Papers and Originals

Follow-up Study of Coeliac Disease

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Summary : In 9 out of 10 adults in whom a diagnosis of coeliac disease had been made in childhood, the diagnosis was confirmed by the finding of a flat intestinal mucosa. None showed abnormal physical signs, but three had a haemoglobin concentration below 10 g./100 ml. and all those not receiving folic acid supplements showed low serum folate levels. Five had moderate to severe symptoms at the time of investigation, but none was receiving treatment with a gluten-free diet.

Periodic investigation of these patients may be necessary throughout life, and if they are found to have malnutrition they should be treated with a gluten-free diet.

Introduction

It is now established that the jejunal mucosa is abnormal in adult patients with idiopathic steatorrhoea. About a third to a half of such patients give a history of childhood coeliac disease (Badenoch, 1960 ; Cooke, Fone, Cox, Meynell, and Gaddie, 1963 ; Stewart, Pollock, Hoffbrand, Mollin, and Booth, 1967), and it has been postulated that a patient presenting for the first time in adult life without a previous history suggesting coeliac disease has had an abnormal mucosa unrecognized throughout life. However, previous studies of patients who have had coeliac disease as children and have remained on a gluten-containing diet have not included a description of the state of the jejunal mucosa.

This paper describes the follow-up study of 10 patients in whom a diagnosis of coeliac disease had been made in childhood and who had received little or no treatment with a gluten-free diet until biopsies were carried out at ages varying from 23 to 40 years. Eight of these cases had previously been described both by Hardwick (1939) and by Lindsay, Nordin, and Norman (1956).

Materials and Methods

Haematological methods were those described by Dacie (1956).

Serum folate concentrations were measured by microbiological assay using *Lactobacillus casei*, as described by Waters and Mollin (1961). Control subjects have levels between 6 and 21 mμg./ml.

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Serum vitamin B_{12} levels were measured with the z strain of *Euglena gracilis* according to the method described by Anderson (1964). Control subjects have levels between 160 and 900 mμg./ml.

Serum calcium, phosphate, and *alkaline phosphatase* were estimated as described by King and Wootton (1956).

Xylose absorption was studied by estimating the five-hour urinary excretion of a 25-g. oral dose of D-xylose by the spectrophotometric method of Roe and Rice (1948). Control subjects excreted more than 5 g. in the five-hour period.

Mucosal biopsies of the proximal small intestine were performed with the Crosby capsule (Crosby and Kugler, 1957). They were first examined with a dissecting microscope (Holmes, Hourihane, and Booth, 1961), photographed (Brackenbury and Stewart, 1963), and then studied histologically (Stewart et al., 1967, modified from Shiner and Doniach, 1960).

Patients Studied

Ten patients who had been diagnosed as suffering from coeliac disease in childhood and who had reached adult life were studied. Eight of these patients were originally diagnosed and treated at the Hospital for Sick Children, Great Ormond Street (Hardwick, 1939). Hardwick based his diagnoses on the following criteria: diarrhoea, anorexia, wasting, abdominal distension, and excess split fat in the stools on more than one occasion. He reported 22 deaths in hospital and four deaths after discharge, and in 1939 was able to trace 37 of the surviving 47 patients.

In 1956 a further review of 25 of Hardwick's patients was reported by Lindsay et al., 18 of whom were seen by these authors.

In 1965 only 11 of these 18 patients could be traced, eight of them being admitted to hospital for investigation. Two further adult patients who had been diagnosed by the same criteria in childhood were also included in the present study.

The original diagnosis was made in nine patients between the ages of 1 year 6 months and 3 years 9 months (mean 2 years 4 months). The tenth patient presented at 7 years 10 months. Two were male and the other eight were female.

TABLE I.—*History, Height, and Weight*

Case	Sex	Age at Initial Diagnosis (Years)	Duration of Childhood Symptoms	Gluten-free Diet	Age at Biopsy	Height cm.	Height in.	Weight kg.	Weight lb.
C.C.	M	3 8/12	5 years	Never	32	175·2	69	60	132
K.H.	M	1½	6½ years	Never	27	166·5	65½	56·5	125
J.A.	F	2 8/12	Never symptom-free	Never	40	151·2	59½	46·6	103
R.B.	F	7 10/12	Never symptom-free	For 1 year at 8 years	23	155	61	42	92
M.E.	F	2½	Never symptom-free	Never	32	152·5	60	50·8	112
P.M.	F	2¾	11¼ years	Never	30	156·2	61½	52·5	116
G.S.	F	3	Never symptom-free	For 3 months	24	143·5	56½	47·6	105
J.S.	F	1½	10¼ years	Never	30	160·8	63½	62·2	137
B.T.	F	3¾	10 years	Never	40	166·5	65½	60·0	132
J.C.	F	2½	Never symptom-free	Never	28	162·5	64	60·8	134

Present Study

History and Clinical Findings.—Two men (C. C. and K. H.) had remained symptom-free since childhood (Table I). Only two of the women (J. S. and P. M.) had no symptoms when investigated, but both had been treated for anaemia with oral iron in pregnancy and one (J. S.) had had diarrhoea in pregnancy. Another (J. C.) complained of no more than mild abdominal discomfort. She had had two uneventful pregnancies. The remaining five women had symptoms for which one was seeing her family doctor and four were attending hospital. The first of these (J. A.) had intermittent diarrhoea and tired easily. Another (R. B.) had mild diarrhoea during adolescence and then developed megaloblastic anaemia during her first pregnancy. One (G. S.) had had recurrent tetany throughout childhood and adolescence and developed megaloblastic anaemia at the age of 13. Another (B. T.) had remained well in adolescence but relapsed with tetany at the age of 25 and later developed megaloblastic anaemia. The last (M. E.) had abdominal pain, vomiting, and diarrhoea at the age of 30 and was admitted to hospital with symptoms on three occasions. None of these patients showed abnormal physical signs except for reduced height and weight (Table I).

Haematological Investigations.—The most striking feature in all patients not receiving folic acid supplements was the low serum folate level (Table II). In four this was below 3 mμg./ml. Serum B_{12} levels were normal in all 10 patients. Both the men had normal haemoglobin levels and blood films, though their serum folate levels were low (2.3 and 3.6 mμg./ml.). Of the eight women four were anaemic and four had normal haemoglobin levels. Only two of the latter had normal blood films. One of these (J. A.) was receiving folic acid and iron, the other (J. C.) was receiving no treatment and had a folate level of 5.4 mμg./ml. All the other patients, despite treatment with iron in two and folic acid in one, showed gross changes, either macrocytosis or microcytosis, or both.

TABLE II—*Haematological Findings*

Case	Hb (g./ 100 ml.)	Signs of Iron Deficiency	Macro-cytosis	Serum Folate (mμg./ ml.)	Serum Vitamin B_{12} ($\mu\mu$g./ ml.)	Past Treatment
C.C.	14·2	−	+	3·6	360	—
K.H.	15·0	+	−	2·3	225	—
J.A.	14·9	−	+	4·8	340	Iron, folic acid
R.B.	9·1	+ +	+ + +	1·0	240	—
M.E.	11·8	+ +	+	4·0	240	—
P.M.	13·5	+	+ + +	0·8	230	Iron
G.S.	13·1	+	−	−	205	Folic acid (currently)
J.S.	9·5	+ + +	+	0·8	490	—
B.T.	9·1	+ + +	−	10·6	370	Iron, recent folic acid
J.C.	14·2	−	−	5·4	490	—

Biochemical Investigations.—The results of these studies are shown in Table III. Only one of the eight patients (R. B.) in whom the serum calcium was estimated had an abnormally low level (3.9 mN). This was found one week post partum when her baby developed fits. Xylose absorption was normal in two patients (M. E. and C. C.), moderately impaired in three (J. S., J. C., and K. H.), and severely abnormal in one (R. B.).

TABLE III.—*Biochemical Findings*

Case	Serum Calcium (mN)	Serum Phosphate (mN)	Serum Alkaline Phosphatase (K.A. Units)	Urinary Xylose Excretion (g.)
C.C.	5·2	1·5	5	7·1 1
K.H.	4·9	2·2	11	4·1
J.A.	5·7	1·7	10	—
R.B.	3·9	1·7	12	2
M.E.	5·0	2·0	6	5·8
P.M.	4·6	2·2	9	—
G.S.	—	—	—	—
J.S.	4·7	1·7	8	4
B.T.	4·8	1·8	10	—
J.C.	—	2·0	6·4	4·8

Intestinal Biopsies.—Specimens were obtained from all 10 patients. All showed a flat or flat with mosaic mucosa with subtotal villous atrophy, except for one (C. C.) who had normal mucosa and whose original diagnosis is considered, for reasons given below, to have been incorrect. The biopsies are described in detail in Table IV. A typical mucosal appearance from a patient (J. S.) aged 30 and symptom-free for 20 years is shown in Figs. 1 and 2.

TABLE IV.—*Intestinal Biopsies*

Case	Site*	Dissecting Microscope Appearance	Villous Height (μ)	Mucosal Thickness (μ)	Surface Cell Height (μ)	Inflamm. Cells
C.C.	J1	Finger-like villi	555	148	30·6	±
K.H.	J2	Flat with mosaic	0	329	21·5	+
J.A.	D4	Flat	0	360	17·7	+ +
R.B.	J2	Flat with mosaic	0	332	19·2	+ +
M.E.	D3	Flat with mosaic	0	286	21·3	+ +
P.M.	J2	Flat with mosaic	0	205	21·4	+ +
G.S.	D4	Flat	0	308	18·5	+ +
J.S.	J1	Flat with mosaic	0	286	19·0	+ +
B.T.	J1	Flat with mosaic	0	364	16·1	+
J.C.	J1	Flat with mosaic	0	344	19·7	+
Control subjects†	Proximal intestinal mucosa	Finger-like to broad leafy villi	330–636 (489)	65–170 (109)	29·3–36·8 (32·7)	− to +

* Site: numbers denote part of duodenum or loop of jejunum from which biopsy was taken.
† Stewart *et al.* (1967).

Discussion

The results of this investigation show that children with coeliac disease retain their abnormal jejunal mucosa for as long as 18 to 38 years after developing symptoms in childhood. Nine of these patients had flat or flat with mosaic proximal intestinal mucosa (Table IV).

The one exception was the patient (C. C.) who had a normal jejunal biopsy. Reappraisal of this patient's early history and further progress casts doubt on the original diagnosis of coeliac disease. He presented at 3 years 8 months with a two-year history of anorexia and was found to have severe anaemia (Hb 3.3 g./100 ml.). There was no diarrhoea or distension, though stool analysis showed a fat content of 45%. Though

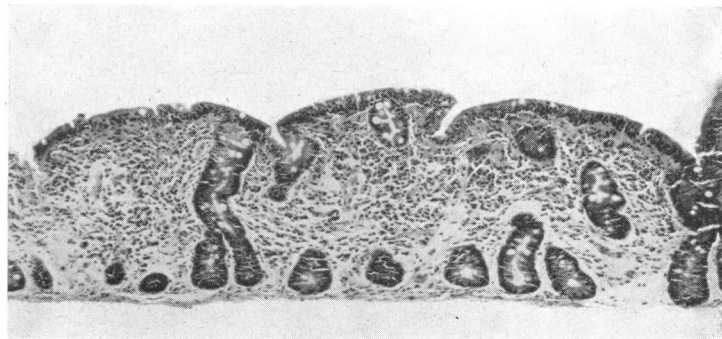## P. E. MORTIMER *ET AL.*: FOLLOW-UP STUDY OF COELIAC DISEASE

FIG. 1

FIG. 2

FIG. 1.—Flat mucosa with mosaic pattern from the jejunum of a patient (J. S.) aged 30 and symptom-free for 20 years. (×35.)

FIG. 2.—Histological section of mucosa shown in Fig. 1. (H. and E. ×85.)

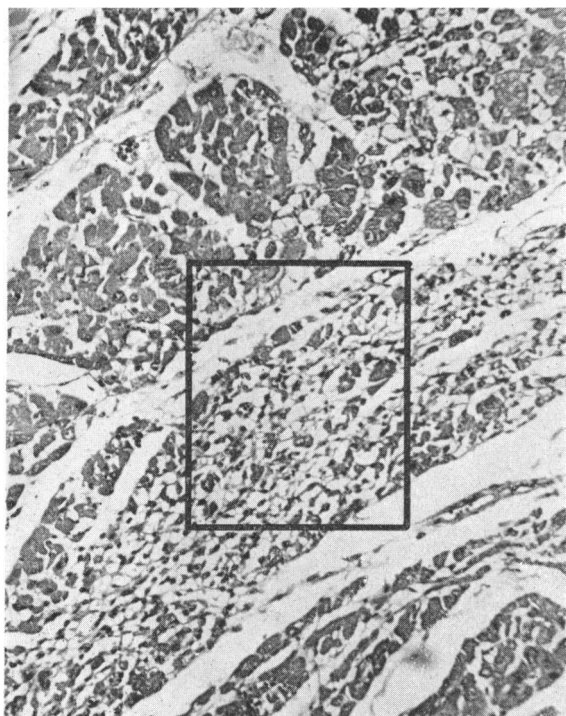## RICHARD C. R. CONNOR: HEART DAMAGE ASSOCIATED WITH INTRACRANIAL LESIONS

FIG. 1.—Myocardium. There is normal muscle above and below an area showing myocytolysis. Empty sarcolemmal sheaths and bare nuclei can be seen. (Haemalum and eosin. ×160.)

FIG. 2.—Myocardium. Marked area of lesion in Fig. 1 (K78/65) at higher magnification. In the upper part of the picture there is a damaged vacuolated muscle fibre. Scattered remnants of fibres are seen in the lesion. Sarcolemmal sheaths with and without nuclei are shown. Polymorphs are not present. (Haemalum and eosin. ×400.)

he was thin his weight was just above the third percentile for his age, in marked contrast to the other patients in this series who were all 0.9 to 6.8 kg. (2 to 15 lb.) below the third percentile for weight. He responded more adequately to treatment than the others, gaining weight rapidly during the first 18 months of treatment on a " coeliac diet " in 1936 to 1938, to reach the fiftieth percentile for his age, and 1.3 kg. (3 lb.) overweight for his height. From the age of 5½ years he tolerated a free diet. At the time of the present survey he was symptom-free and 175 cm. (5 ft. 9 in.) in height. He regarded his bowels as constipated (bowel action alternate days) and ate freely of a normal diet. The serum folate level was 3.6 mμg./ml., Hb 14.2 g./100 ml., and blood film normal. It is therefore uncertain whether his original illness was in fact coeliac disease.

The comparative well-being of some of the present patients, in spite of flat or flat with mosaic proximal intestinal mucosa, is in keeping with the observation of Cooke *et al.* (1963), who found that a flat jejunal mucosa was fully compatible with a normal working life. The most likely explanation seems to be that the clinical state depends not on the severity of the lesion at any one point but on its extent down the small intestine (MacDonald, Brandborg, Flick, Trier, and Rubin, 1964) and on the function of the relatively normal ileum (Stewart *et al.*, 1967).

Nevertheless, six patients had symptoms. One patient had had tetany in adult life, but the effects of malabsorption were confined mainly to evidence of folic acid deficiency. When this form of malnutrition occurs in pregnancy it may be associated with an increased incidence of foetal abnormalities (Hibbard, 1964 ; Hibbard and Smithells, 1965).

Replacement therapy in the present patients was not always sufficient to restore health, and it seems that periodic investigation may be necessary throughout life. If haematological or biochemical evidence of malnutrition is found, treatment with a gluten-free diet appears more rational than the use of dietary supplements. Ideally it may be best, especially for women in the childbearing years, to keep strictly to a gluten-free diet.

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Three Cases of Frontal Meningiomas Presenting Psychiatrically

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Summary : The clinical presentation of three patients with meningiomas at different frontal sites is described. They had been ill for 3, 25, and 43 years before the tumour was demonstrated radiologically. Apathy, incontinence, dementia, and fits were seen in association with middle and superior frontal lesions, and may be mistaken for symptoms of involutional depression or presenile cerebral atrophy. In contrast, excitement and hallucinosis were seen in association with a basal frontal lesion, and may mimic psychotic syndromes like hypomania and schizophrenia, particularly if the tumour encroaches on the third ventricle and adjacent structures. Irreversible loss of myelin and axons in the frontal areas of brain surrounding the tumour may have contributed to the clinical picture of the syndrome shown by these patients.

Introduction

" In the later stages of those cases of tumour in which the mental deterioration is extreme the patient may make no complaints, and the symptoms of ' coarse ' lesion may be so little marked as to pass unnoticed. It is obvious that under such circumstances the condition may be mistaken for ordinary dementia. . . . Again, in those rare cases of intracranial tumour in which maniacal symptoms are developed, unless the previous history and course of the case are known to the physician, the presence of a tumour may be unsuspected " (Byrom Bramwell, 1888).

Blackburn's pioneer monograph *Intracranial Tumors among the Insane* was published in 1903. It was based on the study of 29 cases found in 1,642 necropsies. The majority were what are now called meningiomas and the site of predilection was the frontal region. Such cases may still be missed for a number of reasons. McIntyre and McIntyre (1942) pointed to lack of " tumour consciousness." Morse (1920) blamed the fact that in mental hospitals " the point of view of the physician . . . is psychiatric rather than neurologic, and he is preoccupied with the mental symptoms." Furthermore, " use of the term ' organic dementia ' as a sufficient designation discourages any refinement of diagnosis." To these reasons may be added lack of investigative facilities and a tendency to ignore physical causes as the basis of mental symptoms until they become obtrusive and the lesion becomes advanced.

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