THE PRESENT POSITION IN COELIAC DISEASE

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HIPPOCRATIC writings praise wheat. Religious beliefs have been founded on the faith that God intended the wheat berry as the ideal food for man. This is not surprising: whole wheat-meal contains nearly 12% protein. It is grown in vast areas of the earth: the annual world production in 1960 reached 220 million tons. Nations depend upon it for basic nutrition. Napoleon urged his young troops when on the march to chew wheat for sound sustenance. The superior growth of animals receiving wheat is well known (Chick, 1942). Wheat flour, added to milk, provides excellent nutrition for normal infants. Clearly, therefore, optimal amounts of gluten-containing protein are advantageous in normal human physiology. But, in the natural variation of man, there are ranges of intestinal tolerance to gluten. Normal young children may suffer acute abdominal discomfort and temporary steatorrhœa immediately following a debauch of bread and cakes at a birthday party. Some healthy adults may learn by experience to avoid excess cereal or bread to prevent unformed pale stools. Cœliac disease was formerly sometimes unrecognized until after childhood: the syndrome occurred as persisting steatorrhœa in an adult with consequential clinical effects. The relationship of idiopathic steatorrhœa in adults to cœliac disease in childhood is close. The present evidence suggests they are the same condition.

In the second century A.D., Aretæus, a great Greek clinician, noted that in some persons 'bread contributes little towards strength': he probably coined the term 'the cœliac diathesis'. Seventeen centuries later Samuel Jones Gee, in his brilliantly lucid exposition 'On the Cœliac Affection', 'especially apt to affect children between one and five years old', emphasized that 'to regulate the food is the main part of treatment—the allowance of farinaceous food must be small and cornflour is unfit'. Gee was remarkably near the truth. Sixty years were to pass before Gee's intuition crystallized in clinical and biochemical proof of the cause of cœliac disease (Dicke, 1950).

The noxious effect of gluten, and especially

after the ingestion of wheat and rye flour, was proven (Van de Kamer, Weijers and Dicke, 1953). The evidence indicates a specific sensitivity creating gluten enteropathy. How far is this an inborn error of metabolism with its site of action in the wall of the small intestine? (Badenoch, 1960). Withering of the villi in active cœliac disease is of immense importance: it is probably a response to an absolute intolerance to gluten derivatives. Does a specific enzyme defect exist in the intestinal mucosa in this disease? Rubin (1960) considers further investigations essential to complete the suggested causal chain, which begins with a specific metabolic defect and ends in a clinically apparent illness.

Inheritance

Some familial aggregation exists. The disease may occur in identical twins. There is an increasing interest in the question of familial predisposition. The incidence among relatives is too high to be chance (Ebbs, 1950). Boyer and Anderson (1956) studied the pedigrees of 50 children with cœliac disease and noted a significant incidence in siblings. Davidson and Fountain (1950) in 1,077 cases found an equal distribution in the sexes. No effect of maternal age, birth order or social class, but a definite increase in the incidence was found by Carter, Sheldon and Walker (1959), in the near relatives of patients. There appears to be a risk of about 1 in 3,000 in the general population but five of 205 brothers and sisters had proved cœliac disease. The genetic element in the causation of the disease may be only a predisposition. Further studies of the families of affected children will need to be carried out, giving attention not only to clinical and biochemical factors but also to intestinal biopsy. There is an excess of blood type O in idiopathic steatorrhœa in adults. No similar study has yet been carried out in cœliac disease in childhood. Clearly, further intensive clinico-genetic studies should be carried out.

The Intestinal Villi

Gee (1888) was confounded but intuitional—

'nothing unnatural can be seen in the intestines . . . but whether atrophy of the glandular crypts be ever or always present, I cannot tell'.

The early observations of Kokas and Ludány (1930) have interest. Movements of intestinal villi were clearly seen in fed dogs but they were absent in fasting animals, and movements of the villi were observed only in those parts in which absorption was taking place. It was suggested that local chemical reactions rather than systemic factors were of importance in activating villous movements. When the mucous membrane was separated from the plexus of Meissner villous movement ceased, which suggested to Kokas and Ludány that a controlling local neural mechanism for the movements lay in the submucous nerve plexuses of the intestinal canal. Their micro-cinematic (x 30) photographs of the villi give a good illustration of the kinetics of individual villi. Normal villi have their rhythmical movements and contractions, each appearing to have some independent action, 'some shorten quickly and lengthen more slowly (Verzar and McDougall, 1936).

Sakula and Shiner (1957) opened up an entirely new enquiry by developing small intestinal biopsy, via the oral route, and observing mucosal atrophy confined mainly to the villi. In a child, aged 2½ years, with celiac symptoms for at least one year no villi at all were found and the surface epithelium appeared grossly abnormal (Shiner, 1960). Similar findings were made by Rubin, Brandborg, Phelps and Taylor (1960) and their illustrations of the intestinal lesions in celiac disease are beautifully realistic of the specific nature of the changes in the duodenal and proximal jejunal areas. Through the dissecting microscope three-dimensional views of intestinal biopsy material reveal detailed changes in villi, especially in the convolational appearances in partial villous atrophy (Holmes, Hourihane and Booth, 1961a). This has been further demonstrated by Holmes, Hourihane and Booth (1961b) who point out that there is a considerable range of changes in the jejunal biopsies: in some cases the mucosa is entirely flat and featureless, showing complete loss of villi with disorganised blood vessels visible through the epithelium. Even in some young children, intestinal biopsies over a period of five weeks, one year and two years after commencing gluten-free diet failed to show more than minimal improvement in many of the villi. More favourable findings were reported by Cameron, Astley, Hallowell, Rawson, Miller, French and Hubble (1962), who are more optimistic concerning possible complete or near-complete reversion of the mucosa to normal on a gluten-free diet. Histochemical methods have revealed complex

changes in the cells of the villi and a probable increased rate of villous-cell loss (Padykula, Strauss, Ladman and Gardner, 1961). Three dimensional observations on biopsy material with a dissecting microscope provide a particularly efficient and rapid diagnostic assessment.

By the electron-microscope the 'brush border', short irregular and loosely packed 'microvilli', of the surface epithelium may be noted. Moreover, a good correlation was found between the light microscope appearances of villous atrophy and decrease in surface cell height and the electron-microscope microvillous changes (Shiner and Birbeck, 1961). Jejunal biopsy in long-standing cases of celiac disease reveals serious and almost complete atrophy of the villi (Fone, Cooke, Meynell, Brewer, Harris and Cox, 1960). When wheat or rye gluten are instilled into the small intestine of patients with 'idiopathic sprue' characteristic mucosal lesions develop in the vicinity of the wheat instillation. Gluten exposure is a definite precursor to the anatomic changes in the mucosa (Rubin, Brandborg, Flick, Parmentier, Phelps and van Niel, 1960). Instillation of 50 g. of wheat directly into the ileum caused biopsy changes in the mucosa similar to those seen in the jejunum in celiac disease. Acute changes could be observed in the mucosa after an ileal instillation and this was apparently sufficient to diminish absorption of vitamin B₁₂ for a considerable time (Hawkins, 1961). A faulty barrier-function of the small intestine may be said to arise as a result of gluten action in celiac disease.

Intestinal Tone and Motility

Clinical evidence has long suggested that small intestinal tone and motility are diminished in celiac disease. Barbero, Kim and Davis (1958) found no significant difference in the intraluminal pressure in the duodenum in normal and in celiac infants and children. Some protein sources, such as gluten, will inhibit the peristaltic reflex in the isolated rat intestine, whereas no inhibition takes place with casein or albumin under the same conditions. The deleterious agent inhibits the peristaltic reflex in the isolated rat intestine if it is applied to the serosal surface, but it is ineffective when applied to the mucous membrane. The effective material appears to be a protein of less than 20,000 molecular weight, and unlikely to be a whole protein or a free amino-acid (Schneider, Bishop and Shaw, 1960). Experimental work has led Schneider, Bishop, Shaw and Frazer (1960) to the conclusion that wheat gluten, which is pathogenic in celiac disease, contains a factor which depresses the peristaltic reflex of an isolated strip of intestine. This factor may depress acetylcholine output or it may prevent release of

acetylcholine from the bound state. Most recently, Schneider, Bishop, Shaw and Frazer (1961) report their belief that inhibition of the peristaltic reflex is due to a peptide which depresses the release of acetylcholine at cholinergic nerve endings. Biopsy material from normal persons and from those not gluten-intolerant rapidly destroys the motility inhibiting factor, whereas biopsy material from persons with gluten intolerance is unable to do so (Frazer, 1962).

The 'Toxic' Agent

Aretæus thought that 'the food is not converted to its proper chyme, but leaves its work half finished'. Gibbons (1889), who gave much original thought to the nature of celiac disease, suggested that 'the absorption into the blood of deleterious elements produces the profound ill-health in these patients'. Children with celiac disease and normal children digest gluten equally efficiently, but harmful effects in celiac disease can be demonstrated by giving a water-soluble peptide derived from fractionation of the enzymic hydrolysate obtained from gluten (Frazer, 1956). The peptic/tryptic digest degradation product of wheat gluten contains a water-soluble fraction III which has antigenic properties and is of equal toxicity to the gluten from which the fraction is derived: after ingestion this fraction quickly induces steatorrhœa (Frazer, Fletcher, Ross, Shaw, Sammons and Schneider, 1959). The deleterious material has a relatively low molecular weight, is ultrafiltrable and resistant to peptic/tryptic digestion, but it can be destroyed by enzymes present in normal pig intestinal mucosa, which suggests that there may be an enzyme present in normal small intestine mucosa which copes normally with the deleterious substance and prevents mucosal (villous) damage and disturbance of motility (Frazer, 1960). Recent analysis has shown that the toxicity of wheat gluten is attributable to the straight-chain peptides occurring in gliadin (Van Roon and Haek, 1961). A thesis is that the intestinal cells are deficient in enzyme which splits glutamine-containing polypeptides. Oral loading with gliadin, although perhaps leading to a rise of glutamine level in the blood of celiac patients, does not increase free blood-gliadin but probably increases a peptide-bound glutamine (Weijers and Van de Kamer, 1959). An enzymatic defect of the intestinal wall may enable general systemic toxic effects due to the unrestrained passage of unsplit peptide into the blood. Gliadin loading curves suggest this possibility (Weijers and Van de Kamer, 1960), but Gerrard, Marks and Buchan (1960) were unable to confirm that celiac disease is related

to toxic glutamine-containing peptides in the blood. It is, however, of extreme interest that Wright, Taylor, Truelove and Aschaffenburg (1962) have developed a method for the detection of circulating antibodies to gluten fraction III and antibody may be found in the cord blood of newly-born infants and in the blood of their mothers. In celiac disease, precipitins to wheat gluten and gliadin can be demonstrated in 50% of cases, although there is no present evidence that these create any adverse clinical effects. The significance of this may be revealed in further studies. We could postulate some protective advantages arising from the presence of such passively transferred antibody from the mother to her fœtus.

Alimentary Dysfunction in Celiac Disease

Wheat or rye gluten exacerbates the clinical illness and diminishes fat-absorption from 80 to 10%. In normal infants and children fat is, as a rule, completely split in the intestine and the average amount of fat retained is about 92% and with human milk 96% (Holt, Courtney and Fales, 1919). Studies of the site of fat absorption have been made by using increasing doses of ^{131}I labelled triolein in the rat. By this method Booth, Read and Jones (1961) have shown that a small dose was relatively rapidly absorbed in the jejunum, that with larger doses the healthy jejunum responded to the increased load with an increased absorption and that fat was also absorbed in the ileum. In gluten-enteropathic cases, Parkins (1960), using radioactive-isotope tracers, identified protein malabsorption in some cases and protein loss in others, although this was not directly related to the degree of the histological changes in the small intestine. Undoubtedly, steatorrhœa of long standing leads to loss of nitrogen in the fæces. At least some of this protein loss is endogenous, from secretions of the intestinal wall (Crane and Neuberger, 1960). The site of the intestine protein loss has been demonstrated by Waldmann (1961). Abnormal permeability of the intestinal tract to macromolecules may engender hypoproteinæmia, lowered serum albumen and γ -globulin (Gordon, 1959).

There may be several secondary absorption defects consequent upon the villous changes in celiac disease. A general summary of causal and consequential intestinal and general actions are noted by Frazer (1961). The intestinal cell has major metabolic functions as well as absorptive functions (Cooke, 1958). In the allied condition non-tropical sprue, Comfort and Wollaeger (1956) detected impairment of absorption effects of all

nutrients, including minerals and water. Iron absorption is particularly vulnerable. There may also be crises of a deficiency in folic acid. Some reduction in the absorption of folic acid has been detected in 90% of patients (Knowles and Prankerd, 1961). Absorption of vitamin B₁₂ may insidiously and progressively fall. Fortunately, only a small number of children with coeliac disease are found to have impaired absorption of ⁵⁸Co B₁₂, but ten adult cases of coeliac disease, with established abnormal intestinal villi, revealed an intrinsic factor deficit as the cause of their failure to absorb radioactive B₁₂ (Fone, Cooke, Meynell and Harris, 1961). The degree of steatorrhoea and the degree of calcium absorption may have variable relationships, but some 'resistance' to vitamin D recurs on re-introduction of gluten-containing diets in coeliac disease (Nassim, Saville, Cook and Mulligan, 1959).

Hypoparathyroid states may arise in longstanding steatorrhoea, but this has not been observed in coeliac disease (Williams and Wood, 1959). Magnesium deficiency may be concurrent with calcium deficiency and may possibly potentiate overt tetany (Fletcher, Henley, Sammons and Squire, 1960). Faecal loss of magnesium may be the cause of magnesium deficiency and this effect may be more marked with a high calcium intake (Hanna, Booth and Read, 1961). Further investigations may reveal other gluten-enteropathic conditioned disturbances of absorption deficiency in the gut: it would be interesting to know if, for instance, the mechanism of intestinal absorption of glucose and galactose is abnormal. It may be possible that the intestinal sucrase or other disaccharidases are deficient in the intestinal mucosal tissue. Low excretion rate of d-xylose in the urine after ingestion of a known quantity may be used as an indicator of diminished intestinal absorption (Fowler and Cooke, 1960). Low rise in levels of vitamin A after an ingestion test dose is a constant finding in coeliac disease; similarly with carotenoids (May and McCreary, 1941). The reduced activity of the intestinal cellular enzymes coupled with a depleted villous absorptive area and intestinal hypomotility are additive in the direction of intensifying coeliac disease.

The reduced activity of the intestinal cellular enzymes coupled with a depleted villous absorptive area and intestinal hypomotility are additive in the direction of intensifying coeliac disease. This may also have ill association against the normal physiological activity of the epithelial lining of the small intestine which is alleged to be in a state of continuous replacement to maintain a dynamic equilibrium and its multiplicity of functions (Creamer, Shorter and Bamforth, 1961; Creamer, 1962).

Some Morbid Influences of the Coeliac Affection

The multipotent actions of the healthy small intestine are specially revealed when its physiology is deranged as in coeliac disease. The table of 'main symptoms' given by Hawkins (1961), with diarrhoea, lassitude and loss of weight as leading symptoms, indicates some of the gross decline in health attributable to intestinal changes in gluten enteropathy. Losses incurred by malabsorption and other factors precipitate great discord in the normal homeostasis of health. The illness is clearly objective and subjective. Depression, apathy, anorexia and weakness are particularly characteristic effects in coeliac disease. Anaemia and perhaps lowered plasma proteins intensify these influences. Chronic iron-deficiency anaemia may in turn even further reduce intestinal absorption. Moreover, persisting iron deficiency may reflect more generally in tissue metabolism (Jacobs, 1961), and even disproportionately to the reduction in circulating haemoglobin (Beutler, 1957).

Growth and Development

'While the disease is active children cease to grow; even when it tends slowly to recovery, they are left frail and stunted' (Gee, 1888). The arrest of growth in length, which is particularly pronounced, suggested to Still (1918) that coeliac disease was a 'specific morbid entity'. In a longitudinal study of coeliac disease it was noted that while growth may be diminished for years the growth spurt at puberty might be only moderately diminished. The endocrine system would seem to be unimpaired, although hormone efficiencies are undoubtedly altered by inadequate general somatic responses in active coeliac disease. Sexual development and maturation are not necessarily suppressed. Even in clinically severe and longstanding coeliac disease, menstruation may occur within the usual age range (Neale, Smallwood and Shippam, 1935). The initial spurt of growth during the first six months on a gluten-free diet indicates that background forces for growth are intact and become rapidly operative (Sheldon, 1955). In 95 cases all were below average for height and weight before treatment, but on strict diet therapy the growth accelerated 30% and the weight increased 300% after a few months (Sheldon, 1959). In untreated coeliac disease the height may be 20% or more below normal age standard, although there may be little correlation between the sensitivity of the enteropathy and the extent of growth defect. Frazer (1956) asks the question: 'How much growth deficit is due to the enteropathy or is in part due

to an independent effect of inadequately metabolized wheat protein?'

In the course of thoughts on anterior hypopituitarism, Hubble (1952) developed an hypothesis that growth hormone may be depressed in malnutrition and possibly by emotional factors, but thyrotropic and adrenotropic hormones were probably not depressed under such conditions. Volwiler (1957) observed that medicinal adrenal corticosteroid may enable a dramatic, if only temporary, improvement in intestinal absorption, which in extreme cases and circumstances could be life-saving. The often prompt and favourable, though transient, response to ACTH and cortisone indicates something of the complex derangements in the body in coeliac disease. Badenoch and Callender (1960) showed that iron absorption may be rapidly improved during the administration of cortisone, prednisone or corticotrophin, but decreased again on their withdrawal. Hubble (1952) recorded that growth improved and some biochemical improvement occurred in the serum proteins in a boy, aged 9 years, with coeliac disease for whom methyl-testosterone was prescribed intermittently. A good longitudinal study of a case of coeliac infantilism is reported by Foss (1962): in this case growth, sexual maturation and spermatogenesis were achieved through gluten exclusion and androgen treatment. Growth hormone assay in coeliac disease (as in other growth-inhibiting steatorrhœas will add much to our understanding of 'coeliac infantilism'. This is now in active investigation (Marrian, 1962).

Natural History and Diagnosis

Is coeliac disease ever curable or is there a natural recovery?—probably not. The genetically-conditioned metabolic factor is probably permanent. Can the coeliac 'affection' (as so perfectly described by Gee, 1888) be prevented?—certainly yes. Early diagnosis and effective continuous treatment in childhood are both essential. Diagnosis must be accurate and fully ascertained. Steatorrhœa of small intestinal origin in infants and children may have a wide variety of possible causes. The published accounts by Green (1959) and by Carlile and Burke (1962) are a guide. Végheli (1940) rightly emphasizes the coeliac mimicry of chronic intestinal giardiasis. Pseudo-coeliac disease may occur in association with a variable number of other abnormal phenomena; Salt, Wolff, Lloyd, Fosbrooke, Cameron and Hubble (1960) have reported a syndrome of juvenile steatorrhœa, absent betalipoproteinæmia and acanthocytosis, and Mier, Schwartz and Boshes (1960) have noted a similar association with atypical retinitis pigmentosa and ataxic neuropathy.

The appalling clinical states in coeliac disease existent before the gluten-free diet era are happily now rarely seen. The picture might here be described as a possible reminder:—fatty diarrhœa, abdominal distension, severe wasting, anorexia, anæmia, depression, apathy, irritability, growth failure—the psychological disorder sometimes (especially in young children) dominating the scene. The child may be persistently accused of being 'naughty and difficult'. Beyond infancy (age one year plus) tetany, marked dermal and oral effects of hypovitaminosis, pellagrous dermatitis, osteoporosis, rickets and skeletal deformities may appear in the neglected or undiagnosed case. More recently, the full significance of hypoproteinæmia and œdema has been recognised. Strangely, primary dentition may be good and the permanent teeth erupt healthy. This is in line with the views of McCance (1962), Hellman (1923), Boas (1933), Trowell, Davies and Dean (1954), that dental development is more closely linked to the chronological age even where other tissues are impaired by undernutrition.

Physicians have long known the 'occult' coeliac syndrome of late childhood: small child, poor musculature, atrophic glossitis and recurrent angular stomatitis, periodic tetany, constipated but passing infrequent large pale motions, hypochromic, macrocytic or dimorphic anæmia. As Gee (1888) put it: 'To diarrhœa alba add emaciation and cachexia, and we have a complete picture of the disease . . . the course of the disease is always slow . . . whether the patient live or die, he lingers ill for months or years . . . death is a common end and is mostly brought about by some intercurrent disorder, for instance choleraic diarrhœa'. An intercurrent upper respiratory infection may seriously intensify coeliac disease (Anderson, 1947). Fulminating 'dehydration crises' are ominous. Stale wheat flour is particularly noxious (Daynes, 1956). Since introducing gluten-free diets the death rate in coeliac disease has fallen from 15% to practically zero. The greatest mortality was at about the age of 2 years.

Prognosis

Formerly, many were impressed by clinical improvement and diminished steatorrhœa on 'fat-free' diet. The disease lingered and growth was slow and uncertain. The introduction of gluten-free diet enabled such vast improvement that a faith arose that complete cure might be achieved. This proved to be false. It is noticeable that anorexia might quickly return on re-introducing gluten. The coeliac patient can tolerate any variety of starch but it is essential to eliminate all products of flour derived from wheat and rye.

With a meticulous gluten-free diet the proximal

intestinal lesion in juvenile celiac disease may improve or apparently disappear within three months to one year: marked improvement has been seen in intestinal biopsy material in as little as three months. Even in longstanding cases a compulsive gluten-free diet is followed by some proximal mucosal restitution, but the changes are far less dramatic than those seen in young children (Rubin, 1959). In 32 patients, aged 4 to 19 years, all of whom had celiac disease in very early childhood and all of whom had been maintained on a diet containing only minimal amounts of wheat gluten, not one could be labelled recovered after an intense clinical examination (Gerrard, Ross, Astley, French and Smellie, 1955). Similarly, Lindsay, Nordin and Norman (1956), on examining 25 young adults 15 years after they had been first recognized as having celiac disease concluded that celiac disease is a chronic relapsing illness despite, in some, quite deceptive appearances of well-being. Of 95 cases in Sheldon's series (1959) there were 23 clinical relapses on return to gluten-containing food: in 11 of these the intestinal symptoms reappeared, but in 12 others the only overt effect was growth retardation. By contrast, depression of growth is relieved by gluten-free diet.

Influence of Treatment

Favourable response is quickly revealed in the normal rate of growth and an improving texture of the scalp hair, the nails and the skin. Objective gauges of favourable improvement include fall in faecal fat loss, fall in urinary 5-hydroxy-indoleacetic acid excretion, and trends towards restoration of a normal appearance in the jejunal micro-anatomy (McKusick, 1961). The hypochromic anaemia is generally refractory until gluten is excluded from the food, after which dramatic improvement is usual. Iron-therapy will enable increase also in serum vitamin B₁₂ (Cox, Cooke, Meynell and Gaddie, 1962; Cox, Meynell, Gaddie and Cooke, 1959). Serum vitamin B₁₂ level may be quickly raised to normal with oral doses of cyanocobalamine.

Macrocytic anaemia in celiac disease is now quite rare. It was more common; Cooke, Peeney and Hawkins (1953) found macrocytosis in two-thirds of 100 patients with idiopathic steatorrhoea. The defective folic acid state (Doig and Girdwood, 1960; Anderson, Belcher, Chanarin and Mollin, 1960) is easily remedied by oral administration, but improvement in the megaloblastic anaemia may occur before formiminoglutamic acid excretion in the urine returns to normal (Knowles, Prankerd and Westall, 1961). A most favourable response in protein balance may quickly occur

after withdrawal of gluten: faecal losses of labelled protein may rapidly diminish (Crane, 1961).

Trends to Earlier Recognition of Celiac Disease

Celiac disease is especially apt to affect children between one and five years old (Gee, 1888). 'Pap' feeding in the nineteenth century doubtless created havoc with celiac children and fostered the serious effects noted. Now it must be the aim to diagnose the condition even earlier than one year of age. Intestinal mucosa biopsy in infancy is now a possible and usually safe procedure.

The present widespread decline in breast-feeding and its replacement with cow's milk preparations and wheat-containing cereals in the early months of life has led to a shift to earlier onset of signs of gluten intolerance. Wheat-flour cereal benefits healthy infants, but it quickly disturbs the potential celiac infant. Clinical suspicion should be carefully followed up in these infants who fail to thrive after cereal feeding. Celiac 'marasmus' may be diagnostically elusive. Test doses of wheat flour will determine the underlying susceptibility, and replacement by wheat starch enables quick improvement. Gluten enteropathy in early life may present as an acute or subacute illness, diarrhoea and anorexia being prominent signs.

Case 1.—Alan K., aged 4½ months, poor prognosis and low weight gain since starting wheat cereal. Symptoms seemed to start within 14 days of adding this cereal to milk feeds. Frequent unformed fatty stools. Very good progress in growth and weight after omitting all wheat cereals.

Case 2.—Nicholas H., aged 4 months, breast-fed four weeks, N.D. milk three months and wheat flour cereal added. Stools became pale, bulky, offensive. Good general progress since omitting entirely wheat cereal food. Growth in weight and length sustained, but occasionally 'a good dose of Pop-Corn has been allowed' with loose motions and general weakness following.

Case 3.—T. W., at aged 4 months received at least four varieties of gluten-containing cereals. Abdomen became distended; occasional vomiting. After a few months pale and offensive stools, persistent loss in weight. At aged 8 months a 'crisis'—severe diarrhoea, dehydration, great weakness. Jejunal biopsy (Dr. D. Burman) showed marked villous atrophy. Serum proteins normal. Skeleton: Defective calcification shown on X-ray. Continued improvement on removal of all gluten in diet.

Celiac disease, being an inborn error of intestinal function, should be recognized in infancy or early childhood and permanent gluten-free dietary maintained throughout the period of childhood and possibly always. Clinical sensitivity to gluten seems to be variable, in

FIG. 1.—Case 1. Alan K. General appearance on admission to hospital.

FIG. 3.—As in Fig. 1.

FIG. 4.—Case 2. Nicholas H. Aged 4 months.

FIG. 2.—As in Fig. 1.

FIG. 5.—Case 2. Nicholas H. Aged 6 months.

KEY**DELETERIOUS****MILDLY DELETERIOUS****NON DELETERIOUS**

FIG. 1.—The effect of fractions of wheat flour on coeliac patients.

infancy and early childhood it is likely to be severe, but in later years less acute and more insidious in its adverse influences on growth and general nutritional efficiency.

The possible association between intestinal reticulosis and steatorrhœa has been recently reaffirmed by Spracklen and Tonkin (1963). Cause and effect have been in some doubt, but

Gough, Read and Naish (1962) have brought strong evidence that, in some cases, reticulosis of the small bowel may occur as a late complication of idiopathic steatorrhœa or cœliac disease. Spracklen and Tonkin (1963) report a reticulum

cell sarcoma in a case of cœliac disease 30 years after the age of onset of the steatorrhœa.

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