Individual Studies

DISORDERS OF BEHAVIOUR IN CHILDHOOD ASSOCIATED WITH WHEAT PROTEIN SENSITIVITY

" Pre-Coeliac Disease "

By

W. GUY DAYNES, M.R.C.S., L.R.C.P., D.C.H.

Hove

A syndrome that follows infectious illnesses in children will be described. Evidence will be produced to show that this condition is caused by the ingestion of wheat protein at a time when the child is sensitive to it, and can be cured by withholding gluten from the child's diet. The condition will be compared with coeliac disease and canine hysteria, and the relationship to the use of " improved flour " in the diet will be discussed.

The Syndrome

Children of either sex from 6 months to 5 years may suffer from this syndrome. Older children are less commonly affected and in rather different ways. Typically, the child becomes " naughty " and " difficult " about 10 days after the onset of an acute infectious illness such as measles, influenza or gastro-enteritis. This usually occurs as he is recovering from the illness and the trouble is often put down to " spoiling while he was ill ". However, disciplinary measures only aggravate the bad behaviour. The " naughtiness " is worse at night and at meal-times, and the child tends to be irritable, mean and spiteful. Sleep is disturbed and he wakes up many times in the night and cries or screams, often refusing to be comforted for as long as 15 minutes or more. Appetite is poor and he is often very " difficult " over eating and fails to gain weight. The stools resemble those of coeliac disease in that they tend to be bulky, pale, offensive, and sometimes loose and frequent. The complaint of central abdominal pain with or without abdominal tenderness may be encountered in 4 year olds, as may headaches. Some severely affected cases have unduly prominent abdomens and small buttocks as in coeliac disease. They also may develop petit-mal-like attacks that resemble the attacks that puppies get when suffering from canine hysteria. The final characteristic of the syndrome is the prompt disappearance of symptoms following the exclusion of gluten from the diet.

Comparison with syndromes known to be due to ingestion of wheat protein

1. Coeliac Disease. The mode of onset, the behaviour found in the disease, the stools and the response to therapy bear considerable resemblance to the syndrome that has been described.

(*A*) *Onset.* Ebbs, writing in Gaisfords and Lightwood's *Paediatrics* (1954), described the onset as follows :—

The disease may come on in three ways. (1) Occasionally there is a tendency to diarrhoea from birth which gradually progresses to the classical picture. (2) The more usual onset, however, is between the ages of 6 months and 2 years, although it may occasionally be after the second year. Approximately 50% of children have a sudden onset associated with infection. Such infection may be internal, such as dysentry, or parental, commonly nasopharyngitis and its complications. Affected infants develop undigested stools which persist as a loose diarrhoea, some also have vomiting. (3) In the rest of the patients there is an insidious onset with alternating loose stools and constipation, associated with loss of appetite, and loss of or stationary weight. There is also increasing nervous irritability. Many infants develop their first signs during weaning when flour-containing foods are first given. It has been shown that the onset is later in breast-fed infants than in those artificially fed, and also that it is usually later in cases in which there has been no infection, such cases tending to have a more insidious onset. Occasionally a food allergy has been observed at the onset. The early acute phase of the disease, characterised chiefly by diarrhoea, increasing irritability, loss of appetite and failure to thrive lasts from a few to several weeks; it is followed by a chronic state leading to the classical coeliac picture.

Parsons (1954) said that the illness may remain " unsuspected until the child is 5 or 6 years of age." He continued :—

Careful inquiry will nevertheless reveal the fact that the patient has had digestive disturbances for a long time, possibly for years. . . . Occasionally, however, the onset is apparently an abrupt one, and then a few days after the onset of an acute attack of diarrhoea and vomiting the stools are noticed to be large and pale.

Loss of fat tissue from the buttocks and increasing prominence of the abdomen are also fairly early signs.

(*B*) *Behaviour.* Parsons (1954) wrote that the appetite is "always capricious to a marked degree at some periods of the illness." He continues :—

In their periods of improvement the subjects of coeliac disease are most attractive children, although usually somewhat spoilt, and perhaps more easily moved to tears than the normal child, but in diarrhoeal periods they are moody, irritable, and passionate, and their tempers are as capricious as their appetites; nothing pleases them and their misery reaches a degree which makes them a trial to those who have charge of them and would lead one to suppose that it could not be the same child which was previously such a fascinating person—when they are good they are very, very good, but when they are bad they are horrid.

Sheldon (1951) said that the child was " continually grizzling and resenting examination, although no actual pain or tenderness can be discovered."

May (1953) is one of the few who regarded these children's behaviour as being of " great interest and importance ". He wrote:—

They lose all the spontaneity and happiness of the normal infant or child. They lie in their beds apathetic and motionless, never smiling. They show no response

to efforts at entertainment and may recoil from a display of affection. Irritability, fussiness, crying and temper are prominent. It is difficult to satisfy their exacting demands. The parents become desperate as they watch the change from a robust, happy, contented child to a wasted, abject, miserable creature. Uninformed persons may ascribe the behaviour to " spoiling " as the annorexia has frequently led to coaxing and extra attention. All other signs of recovery are preceded by the return of a more normal behaviour.

Holt and McIntosh (1953) report that " sleep is often disturbed."

(*C*) *The Stools.* There is general agreement that in the early phase of the disorder the stools are large and pale, with a tendency to become putty coloured, and that they have a characteristically disgusting smell. Roughly speaking the increased bulk and foul smell seem to indicate excessive starch in the stools, whereas the pale putty colour indicates too much fat. Accurate fat analysis tests are out of the question in general practice, so comparisons can only be made with these simple characteristics.

(*D*) *Response to Therapy.* The sufferers from coeliac disease respond dramatically to a gluten-free diet, and very quickly lose their symtoms particularly the nervous ones, and the physical state responds likewise in due time. Sheldon (1952) said " There is certainly no justification now for accepting anything short of optimal growth as evidence of success in treatment ". A full description of the gluten-free diet has been given by Norman (1954) with details of its administration. Regarding the introduction of cereals into the diet he has stated that gluten-free cereals should not be introduced until " it is evident that recovery is well advanced ". It seems to be accepted that the giving of even gluten-free cereals early in the treatment is occasionally attended by a relapse, though later the child who has relapsed will be able to tolerate them satisfactorily. A further accepted fact is the tendency for children on a gluten-free diet to relapse temporarily when they suffer from any infection, even one so mild as coryza. (Anderson, Frazer, *et al.* 1952.)

Recently Gerrard, Ross and Smellie (1955) have reported their results of the late treatment of coeliac disease with a gluten-free diet. They have shown that sufferers of long standing and in the latent phase of the disease still respond to this diet, and that there was " a striking acceleration of growth in weight and in height accompanied by the disappearance of steatorrhoea ". They also noted that " the vitality and demeanour of all the patients improved ".

2. Canine Hysteria. Mellanby (1946) gives the following description of canine hysteria :

The animal has a frightened look and usually stands with either fore or hind legs rather far apart and ears back. Jerking of the head backwards may be seen.

At this stage the animal will sometimes shake itself, take a drink of water and then recover. . . . In more severe cases the animal sits in a Sphinx-like posture; its head soon starts jerking, and the movement spreads throughout the body. Next it starts running round and round its cage, sometimes barking furiously, and either dashes into the walls, apparently without seeing them, or attempts to jump them, overturning food dishes and water-pots, and getting both itself and its cage into a filthy condition. It may begin to recover at this stage, stop running, and stagger around like a drunken person. It will sit down, looking very miserable, but at the end of about 30 minutes may be more or less normal.

He also reports that the cages of the affected animals were found often in a filthy condition in the morning, "suggesting that the night may be a common time for the attacks". He continues:—

Dogs subject to hysteria can usually be recognised by their general demeanour As compared to normal dogs of the same litter, they tend:

(1) to be less interested in their surroundings.

(2) to run or walk more slowly.

(3) to lift their forelegs high when walking and to bounce along when running.

(4) to have dry mouths.

(5) to stand in a shady corner if the sun is shining and to resist persuasion to run about.

(6) to be less friendly and more frightened.

These manifestations usually precede the onset of the hysterical outbursts, but once having had these a dog will continue to suffer intermittently until the diet is changed.

The attacks

tend to be induced by any sudden stimulus, nervous strain or change of environment. . . . If the harmful diet is continued for some months, the fits may be reduced in number or even stop, but the animal's general behaviour remains abnormal. . . . Affected dogs returned towards normal and the typical hysteria and fits stopped when the agenized flour was removed from the diet and replaced by unimproved flour of the same grist. . . . The degree of susceptibility varied from litter to litter, and even from animal to animal in the same litter. Changing the flour in the diet of a badly affected animal to the untreated variety, resulted in a sudden stoppage of the fits, but the animal might remain nervous and shy for a period. . . . Recovery from the slighter more chronic condition appears to bear a relationship to the length of time the animals have received the treated flour. . . . If they have had it for a long period—e.g. 6 months—recovery may not be complete even after three to four months on the untreated flour, although the more severe abnormalities, such as hysterical and epileptic fits will cease within 24 to 48 hours of the change of diet.

Cases of Wheat Protein Sensitivity

The cases which are summarised in Table I have occurred during the past 2 years in my private general practice in the Brighton area, or in an Infant Welfare Centre in the Piccadilly area of London. The gluten-free diet used was similar to that set out by Norman (1954). Patients were given a list of foods to avoid as in Table II. Where appropriate, advice was given as to inclusion in the diet of pure wheat starch prepared by Energen Food Co. of London.

Table I. **SUMMARY OF CASES**

CASE	SEX	AGE	Clinical Features											Results		
			Length of History (Months)	PRECIPITATING ILLNESS	Abnormal Naughtiness	Waking at Night	Crying at Night	Loss of Appetite	Failure to gain Weight	Prominent Abdomen	Abnormal Stools	Petit-mal-like Attacks	OTHER SIGNS AND SYMPTOMS	Relapses after Start of Diet	CAUSE OF RELAPSE	Now controlled WITH Diet	Now controlled WITHOUT Diet
1. Peter B.	M	4	30	Gastro-Enteritis	+	+	+	+	+	+	+	+	Abnormal Speech, Legs Unsteady, Dry Mouth, Small Buttocks, Abnormal E.E.G.	2	*a* "Cornflour" *b* Chocolate	+	—
2. Anna M.	F	2	12	Tonsillitis	+	+	+	+	+	+	+	+	Small Buttocks	2+	*a* Ice Cream *b* Bread	+	—
3. Alan D.	M	4	12	Tonsillitis	+	+	0	+	0	+	+	+	Abdominal Pain	1	Off Diet	+	—
4. Susan G.	F	4½	3	Resp. Infection	0	0	0	+	0	0	+	+	Abdominal Pain, Wheezing	0	—	—	+
5. Robert S.	M	3	2	Upper Resp. Infection	+	+	+	+	0	0	+	0	—	0	—	—	+
6. Anne W.	F	5	12	Gastro-Enteritis	+	+	+	+	+	0	+	0	—	0	—	+	—
7. Rosemary P.	F	5	3	Measles	+	+	0	+	0	+	+	0	Vomiting	0	—	—	+
8. Sonia L.	F	7	6	Upper Resp. Infection	+	+	0	+	+	0	+	+	Visual Symptons, E.E.G. Abnormal, Headaches	1	Off Diet	+	—
9. Ian G.	M	3	3	Upper Resp. Infection	+	0	0	+	+	+	+	+	—	1	Off Diet	+	—
10. Stephanie G.	F	2	3	Gastro-Enteritis	+	+	+	+	+	0	+	0	—	1	Off Diet	+	—
11. Michael H.	M	5	48	Gastro-Enteritis	+	+	+	+	+	+	+	0	Anaemia (Hb 60 per cent.) Small Buttocks	1	Off Diet	+	—
12. Simon F.	M	1¾	1	Measles	+	+	+	0	0	0	+	0	Eczema on Face	0	—	—	+
13. Kathleen P.	F	3½	6	Tonsillitis	+	+	+	+	0	0	+	0	Abdominal Pain	0	—	+	—
14. Carol W.	F	4	1	Measles	+	0	0	0	0	0	+	+	Tiredness in A.M. Depression	0	—	+	—
15. Oonah B.	F	2½	6	Measles	+	+	+	+	0	0	0	0	—	0	—	+	—
16. Sarah C.	F	3½	24	Gastro-Enteritis	+	+	+	+	0	0	+	0	Teeth Grinding at Night	0	—	+	—
17. Allison B.	F	1½	9	Gastro-Enteritis	0	+	+	0	+	0	+	0	—	0	—	+	—
18. John R.	M	1	5	Upper Resp. Infection	+	+	+	0	0	0	+	0	—	0	—	—	+
19. Madelaine J.	F	2	6	Upper Resp. Infection	+	0	0	+	+	+	+	0	Small Buttocks	1	Off Diet	+	—
20. Alan D.	M	2	8	Upper Resp. Infection	+	+	0	+	+	0	+	0	—	0	—	+	—
21. Richard R.	M	3	2	Tonsillitis	+	+	+	+	0	0	+	0	Eczema on Buttocks	1	Off Diet	+	—

Table II.

The following foods may NOT be given:—

Baked beans in any thick sauce	Pastry
Bread or toast	" Puffed Wheat "
Biscuits	Paste (fish or meat)
Cakes	Rusks
Chocolate	" Ryvita "
Doughnuts	Semolina
Energen rolls	Spaghetti
" Grape nuts "	" Shredded Wheat "
Ice cream (commercial)	Sweets of unknown composition
Macaroni	Sauces (commercial)
Malted milk	Salad cream
Noodles	Sausages
" Ovaltine "	Tinned soups and meats
Procea bread	Vermicelli
" Proferin " rolls	" Vita Wheat "
Packet cake & pudding mixture	" Weetabix "
Packet soups & gravy browning	

Two illustrative cases will be described in detail to give a clearer picture of the syndrome.

Case 2. Anna M. aged 2. Anna's parents were desperate. They had been woken up by her crying two or three times each night for 12 months, so they brought her up from the country to see me in September 1954, as I had attended their eldest child some years back. Anna was the third girl and had been a very satisfactory baby until she was 11 months old, when she was very ill with acute tonsillitis and otitis media. From then on, she had woken at night with crying attacks which had gradually become more severe and more frequent. There were two distinct types of attacks. There were minor crying attacks which occurred once a night at the best and eight times at the worst. These lasted only a few minutes and often she would go off to sleep quite quickly afterwards. The more severe attacks would be ushered in with a piercing scream. Often she seemed awake but confused, not knowing anybody, and would sob until she went off to sleep again, usually with the aid of " strong chloral." These attacks usually occurred two or three times a week, but occasionally she had weeks free from them. She wet the bed each night but was mainly dry during the day. She always behaved badly and did not play well with other children, being spiteful to them. She was pale and had a poor and unpredictable appetite. Her bowels were said at first to be normal, but on closer questioning her mother said that Anna sometimes produced a yellowish stool that had a very offensive smell. Examination revealed little else beyond a pale child who was thin, and perhaps the absence of fat was most marked in the gluteal region. Her tonsils were large and sub-acutely inflamed, and her right ear-drum was retracted. A diagnosis of wheat-protein-sensitivity was made and she was placed on a gluten-free diet, which she started on a Friday. She had a bad screaming attack that night, but on Saturday night was " grizzly only ". On Sunday night she slept the whole way through the night without waking for the first time for a year ! In the next two weeks she had two screaming attacks, each of which had been preceded by an accidental lapse in diet. On one occasion a well-meaning friend had given her a proprietary ice cream and on the other the dog had stolen some bread

put out for the rabbits, had taken it on to the lawn where he and Anna had shared it. When she was next seen, she appeared much happier, behaved well, was eating well and had gained weight. The other children had all commented on how much nicer Anna was now. A month after she started the gluten-free diet her mother wrote, " Anna is now a perfectly normal child and is sleeping through the night. She is looking so well and is happy and contented. It is such a joy ". Her progress has continued since then, but any lapse in diet has stopped her gaining weight and caused a slight recurrence of symptoms.

Case 3. Alan D. aged 4. Alan was the elder of two boys, both of whom I had known at my Welfare Clinic since birth. I had always liked him and he was a fine specimen physically. However, in November 1953 he had had a severe attack of tonsillitis and he had never really recovered from it. His mother brought him up to the clinic in December 1953 on account of his complaints of abdominal pain, and incidentally, naughtiness and wakefulness at night. To me the child had certainly changed. He started off in quite a friendly way, but soon tired of this and became extremely restless, charging about the consulting room, trying to capture my instruments or his brother's toys. Examination of his abdomen on two separate occasions revealed mild but definite tenderness in the right iliac fossa, with little else abnormal. He was referred to the Westminster Children's Hospital for an opinion on his abdominal condition, but when he arrived there he behaved so badly that examination was inconclusive, so was referred back with an open verdict. It was then that the association between his abnormal behaviour and his other symptoms suggested to me wheat-protein-sensitivity. His mother then told me that his motions were " rather nasty " and putty-coloured, and that he himself had " looked rather odd " on occasions recently. Further enquiry showed that his mother was referring to attacks when he suddenly " went blank ", gazed into space and stood very still; and then jerked his head and carried on doing what he was about to do. I was lucky enough to watch one of these, and, to me, the attack was indistinguishable from petit mal. There was no family history of epilepsy. However, in view of my previous cases, I tried him on a gluten-free diet, and he quickly recovered from his bad behaviour, blank attacks and abdominal pains in that order. The stools also returned to normal. After 3 weeks his mother gave up the diet and he relapsed almost at once, sleeping badly, being naughty, and complaining of abdominal pain. About a year after the onset, his mother gradually relaxed his diet and as he was none the worse, was able to put him back on normal food with no adverse effects.

Discussion

These cases bring many questions to one's mind.

(1) *Has the evidence offered by my cases established wheat protein as a clear causative factor?* or does the matter remain in the dangerous cross currents of " post hoc, propter hoc " reasoning ? I contend that the number of cases and the fact that many of them have been controlled against themselves by the stopping and starting of wheat protein in the diet, put the affirmative answer to the first question beyond all reasonable doubt. Truly the " post hoc, propter hoc " reasoning has been used, but the deduction does not rest on this theory alone; it also is supported by the similarity of the disease patterns of my cases to those of the conditions known to be due to the presence of wheat protein in the diet.

(2) *Are these cases instances of a common condition or are they rare manifestations of allergy to wheat protein ?* My 21 cases have mostly occurred during the past year and a half and I estimate that the number of

patients of all ages at risk during that period was unlikely to exceed 1,200, even including my Infant Welfare Clinic patients. This must mean that cases such as I have described are *common*, especially in the milder forms. Therefore, I hope and expect that other general practitioners will be able to recognise a great many similar cases once they are on the look-out for them; these conditions are much more likely to be found in general practice than in consulting practice.

(3) *What is the significance of the petit-mal-like fits? Can they lead to epilepsy?* Superficially there is considerable resemblance to petit mal, particularly when the fit is momentary as in the one that I was lucky enough to observe in Case 3 and confusion between the two conditions is probable. There may well be curable cases of wheat-protein-sensitivity lurking among the therapeutically unresponsive petit mals, and a review of such cases would seem to be indicated. The points of dissimilarity are the length of time of some of the attacks, the presence of other manifestations of wheat-protein-sensitivity, and perhaps the E.E.G. changes. Clearly, further E.E.G. studies must be made to show the range of wave patterns to be expected in this condition and the length of time they may remain abnormal after the clinical condition is seemingly cured. We may ask ourselves whether these changes are mild forms of temporal lobe involvement like those discovered at operation by Falconer and his colleagues (1955). These workers have associated many of their temporal lobe epileptic cases with past infections in childhood. Likewise, the personality disorders seem comparable in both groups, though the frank epileptic cases show the more severe type of disorder.

There is such a striking resemblance between the fits that occurred in Case 1 and those of puppies suffering from canine hysteria that a full description of this child's attacks and behaviour prior to going on to a gluten-free diet is worth recording.

Case 1. Peter B. aged 2. The attacks were taking place two or three times a night as well as during the day; transferring him from the nursery to his high chair in the dining room nearly always brought on an attack, unless his attention was held by someone playing with him. The attack would start by him becoming stock still and staring in front of him, sometimes for as long as a minute; then his head would twitch, there was a fluttering of his eyes and a spasmodic movement chiefly of the upper limbs, and he would often pant. During this time there was a rush of words and sentences, generally lacking coherence, and often ending with a scream. The attacks were worse following any excitement during the previous 24 hours. A further curious symptom, for which I had no explanation, was a dryness of the mouth, the child seeming to have difficulty in eating anything other than moist foods. His appetite was very poor and highly capricious. His play was characterised by over-activity, charging about the nursery, often knocking into furniture and indeed the wall, so much so that anything breakable had to be removed from the room. His speech at this time was most odd; he talked very slowly with an exaggerated drawl, so that some words seemed as though they would never stop! His gait was strange, and he was wobbly if made to

stand still. General examination never revealed any abnormal neurological sign apart from those described above. There was no family history of epilepsy in his case.

The trigger mechanism of a change from one room to another, the momentary vacant look, the shake of the head, the abnormal walking and running, the dryness of the mouth, the miserable look and the resumption of normal activity after the attack is over, are all similar. Added to these, we have the fact that both dogs and children are cured by the exclusion of wheat-protein from their diet.

(4) *Are these petit-mal-like fits caused in the same way as the fits of canine hysteria?* The toxic agent responsible for the canine hysteria has been proved to be a substance called methionine sulphoximine (Horder, Dodds and Moran 1954). They state that this substance, while toxic to almost all animals to some extent, is only slightly toxic to monkeys but much more so to dogs, rabbits and ferrets. None has, as yet, been fed to human subjects (Moran 1955) but regarding the possible toxic action on man, Horder, Dodds and Moram say:— " Flour treated with the normal commercial dose of nitrogen trichloride contains about 2 p.p.m. of the sulphoximine, it would take man 160 years to build up the dose which is toxic to monkeys. This may be the explanation why there is no evidence that agenized flour in the normal diet of man is harmful ". This, of course, neglects the possibility of special individual sensitization to sulphoximine and, since direct toxic action is most unlikely, this would seem the only remaining method of explaining a common etiology. Let us then, examine the hypothesis that the cases I have described as wheat-protein-sensitivity (pre-coeliac disease) are caused by an allergy to methionine sulphoximine. This substance is found in the gliadin fraction of the wheat-protein in flour that has been " improved " by agene gas, which process is very extensively used in this country and apparently has been for more than 20 years. Mellanby (1946) quoted a miller as saying " he would not be surprised if as much as 90 per cent. of flour milled in this country and used for bread-making was agenized ". There has been a reduction in the practice in this country since that time, but following Mellanby's discovery the U.S.A. and Canada in 1950 abandoned the use of agene altogether and replaced it by chlorine dioxide. However, even this process cannot be regarded as blameless (Sheldon and Yorke 1953). " The milling industry in this country have hesitated to make the change-over until further work had been carried out on its action on flour " (Horder, Dodds and Moran 1954), but it is finally abandoning agenization at the end of this year. We have good evidence that this known toxic substance has been included in the dietary of the vast majority of people in England for many years, so that there is ample opportunity for

individual sensitization to occur. Most authorities will agree that sensitization tends to follow contact between the sensitizing substance and cells damaged by virus infection or other means, and that the more toxic the substance the more likelihood is there of this occurring. Furthermore, once cells have become sensitized to one substance, they often become sensitive to other chemically related substances—this being known as cross-sensitization (Baer, 1945). Some cells seem to retain a sensitivity to certain substances for a very long time, passing on this attribute to new cells. In other instances, sensitization is relatively short-lived and simple wheat protein sensitivity seems to behave more in this way than the former.

In all my cases there was a preceding history of a single fairly severe infection, or recurrent minor infections. If we admit sensitization to methionine sulphoximine following tissue damage during infections as a possibility, then we can reasonably accept the possibility of sensitization to other amino-acids of a like nature following in its wake.

(5) *What is the relationship of coeliac disease to my cases, and can it also be explained on the allergic hypothesis?* This is a much more complicated question to answer. If the diagnostic criteria of Andersen, Paul and di Saint'Agnese (1948) for coeliac disease be accepted, some of my cases are so similar that they might even be regarded as coeliac disease. They suggest that for all practical purposes a clinical diagnosis can be made on:

(1) A history of periodic episodes of large foul stools usually in association with respiratory infections, (2) Demonstration of excess starch in the faeces, (3) The clinical response within a few days to a well-planned coeliac regimen and a reappearance of symptoms within a few days or weeks after return to a normal diet.

This is a much less rigid diagnosis than that laid down by authorities in the past and, thus encouraged, I have been tempted to call the syndrome " pre-coeliac disease."

The disease label matters little: What counts is the disease pattern and basic defect in the illness. The disease pattern of early coeliac disease is in many respects similar to that of the cases I have described. One of the most characteristic manifestations of coeliac disease is their peculiar form of spiteful naughtiness; they are mean and unkind. Well do I recall one, who gained complete control of the whole ward through his ability to flick food with unerring aim. I only had to cross him to expect a spoonful of fish pie slap in the face the next time I entered the ward at dinner time. This is the sort of nasty naughtiness shown by the cases I have described, and is a diagnostic feature. It can best be summed up as the sort of naughtiness that makes other children dislike them. This is in direct contrast to the naughtiness of our own healthy children which seems to make them the idols of the kindergarten.

Similarity of the disease pattern always suggests similarity of the basic defect. Against this we have two stumbling blocks. Coeliac disease was first described in 1888, long before agene was thought of as an improver substance, but the diagnosis then included conditions now separately diagnosed, such as fibrocystic disease of the pancreas. Then we have the statement referring to the cause of coeliac disease: " Agenisation of wheat flour seems to play no part in this " (Andersen, Frazer *et al.* 1952). This dictum, which has apparently received universal acceptance, seems to be based on observations of one very severe case of coeliac disease who was rendered normal by 3 months treatment on a wheat-free diet, and was then made to relapse on re-introducing agenised wheat flour. She was given a respite of a further 3 months and made to relapse again with non-agenised wheat flour. However, judging from the charts, this relapse does not appear to have been quite so severe and took a little longer to reach its peak, but there is no comment on this. If the wheat-protein allergy hypothesis is accepted, all that these observations have shown is that the child was not *only* sensitive to sulphoximine, but was also sensitive to other amino-acids in non-agenized wheat flour. The only certain way of excluding sulphoximine sensitivity as a cause would be to give an appropriate quantity of the pure substance to the child by mouth. The child should be unaffected if sulphoximine is unconnected with the disease; but the procedure might be dangerous in a hypersensitive child (Dodds 1955) and, as far as I am aware, has not been done either here or in America. Such an investigation should only be performed by paediatricians in hospital with full facilities for dealing with any untoward reaction that might occur; therefore I have been unable to carry my observations to their logical conclusions.

Observation of the dietry of my cases has suggested that the more the flour is matured, either by storage or by chemical additions, the more severe become the reactions it initiates.

I have observed on a few occasions that " stress " in the form of an illness or emotional upset seems to result in an exacerbation of symptoms in the more severe cases, notwithstanding adherence to the gluten-free diet. The exacerbation only lasts a day or two and the longer the patient had been under dietetic treatment the less the effect of stress upon the symptoms. This reaction to stress is similar to that which occurs in accepted allergic conditions such as asthma or eczema.

Further support for the allergic hypothesis as an explanation of coeliac disease, and consequently of my cases, comes from Prof. Frazer. In suggesting an allergic cause for coeliac disease, he said: " Il est possible qu'une réaction allergique se produise dans l'intestin gréle supérieur de ces enfants. Cette réaction cause un

délai d'absorption sans diminution de l'absorption totale." He adds: " Les explications peuvent démontrer la plupart des faits connus dans la maladie coeliaque, mais la preuve finale concernant une réaction allergique n'a pas encore été obtenu."

Yes, " La preuve finale " has yet to be reached. Nevertheless, I contend that we are a stage nearer, and if hospital and scientific workers persue the threads indicated, and general practitioners search in their practices for cases similar to those I have described, where possible passing them on for investigation, final proof will be achieved in the near future.

Conclusions

1. The syndrome of naughtiness, wakefulness, crying at night, poor appetite, failure to gain weight, pale and offensive stools and sometimes petit-mal-like fits is a distinct entity and may be called for convenience " pre-coeliac disease ".

2. Pre-coeliac disease follows measles, acute upper respiratory infections, and possibly other diseases that cause tissue damage.

3. Pre-coeliac disease may be the result of damaged brain and intestinal tissue becoming temporarily allergic to wheat protein.

4. Pre-coeliac disease is a common condition and most general practitioners will find cases if they look for them.

5. Pre-coeliac disease can probably be prevented by prescribing a gluten-free diet during and for a few days after any acute infective illness.

6. There is now sufficient evidence to justify millers and bakers making and marketing bread made from flour which has not been " improved " in any way, and labelled as such so that doctors may prescribe this for patients liable to become sensitive to flour " improved " by the customary methods.

REFERENCES

Andersen, Paul & di Saint 'Agnese (1948) in Brennerman's *Practice of Paediatrics* ", Hagerstown, Maryland. **29**; 8.

Anderson C. M., Frazer A.c. *et al.* (1952) *Lancet* **1**; 836; 26th April, 1952.

Baer, R. J. (1954) in MacKenna's *Modern Trends in Dermatology* (2nd Series)—London, p. 232.

Dodds, Sir E. C. (1955) Personal communication.

Ebbs, J. (1954) Gaisford & Lightwood's *Paediatrics*—London. **2**; 232.

Erickson, T. C., *et al.* (1947) A Research Nerv. & Ment. Dis. Proc., **26**: 164: 174.

Falconer, Hill, *et al. Lancet*—23rd April, 1955, p. 827.

Frazer, A. C. (1953) Acta Gastroenter. Belg. **16**: 8-9, Aug.-Sept., 1953.

Holt and McIntosh (1953) Holt's *Paediatrics*—New York, p. 277.

Horder, Dodds & Moran (1954) *Bread.* London, p. 202.

May, C. D. (1953) Garrod, Batten & Thursfield's *Diseases of Children*, edited by Moncreif & Evans. **1**; 335.

Mellanby, Sir E. (1946) *Brit. Med. J.*, 14th Dec., 885-887.

Moran, T. (1955) Personal communication.

Norman, A. P. (1954) in *Recent Advances in Paediatrics*, edited by Gairdner, London. p. 241.

Parsons, Sir L. (1954) *Diseases of Infancy and Childhood*—London. **1**; 387.

Sheldon, G. C. & Yorke, A. (1953) *Lancet*, 21st March, 1953.

Sheldon, W. (1951) *Diseases of Infancy and Childhood*—London, p. iii.

Wagner, J. R. & Elvehjem, C. A. (1944) *J. Nutrition.* **28**: 431: 441.

Widdowson, E. M. & McCance, R. A. (1954) *M.R.C. Spec. Report*, Series No. 287. p. 58.