Primary malabsorption following extreme attempts to lose weight¹

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EDITORIAL SYNOPSIS Two patients are reported in whom a malabsorption syndrome was precipitated by a drastic weight-reducing regime. It is suggested that the protein deficiency might have caused an abnormal sensitivity to gluten in the intestinal cells.

It has been postulated that susceptibility to coeliac disease is inherited. A familial incidence (Davidson, Girdwood, and Innes, 1947; Davidson and Fountain, 1950; Thompson, 1951; Cooke, Peeney, and Hawkins, 1953; Boyer and Andersen, 1956; Carter, Sheldon, and Walker, 1959; Rubin, Brandborg, Phelps, Taylor, Murray, Stemler, Howry, and Volwiler, 1960b; Rubin, Brandborg, Flick, MacDonald, Parkins, Parmentier, Phelps, Sribhibhadh, and Trier, 1962) and an increased frequency of blood group O Rh positive (Joske and Benson, 1958; Benson, Kowlessar, and Sleisenger, 1964) have been reported. The purpose of this report is to describe studies of two obese adults who developed coeliac disease following unusual efforts to lose weight.

REPORT OF CASES

CASE 1 A 36-year-old Negro was admitted to hospital because of weakness of all extremities, hoarseness, peripheral oedema, and chronic diarrhoea. Two years before admission, when in good health but obese (weight 276 lb.), the patient attempted rapid weight reduction by eliminating everything from his diet except turnip greens and a sugar-free soft drink. At the end of one month, after losing 20 lb., he resumed a normal diet. During the following month he continued to lose weight, although his appetite was good and his food intake above average. One month after resuming a normal diet he developed fatigue, listlessness, and painless, non-bloody diarrhoea consisting of 10 to 12 loose, bulky, unusually foul movements daily. Weakness of both legs, decreased sensation and paraesthesias in the hands and feet, and hoarseness developed gradually over the next eight weeks. At this time he had difficulty in walking because of weakness. Ten months later he was seen at another hospital where a diagnosis of pernicious anaemia was made and parenteral

vitamin B₁₂ therapy begun. During the next nine months the weakness, hoarseness, and diarrhoea became increasingly more severe. Because a friend suggested it, he began to eat large quantities of bread and cereals one month before he was admitted to hospital. During this month his symptoms became increasingly severe, and the legs became swollen. He was seen in the Out-patient Department and admitted for evaluation. His weight at that time was 171 lb., a loss of 105 lb. There was no history of diarrhoea, anaemia, or failure to thrive in childhood, and no familial history of intestinal disease.

At physical examination he was noted to be obese and anxious. Temperature was 102°F. Pulse, blood pressure, and respirations were normal. The tongue was red and smooth, and cheilosis was present. The remaining positive findings were neurological. There was generalized muscle weakness, so that he was unable to walk or raise himself from the bed. Deep tendon reflexes were markedly hypoaffective or absent throughout. Vibratory sense was impaired in the feet. The left vocal cord was paralysed.

There was a moderate amount of protein in the urine. The haemoglobin was 8.7 g./100 ml.; haematocrit, 27%; white cell count, 8,900/mm.³ (70% neutrophils, 23% lymphocytes, 4% monocytes, and 3% eosinophils); erythrocyte sedimentation rate was 54 mm. in one hour; reticulocyte count, 1.9%. Bone marrow examination showed many target cells and occasional megaloblasts. The faeces were voluminous, liquid, pale, unusually foul-smelling, and negative for occult blood, and microscopic examination disclosed numerous fatty acid crystals. Further laboratory investigations demonstrated multiple nutritional deficiencies and marked intestinal malabsorption. The serum carotene level was 0 µg./100 ml.; serum potassium, 3.3 mEq./l.; serum carbon dioxide-combining power, 18 m.mols; serum calcium, 4.5 mg./100 ml.; serum phosphorus, 3.8 mg./100 ml.; serum magnesium, 1.1 mEq./l. (normal, 1.6-2.1 mEq./l.); total serum cholesterol, 122 mg./100 ml.; serum iron, 44 µg./100 ml.; serum albumin, 2.5 g./100 ml.; serum globulin, 5.6 g./100 ml. (serum electrophoresis and scanning); serum folate, 1.3 µg./ml. Oral glucose tolerance tests showed a peak

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FIG. 1a.

FIG. 1b.

FIG. 1c.

FIGS. 1a, 1b, and 1c. Jejunal biopsy from case 1. Diffuse, severe loss of normal villous pattern is seen at low power (Fig. 1a, haematoxylin and eosin $\times 35$). Increased infiltration of the lamina propria with round cells, fusing of the villi, and deepening of the crypts are present (Fig. 1b, haematoxylin and eosin $\times 100$). High magnification shows distortion and flattening of the surface epithelial cells. (Fig. 1c, haematoxylin and eosin $\times 250$).

of 80 mg./100 ml. at two hours; abnormally low serum curves were obtained following oral administration of radiiodinated triolein and oleic acid; the urinary excretion of radiocobalt vitamin B₁₂ without intrinsic factor was 2.16% (normal, over 10%); free HCl was present in the gastric secretion. The urinary excretion of xylose following a 25 g. oral dose was 1.46 g. in five hours. A barium meal demonstrated dilated jejunal loops and loss

of the normal mucosal pattern with widening of the mucosal folds. A peroral jejunal mucosal biopsy was obtained several inches beyond the ligament of Treitz with the Crosby-Kugler intestinal biopsy capsule (Crosby and Kugler, 1957). The mucosa appeared flattened and convoluted when viewed with the dissecting microscope (Holmes, Hourihane, and Booth, 1961), and histological examination revealed total villous atrophy, abnormalities

of the surface epithelial cell layer, deepening of the crypts, and increased infiltration of the lamina propria with plasma cells and lymphocytes (Fig. 1), changes characteristic of coeliac disease (Shiner, 1957; Rubin, Brandborg, Phelps, and Taylor, 1960a; Yardley, Bayless, Norton, and Hendrix, 1962; Cameron, Astley, Hallowell, Rawson, Miller, French, and Hubble, 1962). Biopsy of a peripheral nerve was performed and mild degenerative changes were found. Muscle biopsy showed non-specific myopathy.

During the patient's first month in hospital, although he ate a normal hospital diet, his weakness decreased but the diarrhoea and anaemia remained unchanged. He was then begun on a gluten-free diet, folic acid, and parenteral iron. At the time of discharge one month later there was evidence of marked neurological improvement, the diarrhoea had decreased to two or three semiformed movements daily, and he had begun to gain weight.

When seen nine months later in the Out-patient Department, the patient had no symptoms and appeared obese, but well. He had followed the gluten-free diet strictly. His weight was 217 lb. General physical and neurological examinations were normal. The haemoglobin was 12.5 g./100 ml.; haematocrit, 38%; white cell count, 5,800/mm.³ (52% neutrophils, 28% lymphocytes, 1% monocytes, 1% basophils, and 18% eosinophils); serum albumin, 3.6 g./100 ml.; serum globulin, 4.3 g./100 ml. The values for serum sodium, potassium, chloride, carbon dioxide-combining power, calcium, and phosphorus were normal. He was advised to continue the gluten-free diet and to decrease his intake of calories to control the obesity.

CASE 2 A 38-year-old white woman was admitted to hospital for evaluation of abdominal pain, weakness, fatigue, and diarrhoea of four weeks' duration. Beginning two years before admission the patient had taken one tablet of a long-acting amphetamine and up to one pint of milk of magnesia nightly and one tablet of acetazolamide (Diamox) each morning in an attempt to lose weight. On this programme of weight reduction she had two to four loose bowel movements each day and her weight fell from 135 to 121 lb. Four weeks before admission she began to have episodes of sharp, crampy epigastric pain after her nightly medications, and also in the mornings, associated with occasional nausea and retching. She noticed that she now had up to six watery, unusually foul-smelling bowel movements each day. She also began to tire easily, feel weak, have decreased appetite, and to lose weight. One week before admission her private physician noted that she had peripheral oedema and he prescribed chlorothiazide, 250 mg. daily, but the symptoms became progressively severe. There was no history of diarrhoea, anaemia, or failure to thrive in childhood, and no familial history of intestinal disease.

At the time of admission the patient weighed 113 lb. Physical examination was normal except for minimal epigastric tenderness. Urine analysis was normal. The haemoglobin was 12.0 g./100 ml.; white cell count, 16,650/mm.³ (62% neutrophils, 31% lymphocytes, 5% monocytes, and 2% eosinophils); the red blood cells appeared hypochromic on smear; erythrocyte sedimentation rate was 37 mm. in one hour; the levels of total

serum cholesterol, 147 mg./100 ml., serum amylase, 100 M and K units, serum albumin, 2.8 g./100 ml., serum globulin 2.8 g./100 m. (serum electrophoresis and scanning), and serum carotene, 28 µg./100 ml. The faeces were liquid, pale, unusually foul-smelling, and intermittently positive for occult blood; microscopic examination disclosed numerous fatty acid crystals. The urinary excretion of xylose following a 25 g. oral dose was 1.54 g. in five hours. A barium meal demonstrated enlarged gastric folds and loss of the normal jejunal mucosal pattern with widening of the mucosal folds. A peroral jejunal mucosal biopsy was obtained 24 inches beyond the ligament of Treitz. The major portion of this biopsy appeared flat and convoluted when viewed with the dissecting microscope. There was one area of the specimen where a few blunted, shortened villi remained. The histological appearances of this mucosa were similar to those of the jejunal mucosal biopsy specimen obtained from case 1, and were characteristic of coeliac disease.

A gluten-free diet was started three weeks after admission. Within a few days the patient had ceased to have abdominal pain and had less diarrhoea. By the time of discharge from hospital, two weeks after starting the gluten-free diet, the diarrhoea had ceased. Ten months later she was readmitted for an uneventful delivery of twins. She had ceased to have symptoms during the second month of the gluten-free diet and had gained 15 lb. At the time of readmission the physical examination was normal. The haemoglobin was 15.3 g./100 ml.; white cell count, 5,000/mm.³; serum carotene, 90 µg./100 ml. After discharge from hospital she ceased to follow the gluten-free diet, yet experienced no abdominal pain, diarrhoea, or weight loss. One year later, when seen by her private physician, she had no complaints, appeared well, and her haemoglobin and serum carotene levels were normal.

COMMENT

The multiple nutritional deficiencies and fatty diarrhoea of coeliac disease are caused by abnormalities of the mucosa of the small intestine. The aetiological relationship of gluten, gliadin (the fraction of gluten soluble in alcohol), and peptides obtained by peptic-tryptic digestion of gluten and gliadin to the clinical and mucosal abnormalities has been demonstrated in several studies (Dicke, 1950; Dicke, Weijers, and Kamer, 1953; Anderson, Frazer, French, Gerrard, Sammons, and Smellie, 1952; Sheldon and Lawson, 1952; Kamer and Weijers, 1955; Schwartz, Slesinger, Pert, Roberts, Randall, and Almy, 1957; Krainick, Debatin, Gautier, Tobler, and Velasco, 1958; Krainick and Mohn, 1959; Frazer, Fletcher, Ross, Shaw, Sammons, and Schneider, 1959; van Roon, Haex, Seeder, and Jong, 1960; Rubin, Brandborg, Flick, Phelps, Parmentier, and van Niel, 1962; Bayless, Yardley, Norton, and Hendrix, 1962; Pittman and Holub, 1965). Several authors have postulated that patients with coeliac disease have abnormal peptidase activity of the small intestinal mucosal epithelial cells which prevents the

normal degradation of certain peptides derived from the intraluminal digestion of gluten or gliadin (see Frazer, 1962). These peptides are thought to enter the epithelial cells and begin the harmful chain of events which results in the flattened, infiltrated mucosa with its abnormal epithelial cell layer. There is also evidence that immunological phenomena play a role in the pathogenesis of coeliac disease (see Jeffries, Weser, and Sleisenger, 1964). However, the exact mechanism of the harmful action of gluten, gliadin, and the peptides is unknown.

Although there is evidence that heredity is a predisposing factor for the development of coeliac disease, many adults with the disease have no family history of intestinal disorders and were perfectly healthy during infancy and childhood. The two patients described in this report not only had negative family histories for intestinal disease and no history of disease during infancy and childhood, but also had been obese for several years before the onset of their illnesses. Although it is possible that both of these patients were suffering from coeliac disease in an asymptomatic form before they began their regimens, it is likely that factors related to the unusual attempts to lose weight produced alterations in the mucosa of the small intestine which made it susceptible to the toxic effects of wheat protein. The deleterious effects of gluten in the diets of these patients was suggested by the rapid response to a gluten-free diet in both patients after a control period of a normal hospital diet. Since in one of the patients (case 2) neither symptoms nor anaemia were exacerbated after resuming a normal diet, it is likely that the defect in the mucosa which made it susceptible to gluten toxicity disappeared as the mucosa of the small intestinal tract regenerated during the period of gluten-free diet therapy.

The specific factors which are postulated to have produced alterations in the mucosa of the small intestinal tract mucosa and made it susceptible to the toxic effects of wheat protein were not determined in this study. It has been demonstrated in experimental animals that the mucosa of the small intestine can be altered by factors which could have been operative in these two patients. Extreme acute starvation in mice produced abnormalities of small intestinal mucosal epithelial cells: morphological changes and impaired differentiation of the epithelial cells were observed to accompany reduced cell renewal (Brown, Levine, and Lipkin, 1963). The rate of migration of the epithelial cells to the tips of the villi was also reduced. Pigs fed a protein-calorie-deficient diet developed abnormalities of small intestinal tract mucosa similar to those found in coeliac disease (Platt, Heard, and Stewart, 1964). Similar studies have not been carried out in man.

The findings in the two patients reported here indicate another, and unusual, hazard of extreme attempts to lose weight. They also suggest that factors other than heredity may predispose to coeliac disease.

SUMMARY AND CONCLUSIONS

A form of adult coeliac disease with multiple nutritional deficiencies, fatty diarrhoea, and characteristic changes in the jejunal mucosa was observed in two obese adults after extreme attempts to lose weight. Both patients were treated successfully with a gluten-free diet. It is suggested that factors related to the unusual attempts to lose weight may have produced alterations in the mucosa of the small intestinal tract which made it susceptible to toxic effects of wheat protein.

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REFERENCES

- Anderson, C. M., Frazer, A. C., French, J. M., Gerrard, J. W., Sammons, H. G., and Smellie, J. M. (1952). Coeliac disease: gastro-intestinal studies and the effect of dietary wheat flour. *Lancet*, **1**, 836-842.
- Bayless, T. M., Yardley, J. H., Norton, J. H., and Hendrix, T. R. (1962). Adult coeliac disease: rapid sequential changes in jejunal mucosa with alterations of dietary gluten. *J. clin. Invest.*, **41**, 1344.
- Benson, G. D., Kowlessar, O. D., and Sleisenger, M. H. (1964). Adult coeliac disease with emphasis upon response to the gluten-free diet. *Medicine (Baltimore)*, **43**, 1-40.
- Boyer, P. H., and Andersen, D. H. (1956). A genetic study of coeliac disease. Incidence of coeliac disease, gastrointestinal disorders, and diabetes in pedigrees of children with coeliac disease. *Amer. J. Dis. Child.*, **91**, 131-137.
- Brown, H. O., Levine, M. L., and Lipkin, M. (1963). Inhibition of intestinal epithelial cell renewal and migration induced by starvation. *Amer. J. Physiol.*, **205**, 868-872.
- Cameron, A. H., Astley, R., Hallowell, M., Rawson, A. B., Miller, C. G., French, J. M., and Hubble, D. V. (1962). Duodeno-jejunal biopsy in the investigation of children with coeliac disease. *Quart. J. Med.*, **31**, 125-140.
- Carter, C., Sheldon, W., and Walker, C. (1959). The inheritance of coeliac disease. *Ann. hum. Genet.*, **23**, 266-273.
- Cooke, W. T., Peeney, A. L. P., and Hawkins, C. F. (1953). Symptoms, signs, and diagnostic features of idiopathic steatorrhoea. *Quart. J. Med.*, **22**, 59-77.
- Crosby, W. H., and Kugler, H. W. (1957). Intraluminal biopsy of the small intestine. The intestinal biopsy capsule. *Amer. J. dig. Dis.*, **2**, 236-241.
- Davidson, L. S. P., Girdwood, R. H., and Innes, E. M. (1947). Folic acid in the treatment of the sprue syndrome. *Lancet*, **1**, 511-515.
- , and Fountain, J. R. (1950). Incidence of the sprue syndrome with some observations on the natural history. *Brit. med. J.*, **1**, 1157-1161.
- Dicke, W. K. (1950). Coeliakie. Een onderzoek naar de nadelige invloed van sommige graansoorten op de lijder aan coeliakie. *Doctoral Thesis, University of Utrecht*.
- , Weijers, H. A., and Kamer, J. H. van de (1953). Coeliac disease. II. The presence in wheat of a factor having a deleterious effect in cases of coeliac disease. *Acta paediat. (Uppsala)*, **42**, 34-42.

- Frazer, A. C. (1962). The malabsorption syndrome, with special reference to the effects of wheat gluten. *Advanc. clin. Chem.*, 5, 69-106.
- , Fletcher, R. F., Ross, C. A. C., Shaw, B., Sammons, H. G., and Schneider, R. (1959). Gluten-induced enteropathy. The effect of partially digested gluten. *Lancet*, 2, 252-255.
- Holmes, R., Høurihane, D. O'B., and Booth, C. C. (1961). Dissecting-microscope appearances of jejunal biopsy specimens from patients with 'idiopathic steatorrhoea'. *Ibid.*, 1, 81-83.
- Jefferies, G. H., Weser, E., and Sleisenger, M. H. (1964). Malabsorption. *Gastroenterology*, 46, 434-466.
- Joske, R. A., and Benson, J. A., Jr. (1958). ABO blood groups and nontropical sprue. *Ibid.*, 34, 408-409.
- Kamer, J. H. van de, and Weijers, H. A. (1955). Coeliac disease. V. Some experiments on the cause of the harmful effect of wheat gliadin. *Acta paediat. (Uppsala)*, 44, 465-469.
- Krainick, H. G., Debatin, F., Gautier, E., Tobler, R., and Velasco, J. A. (1958). Weitere Untersuchungen über den Schädlichen Weizenmehleffekt bei der Cöliakie. I. Die akute Gliadinreaktion (Gliadin shock). *Helv. paediat. Acta*, 13, 432-454.
- , and Mohn, G. (1959). Weitere Untersuchungen über den schädlichen Weizenmehleffekt bei der Cöliakie. 2. Die Wirkung der enzymatischen Abbauprodukte des Gliadin. *Ibid.*, 14, 124-140.
- Pittman, F. E., and Holub, D. A. (1965). Sjögren's syndrome and adult celiac disease. *Gastroenterology*, 48, 869-876.
- Platt, B. S., Heard, C. R. C., and Stewart, R. J. C. (1964). The effects of protein-calorie deficiency on the gastrointestinal tract. In *The Role of the Gastrointestinal Tract in Protein Metabolism*, edited by H. N. Munro, pp. 227-237. Blackwell, Oxford.
- Roon, J. H. van, Haex, A. J. C., Seeder, W. A., and Jong, J. de (1960). Clinical and biochemical analysis of gluten-toxicity. No. II. Clinical experiments on patients suffering from idiopathic steatorrhoea after the administration of bromine treated performic acid oxidized polypeptides originating from wheat gluten. *Gastroenterologia (Basel)*, 94, 227-235.
- Rubin, C. E., Brandborg, L. L., Flick, A. L., MacDonald, W. C., Parkins, R. A., Parmentier, C. M., Phelps, P., Sribhibhadh, S., and Trier, J. S. (1962). Biopsy studies on the pathogenesis of coeliac sprue. In *Ciba Foundation Study Group No. 14 on Intestinal Biopsy*, edited by G. E. W. Wolstenholme and M. P. Cameron, pp. 67-83. Churchill, London.
- , —, Phelps, P., Parmentier, C., and van Niel, S. (1962). Studies of celiac sprue. III. The effect of repeated wheat instillation into the proximal ileum of patients on a gluten free diet. *Gastroenterology*, 43, 621-641.
- , —, Phelps, P. C., and Taylor, H. C., Jr. (1960a). Studies of celiac disease. I. The apparent identical and specific nature of the duodenal and proximal jejunal lesion in celiac disease and idiopathic sprue. *Ibid.*, 38, 28-49.
- , —, —, —, Murray, C. V., Stemler, R., Howry, C., and Volwiler, W. (1960b). Studies of celiac disease. II. The apparent irreversibility of the proximal intestinal pathology in celiac disease. *Ibid.*, 38, 517-532.
- Schwartz, M. K., Sleisenger, M. H., Pert, J. H., Roberts, K. E., Randall, H. T., and Almy, T. P. (1957). The effect of a gluten-free diet on fat, nitrogen, and mineral metabolism in patients with sprue. *Gastroenterology*, 32, 232-246.
- Sheldon, W., and Lawson, D. (1952). The management of coeliac disease. *Lancet*, 2, 902-905.
- Shiner, M. (1957). Small intestinal biopsies by the oral route. Histopathologic changes in the malabsorption syndrome. *J. Mt. Sinai Hosp.*, 24, 273-285.
- Thompson, M. W. (1951). Heredity, maternal age, and birth order in the etiology of celiac disease. *Amer. J. hum. Genet.*, 3, 159-166.
- Yardley, J. H., Bayless, T. M., Norton, J. H., and Hendrix, T. R. (1962). Celiac disease. A study of the jejunal epithelium before and after a gluten-free diet. *New Engl. J. Med.*, 267, 1173-1179.