Section of Endocrinology

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DISCUSSION ON SOME PROBLEMS OF STEATORRHŒA AND REDUCED STATURE

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On the Growth Defect in Cœliac Disease

It is well known that a growth defect may occur in children with cœliac disease and this has been largely attributed in the past to lack of some necessary raw materials consequent upon faulty absorption. Recent studies on the ætiology of cœliac disease and other investigations have raised doubts in our minds whether this is the complete explanation of the mechanism of the growth defect. The object of this communication is to put forward an alternative concept.

GASTRO-INTESTINAL SITUATION IN THE CŒLIAC SYNDROME

The upper part of the small intestine is abnormal in the cœliac syndrome, as shown by radiographic studies using non-flocculable opaque medium. Such studies reveal a dilated upper small intestine, devoid of the normal feathery mucosal pattern. Studies on the rate of absorption of sugars, fats, or other substances show a generalized depression and delay. In many cases the interference with small intestinal function is sufficient to cause a defect in over-all absorption. This commonly affects fat, so that the fæcal fat exceeds 5 grams a day on an average. If there is also an over-all defect of carbohydrate absorption, fermentation commonly occurs. This fermentative action results in the formation of short-chain fatty acids and alteration in bile pigments and may ultimately lead to the passage of semi-fluid, pale, bulky, foul and fermenting stools (*see* Fig. 1). In some patients there is also an increase of stool nitrogen, indicative of faulty protein absorption (Frazer, 1955).

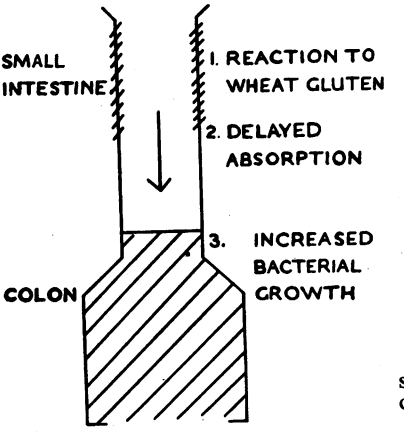

FIG. 1.—Gastro-intestinal situation in the cœliac syndrome.

Under certain circumstances, fat may be synthesized by intestinal organisms (Sammons *et al.*, 1956) and this may make a significant contribution to fæcal fat. However, we have not found these organisms to be present in the patients with cœliac disease so far examined. Labelled fat studies and other tests also indicate that increased fæcal fat is largely due to a fault in fat absorption in this condition.

ÆTIOLOGY OF THE ENTEROPATHY IN CŒLIAC DISEASE

There can be no doubt that the enteropathy in the cœliac syndrome is induced in the great majority of cases by the ingestion of wheat protein. Following an original observation by Dicke (1950), this has been conclusively proved by van de Kamer *et al.* (1953) in Holland,

and by Anderson *et al.* (1952), Sheldon and Lawson (1952) and Ross *et al.* (1955) in this country.

At an early stage it was shown that wheat and rye protein caused deterioration in these children, but other cereal proteins did not do so. The Dutch workers obtained some slight effect with oats, but we did not find this. It was also found that complete acid hydrolysis of wheat gluten rendered it harmless to cœliac children; de-amidation with weak acid had a similar effect.

We have carried fractionation farther. Peptic and tryptic digestion appeared to be normal in cœliac children. Indeed, we have not been able to demonstrate any differences in the digestion of gluten by juices obtained from cœliac or from normal children. Wheat gluten, subjected to peptic and tryptic digestion *in vitro*, was found to be still deleterious to patients with cœliac disease. The enzymic hydrolysate was further fractionated and a water-soluble autoclaved peptide fraction was found to possess the toxic properties of the original gluten (Shaw *et al.*, 1955). Continuing farther, we have been able to show that digestion of this peptide fraction with an extract of pig's intestinal mucous membrane caused disappearance of the toxic effect. We consider that these observations show that the effect of gluten is not dependent on the presence of protein. It appears to be brought about by a glutamine-containing peptide that can be digested by pig's intestinal mucous membrane extract. The cœliac child is presumably unable to handle these peptides as effectively as the normal child. The enzymes concerned would appear to be in the intestinal wall, rather than in the juices secreted into the intestinal lumen.

Such a concept would also explain the observation of van de Kamer and Weijers (1955) that the blood of cœliac children contains a higher quantity of glutamine in bound form than that of normal children after ingestion of gluten. This effect is seen whether the cœliac child is on a gluten-containing or a gluten-free diet. We have also demonstrated a glutamine-containing peptide in the blood in a case that I propose to deal with in greater detail later. Without going farther, we may conclude that faulty handling of certain peptides in wheat gluten during their absorption is a major fault in a child with the cœliac syndrome. Since the child is normal during early infancy and apparently returns to and remains normal on a gluten-free diet, it would appear that the metabolic defect is only revealed under particular dietary conditions.

Other features of the cœliac syndrome.—In addition to this enteropathy, the cœliac child may be pot-bellied and suffer from anorexia and a variable degree of emaciation. An iron-deficient anæmia may also be present. These effects may be directly attributable to the gastro-intestinal changes, or to faulty absorption of nutrients.

However, there are other characteristic changes, the cause of which is not so easily explained. Temperamental changes are observed that change dramatically with the withdrawal or reintroduction of dietary wheat gluten—much more rapidly than the gastro-intestinal effects. Daynes (1955) has suggested that these effects may be more severe in some cases and give rise to attacks of *petit mal* and running fits. Skin lesions may be seen and there is commonly a growth defect. It is this last phenomenon that is our main concern in this paper.

The growth defect in the cœliac syndrome.—There is no doubt that a growth defect commonly occurs in children with cœliac disease. Height may be 20% or more below the normal age standard. The growth defect may result in permanent stunting. Examination of our records and the published figures of other workers (Gerrard, Ross and Smellie, 1955) shows little apparent correlation between the severity of the enteropathy and the extent of the growth defect, especially in those children in whom the gastro-intestinal changes are only moderately severe. Furthermore, the depression of growth is relieved by a gluten-free regime and reimposed if gluten is reintroduced into the diet (Sheldon, 1955). The growth defect, therefore, appears to be an integral part of the cœliac syndrome and closely related to the primary fault. The following case rather dramatically illustrates some of the problems of the growth defect in the cœliac syndrome.

A Case of Cœliac Syndrome in which Dwarfism was the Dominant Feature

M. T. was a normal baby and she was weaned without apparent difficulty. Her childhood was uneventful, but she has suffered from nocturnal enuresis since infancy. Apart from one attack of diarrhœa at about 6 years of age and a very occasional loose stool, she had shown no signs or symptoms of gastro-intestinal dysfunction. Her parents gradually became concerned about her slow rate of growth from the age of 8 years onwards. Her mental development was normal and she did well at school. She was brought to Dr. A. C. Crooke because of lack of growth and development at the age of 13½ years. On finding no basic endocrinological abnormality, Dr. Crooke referred her to us, for investigation of gastro-intestinal function and nutritional status.

Physical examination on admission to the Metabolic Unit at Little Bromwich Hospital: Her height was 127 cm. (expected height for age 160 cm.); span 134 cm.; weight 27·0 kg. She was a pleasant, bright child. Her physical structure was like that of a child of approximately 8 years of age; there

were no signs of pubertal changes. The child was anæmic. Physical examination revealed nothing further of note.

Family history.—Both her parents were healthy; mother's height (163 cm.) and father's (173 cm.) were normal. Her mother has an iron-deficient anæmia (Hb 10·4 grams%, M.C.H.C. 29·5%, M.C.V. 87 cu.μ). There are three siblings and their heights and ages are shown in Table I. One paternal aunt may have had defective growth.

TABLE I.—SIBLINGS OF M. T.

	M. T.	J.	W.	A.
Age (years)	13 6/12	11 2/12	7 7/12	4 9/12
Sex	F	F	M	M
Height cm.	127	132	118	102
% expected height ..	79	91	92	94

General pathological studies.—Blood: Examination of her peripheral blood showed a moderately severe microcytic anæmia.

Hb 9·2 grams %; R.B.C. 3,900,000; M.C.H. 23 $\mu\mu$g.; P.C.V. 32%; M.C.H.C. 28·6%; M.C.V. 80 cu.μ; W.B.C. 8,900.

Fasting serum iron: 22 μg.%. Serology: Wassermann and Kahn reactions negative. Mantoux test 1 : 10,000 positive. Radiography: Chest—small quiescent lesion at the left hilum. Blood biochemistry: Nothing abnormal found. Parasites: No indication of infestation.

Endocrinological studies.—Bone age was normal for 13½ years.

Radio-iodine uptake was 47%, rising to 78% after thyrotrophic hormone. Ketosteroid excretion was normal and responded to adreno-corticotrophic hormone as shown in Table II. Insulin

TABLE II.—URINARY EXCRETION OF KETOSTEROIDS

Day	24 hr. vol. ml.	17-ketosteroids mg./24 hr.	17-O.H. steroids mg./24 hr.	Treatment
1	800	9	7	—
2	800	17	7	7,500 I.U. chorionic gonadotrophin
3	1230	3	7	—
4	1130	5	8	—
5	1550	16	36	ACTH 60 I.U.
6	760	15	33	ACTH 60 I.U.
7	780	18	34	ACTH 60 I.U.
8	1120	16	13	—
9	2140	10	12	—

sensitivity was normal. Visual fields were normal. Gonadotrophin excretion was less than 5 mouse units/24 hours (Klinefelter).

Gastro-intestinal studies.—Fæcal fat: Examination of serial stool samples showed that the fæcal fat was abnormal (more than 10 grams a day). Study with ^{131}I-labelled fat gave an absorption level of 82·3% that corresponded closely with the figure of 82·7% obtained from balance studies. Fæcal nitrogen and volatile fatty acids were normal.

Fat synthesis: No fat synthesizing organisms were found in the stools (Sammons *et al.*, 1956). Pancreatic enzymes (amylase, lipase and trypsin) were normal. Bile salts were normal. Radiography: gross flocculation with simple suspension of barium sulphate; non-flocculable medium showed some dilated loops of intestine. Glucose absorption curve normal. Chylomicrograph flattened.

Assessment.—Assessment of the situation at this stage indicated that this patient had some of the gastro-intestinal changes indicative of the enteropathy of cœliac disease. If so, the iron-deficient anæmia and the growth defect could be regarded as parts of that syndrome. It was, therefore, decided to examine the significance of dietary gluten in this patient.

She was placed on a gluten-free diet. Assessment of her condition was made at intervals and the main points are shown in Table III.

TABLE III.—EFFECTS OF GLUTEN-FREE DIET

Gluten-free diet	A Start	B After 47 days	C After 157 days
Mean daily fæcal fat in grams for 10 consecutive days and S.D. ..	10·5 ± 1·6	8·0 ± 1·7	4·0 ± 0·8
Blood:			
Hb gram.%	9·2	10·4	13·0
M.C.H.C.%	28·6	—	35·0
M.C.V. cu.μ... ..	80·0	—	92·0
R.B.C. × 10^6/c.mm...	3·9	—	4·0

Growth rate	Before A	Gluten	2 months	Hospital	0	cm./month
	A to B	No gluten	47 days	Hospital	2·55	cm./month
	B to C	No gluten?	110 days	Home	0	cm./month
	After C	No gluten	23 days	Hospital	2·60	cm./month

Effect of gluten-free diet.—Fæcal fat: As shown in Table III, her fæcal fat became normal over the course of a few months, and has remained so ever since, so long as she is on a gluten-free diet.

Growth: During the two months previous to being placed on the gluten-free diet she had not grown at all. In the first forty-seven days on the gluten-free period, she grew 4 cm. During the subsequent four-month period that she was at home, she did not grow. Although she and her parents are most co-operative, it is doubted whether a strict gluten-free diet was maintained. In this connexion, it is interesting that on her readmission four months later, her fæcal fat was over 5 grams/day for three days and then came down to $4{\cdot}1 \pm 0{\cdot}25$ grams/day for the next ten days, on a strict gluten-free diet. During this period in hospital she grew at a rate of 2·60 cm./month, provided that she received no gluten.

Blood: The return of her blood picture to normal is shown in Table III.

Nocturnal enuresis: This ceased and has not recurred.

Sensitivity to gluten and gluten fractions.—It is clear, therefore, that on a gluten-free diet her whole condition showed marked improvement. It was now necessary to establish that she was truly gluten-sensitive and because of a number of differences from our usual patients with the cœliac syndrome, it seemed to us advisable to determine whether she was also reactive to our active gluten fractions. The results of some of these studies are shown in Fig. 2. They can be briefly summarized. When gluten was administered, fæcal fat changed

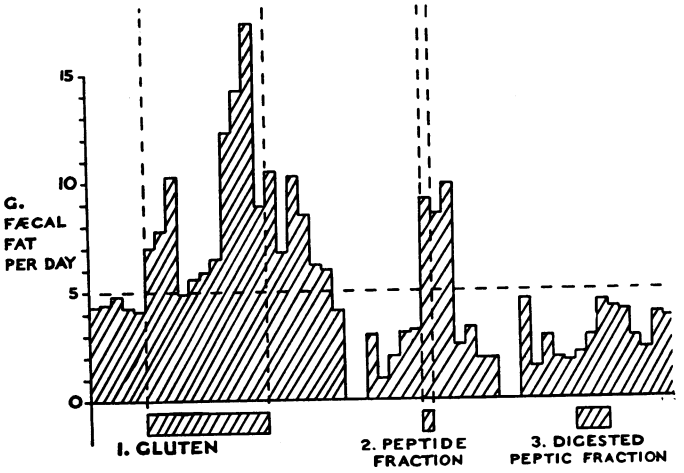

FIG. 2.—The effect on fæcal fat in gluten-sensitive patients of the administration of (1) gluten (2) peptide fraction from enzymic hydrolysate of gluten (3) peptide fraction digested with pig's intestinal mucous membrane extract.

from 4·0 grams/day to $9{\cdot}3 \pm 1{\cdot}1$ grams in consecutive ten-day periods. When the gluten was given in a single dose with fat, the fæcal fat rose to nearly 40 grams a day. This acute effect had not been seen before, but this was a new way of doing this test which is now being further investigated. In several tests, the patient was found to respond to dietary gluten changes much more quickly than most cœliac patients. From these various studies it was clear, however, that the patient was gluten-sensitive.

The glutamine-containing peptide fraction was now tested and the patient reacted to it; when this fraction was digested with pig's intestinal mucous membrane extract, no effect was produced. After the peptide fraction was administered, a glutamine-containing peptide was found in abnormally large quantites in the blood.

We, therefore, concluded that this patient has a metabolic lesion that cannot be differentiated from that of other children with the cœliac syndrome, so far as our present tests go.

To return now to a consideration of the enteropathy and the growth defect in this case:

The enteropathy during childhood was not sufficient to cause any obvious gastro-intestinal signs or symptoms. The interference with absorption mainly affected fat, there was no indication of significant interference with the absorption of protein, carbohydrate or other nutrients except iron. Even the fat absorption defect was relatively slight. However, in spite of these rather moderate changes, growth was severely affected, being more than 20% below the expected level. When placed on a gluten-free diet she rapidly grew. In the first period this was before either the enteropathy or the anæmia had significantly changed. Her increased rate of growth in this period was similar to that observed in the second period, when her enteropathy and anæmia had disappeared. It seems to us, therefore, that this patient indicates a real possibility that the growth defect in the cœliac syndrome may not be fully accounted for as secondary to material deficiencies resulting from the enteropathy, but may represent an independent effect of inadequately metabolized wheat protein.

ACKNOWLEDGMENTS

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Dr. C. E. Dent: *Parathyroid Adenoma with Hyperparathyroidism Developing in a Case of Lifelong Steatorrhœa.*

The case was described of a woman of 41 years with a recent history of severe bone pains and loss of height. On examination she was greatly dwarfed and she had all the biochemical and hæmatological findings of steatorrhœa except that her plasma calcium level was high instead of being normal or low. X-rays showed both osteomalacia and osteitis fibrosa generalisata. It was concluded that she was a case of lifelong steatorrhœa and had recently developed one or more parathyroid tumours and hyperparathyroidism. This was confirmed by exploration of her neck and by her response to removal of two parathyroid adenomas.

It was concluded that her parathyroid adenoma was the direct result of her lifelong steatorrhœa and that she probably passed through a phase of parathyroid hyperplasia before the two adenomas developed. Comment was made on the strange fact that her X-rays were similar to those found in some cases of chronic renal failure since they showed not only osteomalacia and hyperparathyroidism but also the "rugger-jersey" sign of osteosclerosis of the vertebral bodies. This case, together with another case of steatorrhœa showing parathyroid hyperplasia, is reported in detail by Davies *et al.* (1956).

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Professor F. T. G. Prunty: This case of Dr. Dent's is extremely interesting to us, raising as it does the question of the interrelation of osteomalacia and the subsequent development of secondary hyperparathyroidism. Good documentation of this condition is very scanty and I would, therefore, like to mention a further example seen several years ago. A man aged 35 had a ten years' history of steatorrhœa and presented three independent lines of evidence of the co-existence of osteomalacia and hyperparathyroidism. Firstly the serum chemistry showed calcium 8 to 9 mg.%, phosphorus 1·6 to 2·1 mg.% and an extremely high level of alkaline phosphatase of 78 to 97 units. Secondly, X-rays showed typical hyperparathyroid appearances in the skull, jaw and hands, together with considerable generalized decalcification and Milkman's fractures. Thirdly, bone biopsy showed a combination of areas with increased osteoid seams and areas of considerable osteoclast proliferation. Direct examination of the parathyroids was not made as it was assumed they were likely to be hyperplastic. The occurrence of an adenoma in the parathyroid in Dr. Dent's patient is particularly worthy of note.