

GASTROINTESTINAL WHEAT ALLERGY

TWO RECENT EXPERIENCES

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THIS report has been prompted by the recent observation of two patients who demonstrated profound improvement of severe gastrointestinal disability only after a wheat-free diet had been instituted. It is presented primarily as a clinical and therapeutic study in view of the renewed interest in wheat allergy, particularly as this phenomenon relates to the sprue and celiac syndromes.

As the literature is culled for the more authoritative presentations dealing with allergy to wheat and other foodstuffs, one is impressed with the great reserve with which he is cautioned to make such a diagnosis. Most authors stress the general unreliability of skin and passive transfer tests to foods, the leukopenic index, and the other "specific" tests which have been advocated for the diagnosis of an allergic state. Enthusiasm or skepticism is held by both allergists and gastroenterologists alike for the provocative tests, the clinical observations following the use of elimination diets, the roentgenologic evaluation of the effect of barium-specific food mixtures upon the tonus, motility, and mucosal pattern of the intestinal tract, and direct studies of the local reaction to allergens either by gastroscopy or proctosigmoidoscopy. The use of control studies followed by the administration of the suspected noxious agent in a disguised form is frequently suggested.

To complicate the subject further, there are many diverse opinions relating to the actual incidence of both food and gastrointestinal allergy. As Ingelfinger, Lowell, and Franklin¹ have stated, "Gastrointestinal allergy is a diagnosis frequently entertained, occasionally evaluated and rarely established. It offers to its enthusiastic supporters a reasonable explanation for many obscure abdominal complaints." Many authors interested in the psychodynamics of food intolerances and allergy stress the psychic identification of patients to food, and the great difficulty in separating the salutary effects of the elimination diet itself, on the one hand, from the combination of dietetic ritual and the physician's interest and enthusiasm on the other. The reader is referred to the standard allergy texts and to the reviews by Tuft,² Andresen,³ Schloss,⁴ Rowe,⁵ Ingelfinger and his associates,¹ Graham and his associates,⁶ Withers,⁷ Kaufman,⁸ Loveless,⁹ Cooke,¹⁰ and Hill¹¹ for further general discussions of the problem.

Within the past five years, interest in wheat and gluten allergy has been revived. This has been due chiefly to the reports in Holland by Dicke¹² and Weijers and Van de Kamer¹³ and in England by Anderson and his associates¹⁴

and Sheldon and Lawson^{15, 16} of the remarkable improvement noted clinically and biochemically in celiac disease when wheat and rye flour are excluded from the diet. In one study, the fecal fat content returned to normal in six out of seven children.¹⁴ The gluten fraction apparently has been specifically incriminated, and the maintenance of a gluten-free diet is now the objective in the dietary management of these children. In fact, one company in England now separates wheat flour into its protein and starch components in the course of preparing their particular food commodities. It makes available for celiac children the whole wheat starch which, by means of special recipes, can be made into bread, biscuits, and cakes, thus taking the place of whole wheat flour. (Such special recipes are necessary because, in the absence of gluten, a wheat starch loaf would crumble to pieces unless some substitute for the binding properties of gluten were used. Its place is taken by fat and milk.)

In adults, significant wheat or gluten allergy in sprue and other gastrointestinal disorders has been given more specific consideration since the recent report by Ruffin and his colleagues.¹⁷ The case was presented of a 39-year-old woman who experienced a clinical, biochemical, and even a radiologic remission on a wheat-free diet after sprue which had remained severe in spite of intensive treatment with folic acid, liver extract, and vitamin B₁₂. The patient with sprue herein reported confirms this observation. All the authors who have written recently on this subject imply that the beneficial effects in both sprue and celiac disease of such varied diets as the banana diet, the vegetable-fruit diet, the starch-free diet, and the many others advocated may actually be due to the absence of wheat. In his radiologic text, Golden¹⁸ describes the striking case of a patient with the clinical and x-ray diagnosis of sprue who remained in good health on a regime of bananas, vitamin B complex, and oral liver; if he ate wheat, diarrhea would promptly ensue. Even before the modern concept of allergy existed, such instances were known to occur in both man and animals, and were diagnosed as "buckwheat poisoning."¹⁹ Although Andresen, Rowe, Walzer, and Vaughn²⁰ have constantly alluded to the importance of wheat allergy in these conditions, attention heretofore has not been brought out in such clarity as to its significance.

Our unsuccessful experience with the use of cortisone prior to the institution of the wheat-free diet has raised several additional postulates in our thinking concerning the beneficial effect of cortisone, hydrocortisone, or corticotropin reported by others in the primary sprue syndrome. Since those patients who did respond to hormonal treatment uniformly relapsed one to three weeks after cessation of the steroids, notwithstanding the continued administration of liver extract, vitamin B₁₂, and folic acid, it is apparent that the explanation for this improvement must be other than one of simple replacement therapy. In view of the recent evidence demonstrating both the hydrocholeretic and true choleretic effects of cortisone,²³ it is possible that

this action may have improved the defective intestinal absorption somewhat. This seems less likely in the universally noted absence of improvement after the administration of large amounts of the bile salt preparations.

Attempts have been made to relate the etiology of the primary sprue process to adrenocortical insufficiency on the basis of the diminished fat absorption in Addison's disease, the flat oral glucose tolerance curves, the diarrhea and weight loss, and the superficial resemblance of the sprue and Addisonian patients.²⁴⁻²⁶ Almy²⁷ and Paniagua and associates²⁸ have independently studied this problem and conclude that the adrenal cortical reserve is normal in both tropical and nontropical sprue.

It is quite possible, on the other hand, that these steroids do interfere with allergic reaction to wheat or gluten in some temporary manner which we are as yet unable to explain. This observation is enhanced by the fact that the progressive course of the sprue syndrome secondary to such diverse entities as lymphoma, amyloidosis, Whipple's disease, and extensive mesenteric tuberculosis cannot be influenced by hormonal therapy. It has even been emphasized that steroid therapy should be administered with caution in sprue. If one is not constantly aware of the fact that the steroids enhance potassium excretion and that a marked potassium deficiency may already exist, a serious hypokalemic hypochloremic alkalosis is likely to ensue.²⁹ Furthermore, these agents have been clearly shown to interfere with calcium therapy.³⁰ Consequently, their use in sprue, hypoparathyroidism, and other hypocalcemic states can readily produce clinical tetany, such as occurred in our first patient.

The specific sensitization of patients to the products of food digestion in the form of primary and secondary proteoses has been investigated intermittently for many years (Cooke,³¹ Tuft and Blumstein,³² Ancona and Schumacher,³³ Wacker and co-workers³⁴). Enthusiasm for this theory waxed notably when the favorable results from the use of propeptones were reported in the treatment of gastrointestinal food hypersensitivity.^{35, 36} It had recently waned with the report of Bloom, Markow, and Redner,³⁷ in which it was concluded that "changes in the antigenicity of foods as a result of digestion, as indicated by skin tests and intentional feeding tests, are an infrequent occurrence. In the search for the etiologic agent in nonreactive cases, the use of digest extracts for testing purposes will offer no advantage over a thorough and carefully taken history, confirmed by test feedings." In this regard, it is of interest that in the second patient here reported, with a severe gastrointestinal allergy to wheat manifested by diarrhea, a marked eosinophilia, and abdominal pain, the symptoms were experienced *only if wheat were ingested*. Exposure to wheat flour during the course of his occupation as a baker produced no symptoms, provided he maintained his wheat-free diet.

CASE REPORTS

CASE 1.—T. M. N., a 61-year-old white man, was hospitalized in June, 1954, complaining of increasing weakness, difficulty in walking, and diarrhea. He had been well until about one year previously, when typical angina pectoris was experienced along with marked weak-

ness. An examination by his family physician disclosed the presence of a macrocytic anemia. The patient was subsequently treated with vitamin B₁₂ and did well for a period of six months, at which time he discontinued treatment. Several weeks thereafter, he developed stiffness of the joints, weakness, and diarrhea. His symptoms gradually increased in severity, particularly the diarrhea, which was described as consisting of from three to five loose, yellow, foul-smelling stools daily. He had lost 40 pounds in an eight-month period. Anorexia, soreness of the tongue, dysphagia, and vomiting were denied.

Physical examination disclosed a fairly well-developed but undernourished, gray-haired, blue-eyed man who appeared chronically ill. The pertinent findings were as follows: The blood pressure was 130/75. The temperature was normal. Moderate emphysema was present. The liver was palpable 5 cm. below the right costal margin; the spleen was not felt. There was a moderate dorsal kyphoscoliosis.

Laboratory and X-ray Data.—The hemoglobin was 13.8 Gm. per cent; hematocrit, 44 per cent. A white cell count was 6,200, with a normal differential count. The urinalysis and serology were negative. An iliac crest marrow aspiration revealed a mild erythroid hyperplasia. The fasting blood sugar was 90 mg. per cent. The serum albumin was 3.6 Gm. per cent, and the serum globulin was 2.3 Gm. per cent. Blood urea nitrogen was 11 mg. per cent. Stool examinations repeatedly revealed the presence of large amounts of neutral fat and fatty acid needles. The serum calcium was 5.2 mg. per cent. The alkaline phosphatase was 6 Bodansky units. A gastric analysis revealed a complete histamine achlorhydria. The oral glucose tolerance test produced a flat curve. A small bowel series showed generalized segmentation, fragmentation, thickened folds, flocculation of the barium, and the "moulage" sign. The stomach and large bowel pattern appeared normal. An x-ray examination disclosed a generalized decalcification of the bones of the spine, pelvis, and knees. Electrocardiograms revealed the presence of a right bundle branch block.

Clinical Course.—Since he had already received large amounts of vitamin B₁₂, the patient was started on cortisone acetate orally. This had to be discontinued in several days, however, because of the occurrence of carpal-pedal spasm. He was then placed on folic acid, supplementary calcium, and vitamin D. After several weeks, he still showed no improvement.

The patient was then started on a wheat-free diet. Within two weeks there not only had been profound symptomatic improvement, but his stools had become darker in color and less offensive in odor. By the time of discharge, he was having only one to two normal bowel movements daily and his serum calcium and phosphorus had both returned to normal. He was advised to remain on a wheat-free diet along with supplemental calcium. One month later, he was feeling well in all respects and was having normal bowel movements. He had gained approximately ten pounds in weight. Four months later, he was requested to return for further biochemical and x-ray studies, but he declined to do so because he felt so well. Several days after that, the patient died suddenly, presumably due to a myocardial infarction. No post-mortem examination was performed.

CASE 2.—P. D., a 53-year-old white baker, was admitted on Aug. 16, 1954, because of continuous diarrhea and weight loss for the six weeks prior to admission. There had also been associated tenesmus and urgency in the rectal area with diffuse abdominal discomfort, occasionally cramplike and most marked in the right lower quadrant. On one occasion, he had experienced a true shaking chill. He had lost approximately twenty pounds in weight during this time, which was associated with moderate anorexia. He denied ever previously having had any difficulty with his gastrointestinal tract or of having had dysentery while in the Service. Two weeks prior to admission, he was examined by a radiologist who suspected a carcinoma of the cecum because of the local discomfort and irritability observed in that area.

He had had spring hay fever at one time, but denied asthma or other significant allergic stigmata. There was no significant family history of any allergy. During the previous year, surgical treatment had been performed for bilateral varicose veins, with

an uncomplicated postoperative course. At that time, he was sigmoidoscoped for pruritus ani, which was offered as an incidental complaint; this examination was not remarkable.

Physical examination on admission revealed a well-developed and well-nourished, but somewhat pale, white man of the approximate stated age, complaining of some distress in the right lower quadrant. The vital signs were within normal limits. The significant findings were limited to the following: slight pallor of the conjunctivae; healed appendectomy and herniorrhaphy incisions bilaterally; considerable tenderness on firm palpation in the right lower quadrant area, but with no palpable masses. The rectal examination and several sigmoidoscopic examinations revealed no significant abnormalities.

Laboratory Data.—Repeated urinalyses were within normal limits. White cell counts approximated 10,000 per cubic millimeter, with the differential averaging neutrophils 26 per cent, lymphocytes 37 per cent, monocytes 3 per cent, and eosinophils 34 per cent. The latter eosinophilia was repeatedly obtained. A total eosinophil count was 3,000 per cubic millimeter. Hemoglobin 14.2 Gm. per cent. Hematocrit 45 per cent. His serology was repeatedly negative. Nine stool examinations, freshly passed and carefully examined, were negative for blood, ova, and parasites. Thymol turbidity was 7 units. Total protein was 6.9 Gm. per cent, with an albumin/globulin ratio of 4.9/2.0. Cephalin flocculation was 3+ at forty-eight hours. Stool cultures were repeatedly negative for the enteric pathogens. The remaining liver function tests, including a forty-five-minute bromsulphalein retention, were within normal limits. A bone marrow examination revealed some hyperplasia of the bone marrow, particularly of the eosinophilic myeloid elements; no neoplastic cells were noted. A trichinella skin test was negative. The electrocardiogram was within normal limits on two occasions.

X-ray Data.—Calcifications were seen in the left hilar area and left upper lung field, representing a calcified primary complex which had not changed over several years. Two upper gastrointestinal series, with particular attention focused upon the small bowel, and three barium enemas at intervals of three weeks were all within normal limits. An intravenous pyelogram was interpreted as normal.

Clinical Course.—In view of the patient's age, the recent history of a profound change in bowel habits, and the presumed disease previously noted by the radiologist, he was initially considered to have a carcinoma of the cecal area. The diarrhea persisted, with five to ten brown, semiformal stools daily. His lower abdominal distress also persisted, but he remained afebrile throughout the entire period of his hospitalization. After repeated sigmoidoscopic and gastrointestinal x-ray studies revealed no overt pathology, other diagnoses were considered. These included amebiasis with possible liver involvement, the collagen disorders (lupus erythematosus disseminata, polyarteritis nodosa), trichiniasis, atypical infectious hepatitis or infectious mononucleosis, Whipple's disease and, by exclusion, a gastrointestinal allergy. The diagnoses of pancreatitis and retroperitoneal lymphoma were also considered, but there was no evidence to support these.

In view of the repeated normal bowel studies by both x-ray and proctosigmoidoscopy, the persistent absence of any forms of *Endamoeba histolytica*, the absence of heterophile agglutinins, and the negative trichinella skin test, these diagnoses were also eliminated. In addition to the normal liver function studies, a liver biopsy was performed which was within normal limits; special stains failed to reveal either iron, parasites, or the presence of tumor cells. A second-strength tuberculin test was negative at five days. The gastrocnemius muscle was biopsied (in the absence of any macroscopic nodules); no evidence of any inflammation or parasites could be found.

The patient's history was accordingly intensively reviewed for the possibility of a food or drug allergy. In regard to the latter, he had taken no medication of any nature of which he was aware. He did recall, however, that many years previously when he initially went into baking, he had experienced "baker's asthma" for a brief period. He had always been a well-adjusted family man. A detailed psychological investigation yielded no pertinent information.

Since the number of daily bowel movements had gradually decreased to three, he was placed on a *provocative* allergic diet, consisting of wheat, eggs, milk, and oranges. Shortly after this regime had been instituted, he began to experience a marked exacerbation of his diarrhea along with the right lower quadrant pain and frequent headaches. The addition of Pyribenzamine in adequate dosage had no effect on either these complaints or on his eosinophilia. The patient was then placed on a special allergic *elimination* diet, consisting primarily of rice and rice products, peas, a gelatin drink, raspberries and Jello (modified after Andresen³). On this regime, while keeping a careful diary as to both his complaints and the number of bowel movements daily, the latter decreased to either none or one to two, and were normal in appearance. Once this base line had been reached, additional foodstuffs were gradually added as follows: milk, eggs, oranges, other fruit juices, and finally wheat. He had no difficulty until wheat was added, following which he again began to experience up to seven bowel movements daily, along with his abdominal distress. At no time was there any rise in body temperature. The patient was then placed on a strict wheat-free diet, on which he again experienced a complete clinical remission. During this stage, he was skin tested to various foods, including the available wheat preparations, but no positive skin reactions were demonstrated. It was the opinion of the consultant gastroenterologist that there was no evidence to incriminate any other intestinal disorder; it was the opinion of the consultant allergist that the diagnosis of a food allergy, probably to wheat, was justified.

In view of the fact that the patient had been trained only as a baker, during which work he was constantly exposed to the inhalation of wheat flour, the proper advice concerning his occupation was quite problematic. After thorough deliberation of the subject, particularly with the possibility that he might only be sensitive to a breakdown product of the wheat in his intestinal tract, he was allowed to return to work on a trial basis. After three months of careful observation following the resumption of his occupation and while on a wheat-free diet, he remained completely symptom-free. Several blood counts done in the interim revealed an eosinophilia ranging from 0 to 3 per cent on smear. At the end of the three-month period of observation as an outpatient, the patient was subjected to repeat intestinal x-rays; these again were within normal limits. He admitted that he was now able to tolerate very small amounts of wheat without symptoms; however, the occasional ingestion of any larger amounts would produce distress.

CONCLUSION

The issues of gastrointestinal and wheat allergy have been reviewed as they pertain to the recent literature.

Prompt remissions were observed in two patients treated with wheat-free diets. Their cases are herein reported.

In Case 1, severe primary sprue had been present which had become refractory to vitamin B₁₂, folic acid, and cortisone acetate. After the institution of this dietary regime, the patient remained symptom-free. Both his hypocalcemia and steatorrhea had reverted to normal one month after the diet had been started.

The temporary beneficial effects of steroid therapy previously noted in sprue may be ascribed to the interference with this hypersensitivity state.

The other patient exhibited a severe gastrointestinal allergy to wheat manifested by diarrhea, a marked eosinophilia, and abdominal pain. A complete clinical and hematologic remission was also experienced on a wheat-free diet, even though he was exposed to wheat flour dust during the course of his occupation as a baker. A specific sensitization to gluten or another of the products of wheat digestion has been inferred.

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REFERENCES

1. Ingelfinger, F. J., Lowell, F. C., and Franklin, W.: *Gastrointestinal Allergy*, New England J. Med. **241**: 303, 1949.
2. Tuft, L.: *Foods and Their Relation to Allergy*, Clinics **5**: 414, 1946.
3. Andresen, A. F. R.: *Allergic Manifestations in the Gastrointestinal Tract*, Gastroenterology **23**: 20, 1953.
4. Schloss, E. N.: *Intubation Studies in Intestinal Allergy*, Am. J. Med. **7**: 156, 1949.
5. Rowe, A. H.: *Clinical Allergy—Manifestations, Diagnosis and Treatment*, Philadelphia, 1937, Lea & Febiger.
6. Graham, D. T., Wolf, S., and Wolff, H. C.: *Changes in Tissue Sensitivity Associated With Varying Life Situations and Emotions: Their Relevance to Allergy*, J. ALLERGY **21**: 478, 1950.
7. Withers, O. R.: *Gastrointestinal Allergy*, Ann. Allergy **11**: 637, 1953.
8. Kaufman, W.: *Some Psychosomatic Aspects of Food Allergy*, Psychosom. Med. **16**: 10, 1954.
9. Loveless, M. H.: *An Objective Approach to the Diagnosis of Food Allergy as Applied to Cottonseed Atopy*, Ann. Allergy **8**: 15, 125, 1950.
10. Cooke, R. A.: *Allergy to Theory and Practice*, Philadelphia, 1947, W. B. Saunders Company, Section 7.
11. Hill, L. W.: *Food Sensitivity in 100 Asthmatic Children*, New England J. Med. **238**: 657, 1948.
12. Dicke, W. K.: *Coeliakie*, Inaugural dissertation, University of Utrecht, 1950.
13. Weijers, H. A., and Van de Kamer, J. H.: *Fat Absorption in Normal and Abnormal Infants With Special Reference to Coeliac Disease*, in Technical Publication No. 113, Utrecht, Holland, 1950, Inst. V. voedingonderzoek.
14. Anderson, C. M., Frazer, A. C., French, J. M., Gerrard, J. W., Sammons, H. D., and Smellie, J. M.: *Coeliac Disease; Gastrointestinal Studies and the Effect of Dietary Wheat Flour*, Lancet **262**: 836, 1952.
15. Sheldon, W., and Lawson, D.: *The Management of Coeliac Disease*, Lancet **263**: 902, 1952.
16. Sheldon, W.: *Celiac Disease*, Postgrad. Med. **15**: 79, 1954.
17. Ruffin, J. M., Carter, D. D., Johnston, D. H., and Baylin, C. J.: *"Wheat-Free" Diet in the Treatment of Sprue*, New England J. Med. **250**: 281, 1954.
18. Golden, R.: *Roentgen-Ray Examination of the Digestive Tract*, New York, 1949, Thos. Nelson & Sons.
19. Smith, H. L.: *Buckwheat-Poisoning: With Report of a Case in Man*, Arch. Int. Med. **3**: 350, 1909.
20. Vaughn, W. T.: *Food Idiosyncrasy as a Factor of Importance in Gastroenterology and Allergy*, Rev. Gastroenterol. **5**: 1, 1938.
21. Adlersberg, D., Colcher, H., and Wang, C.: *Oral Use of Hydrocortisone (Compound F) in Treatment of Sprue*, A. M. A. Arch. Int. Med. **92**: 615, 1953.
22. Colcher, H., Drachman, S. R., and Adlersberg, D.: *Management of Intractable Sprue With Cortisone and Adrenocorticotropin (ACTH)*, Ann. Int. Med. **38**: 554, 1953.
23. Patterson, F. R., Dingman, J. F., Schwachman, R., and Thorn, C. W.: *Choleretic Action of Cortisone*, New England J. Med. **251**: 502, 1954.
24. Althausen, T. L., Anderson, E. M., and Stockholm, M.: *Effect of Adrenalectomy and of NaCl on Intestinal Absorption of Dextrose*, Proc. Soc. Exper. Biol. & Med. **40**: 342, 1939.
- 25a. Barnes, R. H., Wick, A. N., Miller, E. S., and MacKay, E. M.: *Effect of Adrenalectomy on Rate of Fat Absorption*, Proc. Soc. Exper. Biol. & Med. **40**: 651, 1939.
- 25b. Stilman, N., Entenman, C., Anderson, E., and Chaikoff, I. L.: *Phosphorylation of Fat in Absence of Adrenal Glands as Measured With Radioactive Phosphorus*, Endocrinology **31**: 481, 1942.
26. Diez Divas, F., Hernandez-Morales, F., and Koppisch, E.: *The Adrenal Gland in Tropical Sprue*, J. A. M. A. **150**: 647, 1952.
27. Almy, T. D.: *A Refractory Case of Idiopathic Steatorrhea (Non-Tropical Sprue), With Observations on the Therapeutic Effects of Salt-Poor Human Albumin and the Adrenocorticotrophic Hormone*, Ann. Int. Med. **3**: 1041, 1951.
28. Paniagua, M. E., Casas, C. B., and Hernandez-Morales, F.: *Studies on Adrenal Function in Sprue: Preliminary Report*, J. Clin. Endocrinol **10**: 939, 1950.
29. *Case Records of the Massachusetts General Hospital (Case 40081)*, New England J. Med. **250**: 334, 1954.
30. Moehlig, R. C., and Streinbach, A. L.: *Cortisone Interference With Calcium Therapy in Hypoparathyroidism*, J. A. M. A. **154**: 42, 1954.

31. Cooke, R. A.: Protein Derivatives as Factors in Allergy, *Ann. Int. Med.* **16**: 71, 1942.
32. Tuft, L., and Blumstein, C. I.: Studies in Food Allergy, *J. ALLERGY* **13**: 574, 1942;
J. ALLERGY **15**: 346, 1944.
33. Ancona, G. R., and Schumacher, I. C.: The Use of Raw Foods as Testing Material in Allergic Disorders, *California Med.* **73**: 473, 1950.
34. Wacker, I. C., Wetmore, A., and Adkinson, J.: Sensitization Tests With Digestive Products of Protein, *Arch. Int. Med.* **32**: 323, 1923.
35. Urbach, E.: Diagnosis and Treatment of Food Allergy Through Propeptans, *Ann. Allergy* **1**: 219, 1943.
36. Price, A. H., Urbach, F., O'Neill, H. A., and Tallant, E. J.: Propeptan Therapy for Gastrointestinal Food Hypersensitivity, *Am. J. Digest. Dis.* **16**: 161, 1949.
37. Bloom, S., Markow, H., and Redner, B.: Studies in Food Sensitivity, *J. ALLERGY* **24**: 64, 1953.