosed with risks more akin to the general population but this was not confirmed.

A key strength of this study is that it is truly population based and therefore unlikely to be biased in the selection of cases. There were over 10,000 person-years of data and 142 deaths in the postdiagnosis period for analysis. Furthermore, in contrast to most other studies, it covered the period before and after the introduction of serological tests and allowed time trends in mortality in relation to this. It was possible to examine the risk of death from pneumonia and liver disease. The interest in coeliac disease in Derby will have contributed to the high numbers of patients diagnosed but if anything this

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should have led to less symptomatic patients being diagnosed and a reduced mortality rate that we sought but it did not.

In this study it was possible to perform a time stratified analysis. Most other studies at the time could not do this because their data did not cover the pre and post serology eras. By doing this we produced important information for clinicians which showed that there remains an increased relative risk of death from lymphoma but the overall mortality increase is modest so that patients can be reassured. It was suggested that further research into deaths from liver disease and pneumonia was warranted and greater consideration should be given to vaccinating against pneumococcal infection which might reduce mortality.

It was envisaged that results from this study would be updated when more diagnoses had been made and there were more deaths to consider and using similar methodology. This was undertaken and included patients with coeliac disease diagnosed to the end of 2014 (51). At this time there was a total of 2515 patients of whom 750 were diagnosed by serological tests alone. 2174 patients in the series had at least 2 years of follow-up (postdiagnosis period) and contributed 23955 person-years of follow-up. The median duration of follow-up had risen from 6.2 to 9.3 years [Table 1]. The mean age at baseline was older for all patients at 46.1 years, compared with 45.6 years previously and in those with at least 2 years of follow-up at 45.5 years compared with 44.8 years previously. There were 284 deaths [Table 1]. So there was much more data available for this new analysis.

Table 2 shows that the SMR for all deaths in the postdiagnosis period was now 1.57 compared with 1.37 previously. Taking the confidence intervals into account, this is a fractional increase without real significance but could be as much as 77% more deaths in this population compared with 62% in the previous study. There were significant increases in deaths for all categories studied except for cardiovascular disease which fell just short of significant. Of interest, in the peridiagnosis period, the SMR reduced in all instances apart from cardiovascular disease.

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When individual causes of death were analysed for the postdiagnosis period there was an increase for non-Hodgkin's lymphoma (SMR 6.32; 95% CI 2.89-12.0) [Table 3]. Breast cancers were non-significantly reduced. No increase or decrease for cancer of the lung was observed. Deaths from pneumonia were significantly increased (SMR 2.58; 95% CI 1.66-3.85) and those from liver disease (SMR 3.10; 1.34-6.10) [Table 3]. A significant increase was found for oesophageal cancer (SMR 2.8; 95% CI 1.03-6.08). No changes for uterine or ovarian tumours occurred.

In this new study, the SMR for deaths after 1 January 2000 has fallen to 1.60 (95% CI 1.32-1.92) from SMR 2.23 (95% CI 1.83-2.70) between 1 January 1990 and 31 December 1999. This is only marginally insignificant. In the previous study there was no trend towards increased or reduced mortality. However, in this new investigation, there was for the respiratory group - SMRs of 1.34 > 2.50 > 2.85 [Table 4]. In other disease areas, risks were greatest during the 1990 to 1999 period but reduced post 2000, which follows the same findings as in the earlier study.

Previously, the overall mortality risk among people with coeliac disease was 14.0 per 1,000 person-years compared with 10.2 in the general population. New figures were 11.9 compared with 10.5, giving an absolute risk difference of 1.4 per 1.000 person-years compared with 3.8 previously. This has reduced by more than half [Table 5]. There was no difference in the attributable risk between causes related to and not related to coeliac disease. Previously, 34% of the overall difference in risk was attributed to coeliac disease deaths while 66% was not. In the new study it was 50/50. This suggests that the differences in risk attributed to coeliac deaths (non-Hodgkin's lymphoma, pneumonia or coeliac disease) is growing.

A strength of this new study is that it analysed a substantial number of non-selected patients with coeliac disease attending a single centre in Southern Derbyshire and the outcome for these was complete for 99.8% of cases. Ascertainment bias was minimised by excluding the first 2 years of follow-up after the diagnosis of coeliac disease. Patients diagnosed by serological tests alone using validated criteria were included. To have ignored these would have removed some 30% of patients from consideration which would have distorted

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the results. It can be speculated that including these cases has impacted on the risk of mortality on the cohort as a whole. According to these data there is an opportunity to improve survival by implementing vaccination programmes for pneumonia and more prompt and aggressive treatment of liver disease.

Conclusions

The publications presented, form a body of research that I have been involved with on the theme of morbidity and mortality in coeliac disease covering the years 1974 to 2018 – a 45 year period. When I began my research at the start of this era, little or nothing was known about conditions leading to morbidity and mortality. I designed my research agenda to try and correct gaps in knowledge with I believe, some success.

In this thesis, I have presented 35 publications, 14 devoted to malignant and 21 to non-malignant associations and complications, covering a wide spectrum of conditions including lymphoma and non-lymphoma malignancy, inflammatory bowel disease, diabetes mellitus, thyroid disease, neurological and psychiatric disorders and disturbances of bone. My publications on malignant complications particularly lymphoma have been ground breaking, well received and widely quoted. My paper, *Malignancy in coeliac disease – effect of a gluten free diet* published in the journal Gut in 1989, was the most quoted paper in the year of publication for that journal. It has been cited over 1120 occasions. More recently I have provided in the final paper, risk estimates for various disorders causing death in contemporary coeliac disease and have indicated how reduced mortality might be achieved in some instances. My publications on associated diabetes mellitus have also been referred to quite widely. For 24 papers where information exists, the total number of citations stands at almost 3,900. This excludes references to my book chapters.

In recent years with the development of methods to identify patients with coeliac disease and more sophisticated approaches to epidemiology, reliable data on conditions contributing to morbidity and mortality in coeliac disease have emerged. My research activity reflects this evolution and I believe has influenced it. It has been an exciting and rewarding time to be exploring these issues for the benefit of patients, their families and carers.

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