

Clinical and immunological perspectives in food sensitivity

A review

*Gerald B. Goldstein, Major, MC, USA, and Douglas C. Heiner, M.D.,
Torrance, Calif.*

EARLY HISTORICAL REVIEW

What's one man's poison, signor,
Is another's meat or drink—Lucretius
Love's Cure Act III, Scene ii

The record of man's relationship to his diet goes back to ancient times, and recorded history has provided many instances in which there have been adverse effects from foods. The *Old Testament* has outlined dietary efforts made by the Hebrews to prevent diseases during biblical times. Their laws stated that certain foods were unclean and therefore unfit for consumption. Interdictions were placed upon animals such as reptiles, fish without scales, birds of prey, and "anything that dieth of itself" (*Leviticus* 11:1-47). Hippocrates was one of the first to record evidence of hypersensitivity with his observation that milk could cause gastric upset and urticaria.¹ Galen (131 to 210 A.D.), the greatest Greek physician after Hippocrates, described a case of allergy to goat's milk,² and in the Babylonian Talmud instructions were recorded for a method of treating intestinal egg sensitivity by means of an appropriate preparation of egg white.³

The Middle Ages was a time of superstition and ignorance, during which mankind was beset with several plagues of epidemic diseases. One, ergotism, caused by growth of the fungus, *Claviceps purpurea*, upon a common rye bread, was characteristic of the times. At least six epidemics were described in France between 944 and 1129 due to contamination of food by this fungus.

From the Department of Medicine, United States Army Tripler General Hospital, and Division of Immunology and Allergy, Department of Pediatrics, University of California, Los Angeles Harbor General Hospital.

Following the Middle Ages, a more scientific approach was taken to the association of foods with disease. In 1679, Thomas Willis⁴ published a paper on asthma in which he observed that ingestion of wine was one of many factors which could precipitate an attack of asthma. In 1859, Salter⁵ published a detailed study noting the significance of inhalants and substances absorbed from the stomach and intestinal tract on the precipitation of asthmatic attacks. He suggested avoiding cheese (especially old and decayed), preserved foods, nuts, and heavy malt liquors, as all these substances could make asthma worse. In addition, he described a young child whose asthma was brought on by ingestion of milk. Samuel Gee⁶ (1888) published the first report on celiac disease in *St. Bartholomew's Hospital Reports*. He accurately described the slow course of the disease: the soft, doughy, distended abdomen, wasting of the limbs, and the pale, loose, bulky stools with an appearance like oatmeal porridge. To this day the role of immunological mechanisms in this disorder is unclear.

Cases of food hypersensitivity were not reported with any frequency until after Von Pirquet⁷ introduced the concept of allergy in 1906. Smith⁸ described buckwheat allergy associated with gastrointestinal symptoms in 1909, and Schloss⁹ reported a child with asthma from egg white, almond, and oatmeal in 1912. He was able to demonstrate positive scratch tests in the patient but was unable to find serum antibodies. Alexander's¹⁰ eight-year-old asthmatic patient with all negative skin tests suggested that perhaps sensitivity could be localized to the bronchial mucosa alone. The diagnosis was made by dietary manipulation, systematically excluding each of the commonly eaten foods until the offending ingested was detected. Coke¹¹ (1932) recognized that individuals could be sensitized by ingestion of wheat or wheat products during infancy or by inhalation of flour in later life (often occupational).

Evidence for absorption of intact protein from the gastrointestinal tract

Early in the twentieth century, experimental evidence began to accumulate showing that sufficient food protein could escape from the gastrointestinal tract into the circulation to be detected by laboratory methods. In 1913, Van Alstyne¹² placed milk into the stomach of a dog and found that blood drawn 1 to 5 hours later contained enough milk protein to cause anaphylaxis in sensitized guinea pigs. Three years later Schloss and Worthen¹³ observed that the GI tract of children with gastroenteritis or eczema was permeable to protein, demonstrable by precipitin tests or by its capacity to sensitize guinea pigs for anaphylaxis. Foreign antigens appeared in the blood and urine but persisted longer in the urine. Anderson and Schloss¹⁴ (1923) studied infants with nutritional disorders with respect to their precipitin response to milk proteins. The precipitins were detected largely after the infants began to gain weight and were thus thought to serve a protective function by combining with milk proteins either in the gut or in the blood stream. Hettmer and Kris-Hettmer¹⁵ (1926) presented further evidence for protein absorption from the gut of the experimental animal by injecting horse serum into a ligated loop of guinea pig small intestine. Their work indicated that an increase in intraluminal pressure enhanced the absorption of intact protein.

Studies by Ratner¹⁶ in 1928 offered a plausible explanation for allergic reactions to food at the time it was first ingested by infants. He was able to demonstrate intrauterine sensitization by injecting horse serum into pregnant guinea pigs prior to delivery and showing that the newborn animals developed anaphylaxis on first contact with intravenous horse serum. Since a single layer of placental cells separates mother from fetus in both the guinea pig and the human being, he concluded an analogous intrauterine active sensitization could take place in infants.

At about this time, Brunner and Walzer¹⁷ modified the Prausnitz-Küstner¹⁸ test for passive transfer of skin-sensitizing antibody by feeding raw fish to passively sensitized volunteers in the fasting state. They found sufficient antigenic material was absorbed from the GI tract to elicit a wheal and flare reaction at the sensitized sites. Other studies have provided similar evidence that protein or antigenic protein fragments may be absorbed from the normal intestine. Smyth and Bain¹⁹ (1931) obtained positive passive transfer (P-K) responses in three newborn infants injected with serum containing reaginic antibodies to egg who were later challenged orally with 1 to 2 ounces of 10 per cent egg albumin in water. In the same year, similar results were obtained in sensitized infants by instilling antigen into the rectum.²⁰ In 1934, Ratner and Gruehl²¹ sensitized children aged 3 to 12 with sera from food-allergic individuals and found that 80 per cent of them responded with wheal and flare reactions upon ingestion of the incriminated foods. They postulated several factors which may protect human beings from widespread sensitization by absorbed proteins, including the relative impermeability of the GI tract to proteins, the hydrolyzing action of intestinal enzymes, urinary excretion of protein, and cooking of foods which renders them more susceptible to digestion and less antigenic. Lippard and associates²² (1936) employed complement fixation to detect milk protein and the subsequent appearance of antibody in the sera of infants. By means of this technique, small quantities of milk protein were often found in the serum of milk-fed infants in the first few months of life. The appearance of complement-fixing antibodies was followed by the disappearance of antigens from the serum, as was the appearance of precipitating antibodies.¹⁴

DEFINITION OF TERMS

Ideally, food allergy and food hypersensitivity are terms which should be restricted to situations in which typical atopic allergic symptoms are induced by the ingestion of a food or to situations in which other symptoms are repeatedly shown to be due to foods and in which there are demonstrable immunologic reactions of a type believed to be etiologic in other forms of allergy.

Food sensitivity on the other hand is considered by us to be a slightly broader term, encompassing both classical food allergies as defined above and certain other conditions in which there is a reproducible exaggerated or abnormal reaction to the ingestion of a specific food or foods. We favor the term "sensitivity" for conditions in which there is a reasonable likelihood that an immunological mechanism may be etiologically important. Clear demonstration of the immunologic pathogenesis need not have been obtained, however.

Unfortunately, by common usage and as a result of gaps in our knowledge, "sensitivity" often overlaps with the term "intolerance." We prefer the term food intolerance when an immunological etiology is unlikely. For example, if a nonimmunologic cause of celiac disease were established, we would favor the term gluten intolerance. At present either intolerance or sensitivity is acceptable because the basic mechanism is very much in doubt. Milk intolerance is a satisfactory term for symptoms due to a primary deficiency of intestinal lactase, whereas the use of the term milk sensitivity could be misleading since it might connote an allergy to some readers. Milk protein sensitivity with secondary lactase deficiency also exists. In the latter instance the proper diagnosis is made by selectively deleting antigenic milk proteins from the diet with resulting improvement both in symptoms and in intestinal lactase activity. A recurrence of the clinical picture results upon reintroduction of milk protein into the diet. Obviously the two conditions are sometimes confused and may have overlapping symptomatology. There are other less well-documented circumstances in which a clinical picture of food sensitivity may merge with that of food intolerance. Clear distinctions in some instances may only be apparent in the future when more discriminating laboratory tests are available.

It is evident as well that all adverse reactions to foods in allergic children are not necessarily related to allergy even though food sensitivity is frequently seen in allergic children.^{23, 24} For example, allergy can coexist with cystic fibrosis in which case bulky loose stools are much more likely to be due to the cystic fibrosis than to the allergy. Allergy may also coexist with galactosemia, alactasia, or other disorders of enzyme function. The probability exists that new non-immunological disorders will be identified from time to time as causes of specific symptoms or syndromes now considered to be due to allergy.

The action of normal enzymes in the gastrointestinal tract may also create new antigens from food proteins.²⁵ Thus one may have to deal with an exceedingly complex group of food allergens just as he may have to consider many enzyme aberrations in studying the spectrum of food sensitivities and intolerances encountered clinically. When one also considers the variable threshold to pain and noxious stimuli of patients, the varying burden of inhalant and other allergens to which they are exposed, markedly different eating habits, etc., it is perhaps not surprising that food sensitivities and intolerances of mild to moderate severity are difficult to identify or even to classify with accuracy.

CLINICAL ASPECTS OF FOOD SENSITIVITY

Cow's milk is a prime offender in infancy, probably because it is the major foreign protein fed during the early months of life.²⁶ It has been estimated that milk sensitivity occurs in 0.3 to 7.0 per cent of children,^{27, 28} the incidence varying with the criteria used for diagnosis and the type of practice from which the cases were selected. Milk sensitivity or intolerance, as well as sensitivity to many other foods, may be manifested by a wide spectrum of symptoms²⁹⁻³¹ and is often overlooked or misdiagnosed. For example, the average infant with milk sensitivity, according to Clein,³² has the onset of symptoms at 2 to 4 weeks of age, and his formula is changed and juggled repeatedly. A group of patients he re-

ported presented with no less than 14 different symptoms, mostly referred to the gastrointestinal tract but also including abnormalities of the skin, respiratory tract, and sensorium.²⁹

The physician is well aware of the immediate symptoms induced in sensitive individuals by the ingestion of certain foods. Indeed, these hypersensitivity reactions may be among the most serious encountered in clinical allergy. Such reactions tend to occur no matter how infrequently the offending allergens are ingested, and the severity of symptoms does not necessarily relate to the quantity of food partaken. In instances of food sensitivity in which chronic symptoms prevail, an adverse reaction may not appear for a number of hours or even days following ingestion of the food, and symptomatology may be perpetuated by continued ingestion of the offending food. Because immediate and dramatic symptoms often are not present in food sensitivity or intolerance, the patient may be unaware that a particular food eaten daily is involved. Food sensitivity tends to improve after several months or years on a diet restricting the offending food, and children may spontaneously improve whether or not dietary restrictions are imposed.

Several specific syndromes involving food sensitivity seem to follow a chronic course. Wilson and associates³³⁻³⁵ found that children with iron-deficiency anemia with or without milk-induced gastrointestinal symptoms often have chronic occult blood loss associated with milk ingestion. They frequently have serum precipitins directed against heat-labile milk proteins in higher concentration than do control subjects. They improve on removing cow's milk or boiling the pasteurized milk used in the diet. Those tested had a recurrence of bleeding when bovine serum was added to a milk-free formula.³⁶ Loss of chromium-tagged red blood cells into the stools generally followed the administration of milk by several hours or a day.

Gryboski³⁷ and Katz and associates³⁸ have reported children with gastrointestinal symptoms in whom precipitins to milk proteins were found in the stool. After elimination of milk from the diet, the infants began to thrive, and the coproantibodies disappeared. Similar stool precipitins were found in children with gluten intolerance associated with celiac disease.³⁹ However, a recent paper⁴⁰ has shown that coproantibodies may be a nonspecific finding in diarrheal stools, so that further studies will be necessary to evaluate the diagnostic significance of this test. An unusual form of milk sensitivity with chronic symptoms, iron-deficiency anemia, and severe recurrent respiratory disease has been described.⁴¹ Gastric or tracheal aspirates contained iron-laden macrophages in four of seven patients. Again, manifestations lagged several hours or days after the introduction and removal of milk from the diet. Serum precipitins to milk components were detected in each of the patients in higher titer than in control subjects and were directed toward multiple milk antigens. Other individuals with rather similar clinical findings were studied by Holland and associates.⁴²

A parallel may be drawn between infants with gastrointestinal milk sensitivity and subjects with celiac disease who are intolerant of wheat gluten.^{43, 44} Both may develop hypochromic iron-deficiency anemia and chronic inflammatory

changes in the small intestine, and both show a tendency to produce an abundance of antibodies to the foods which provoke symptoms.⁴³⁻⁴⁶ A number of reports^{29, 47-50} have suggested that milk sensitivity may precede gastrointestinal intolerance to gluten in some children. One study detected precipitating antibodies to skim milk proteins, including α -lactalbumin, in the stools of eight children with milk-induced diarrhea. Two of these subjects subsequently developed coproantibodies to a gluten fraction and symptoms following introduction of cereal into the diet. In both, the symptoms abated and the antibodies disappeared after elimination of each of the offending foods from the diet.⁵⁰

In 1940, Rubin⁵¹ described a group of infants who had elements of both acute and chronic sensitivity to cow's milk. These patients had moderate to severe intestinal bleeding, mucus-containing diarrheal stools, and failure to thrive, all induced by the ingestion of milk. In such children the relation of symptoms to milk ingestion is frequently not suspected until milk is withdrawn, and the diagnosis is confirmed when milk is again given to the child. Colitis with shock may also result from the ingestion of cow's milk in certain infants,⁵² as may protein-losing enteropathy with hypoproteinemia and eosinophilia.⁵³ Perhaps these disorders are all variants of the same basic pathophysiologic process, but conclusions are hardly warranted until the mechanisms have been better delineated.

HISTORY TAKING; CLINICAL APPRAISAL OF THE PATIENT

Finding the offending allergen in a case of food sensitivity may be a challenging problem for the physician. A careful history inquires into the patient's dietary habits, including food he prefers, those he avoids, and those he suspects may be causing symptoms. Subjects are already aware of severe immediate food sensitivities and usually have excluded such foods from the diet. There appears to be a variable threshold of tolerance, however, and some patients may ingest foods to which they have reaginic antibodies without initially recognizing the relationship between the food and their symptoms. Others have demonstrable reaginic antibodies which are unassociated with symptoms, but these are usually present in low titer. Factors such as concurrent infection, pollinosis, or emotional stress may occasionally increase the likelihood of an adverse reaction to a given food. Some patients state that certain foods are tolerated only after being cooked. In at least some instances this appears to be related to the fact that offending proteins subjected to high temperature in the presence of moisture may undergo denaturation.

When the patient is unaware of the role of foods in producing symptoms, the medical history alone may not be sufficient to permit a diagnosis. In such cases, a diary noting the foods taken at each meal and the times at which symptoms occur may help to correlate the ingestion of a particular food with recurrent symptoms. In practice, however, this technique has proved rather disappointing. Chronic symptoms are best related to a specific food or foods through the judicious use of elimination diets coupled with at least two challenge-induced recurrences of symptoms to establish the food sensitivity.

INVESTIGATIVE TECHNIQUES IN FOOD ALLERGY

Skin testing to foods is generally considered unreliable,⁵⁴⁻⁵⁹ although strongly positive skin tests are frequently considered to confirm the etiological role played by food allergens in severe immediate reactions.^{24, 60} While studying a series of asthmatic children, Hill⁶⁰ found that only 20 per cent of positive scratch tests to foods were of clinical significance, and these were mostly reliable in sensitivity to fish, nuts, egg, and chocolate. Others⁶¹⁻⁶³ have stated that the use of fresh or fresh-frozen foods for skin testing in clinically proved food atopy are more likely to induce a positive wheal and flare response than are commercial extracts. However, in the case of many adverse reactions caused by foods, there is no positive correlation between skin tests and clinical sensitivity.⁶⁴ An example in the recent literature⁶⁵ which illustrates this point is a case report of malabsorption clearly related more closely to oral challenge with β -lactoglobulin than to α -lactalbumin. When the subject was skin tested with milk fractions, results were the opposite of what one would expect, since the strongest response was found at the site of the α -lactalbumin injection, and only a weak response was obtained with β -lactoglobulin.

In an effort to find better diagnostic tests, workers have studied hemagglutinins employing food allergens attached either directly to tanned sheep red blood cells or by chemical linkage with *bis*-diazotized benzidine. A report by Gunther and associates⁶⁶ disclosed that hemagglutinating antibodies to milk antigens were frequently present in the sera of normal infants, especially in those who were bottle fed. They observed that the highest titers occurred between the ages of 3 to 6 months. Other investigators⁶⁷⁻⁶⁹ have also reported that hemagglutinins to food proteins frequently are found in serum, but they have not observed a consistent relationship between such antibodies and symptoms. Most agree that hemagglutination tests add little to the diagnosis beyond what can be learned from a careful history and skin testing.

Rothberg and Farr⁷⁰ and Peterson and Good⁷¹ detected serum antibodies to milk proteins in normal subjects as well as in patients with a variety of acute and chronic diseases. However, in neither instance was it reported that subjects with demonstrable antibodies were evaluated by dietary elimination of milk and subsequent challenge. Nevertheless, their findings are a further indication of the difficulties encountered in making a meaningful interpretation of certain serum antibodies to foods. An increased incidence of multiple serum precipitins to milk antigens in infants with iron-deficiency anemia and proved milk-induced blood loss has been pointed out.⁴³ More than 20 different antigens in milk were found to be sufficiently antigenic upon ingestion to elicit precipitins in these patients, yet no consistent relationship was found between antibodies to any specific milk protein and the presence of symptoms.

Saperstein and associates⁷² detected heat-stable antibodies capable of sensitizing guinea pig skin for PCA in the sera of milk-sensitive subjects.⁷² However, the presence of these antibodies did not correlate well with results of oral challenges with the same protein.⁷³ Collins-Williams and Salama⁷⁴ tried to establish a positive association between proved milk allergy and results of hemag-

glutination tests, PCA, and gel diffusion studies. They could conclude only that there was an increased tendency for milk-allergic individuals to have positive PCA and precipitin tests while ingesting milk.

Pollard and Stuart⁷⁵ described the appearance at gastroscopy of the sensitized GI tract following challenge with the food allergen. They noted local mucosal changes such as hyperemia, thickening and edema of the rugal folds, and decreased peristalsis. Radiologic changes in food-sensitive patients have been described by Cooke⁷⁶ and Fries and Mogil.⁷⁷ After ingestion of a barium-allergen meal, considerable residue remained in the stomach at 6 hours, there was increased small bowel motility, segmentation of contrast medium, and colonic spasm. However, these abnormal findings are by no means a constant feature of gastrointestinal food sensitivity, and their presence is significant only after extensive controls are employed to eliminate nonspecific effects.⁵⁴

Examination of stool mucus may provide additional evidence for an allergic process in the bowel. Sixty patients with colic, diarrhea, and emesis were reported to have stool mucus eosinophilia until the offending allergen was eliminated from the diet.⁷⁸ In another study, Waldmann and associates⁵³ described cases of milk-induced allergic gastroenteropathy with hypoproteinemia, anemia, and the presence of Charcot-Leyden crystals in the stool.

Special investigative techniques such as studies of the excretion of radio-labeled plasma albumin or red blood cells in the stools may be needed to establish a relationship between food ingestion and protein-losing or blood-losing enteropathies. One obviously must be aware of other nonallergic causes of enteropathy and of the investigative techniques which may be used for each in reaching the correct diagnosis.

PATHOGENESIS OF FOOD SENSITIVITY

Association of reaginic antibodies and food allergy

The production of reagins to food proteins and their relationship to atopic symptoms has been recognized for some time, and clinical and immunochemical studies have been carried out to determine the nature of the particular food allergens responsible for stimulating skin-sensitizing antibody. A review of all the work pertaining to reaginic food hypersensitivity is not feasible, but a few representative studies will be considered.

Walker⁷⁹ (1917) found that wheat-sensitive asthmatic patients were more likely to have positive skin reactions if tested with individual wheat protein fractions rather than whole wheat. By correlating results of skin tests with the clinical history, Sanford⁸⁰ (1920) found wheat proteose and rye were common offenders in grain allergy.

An early report by Duke⁸¹ (1934) showed that soybean, an economically important foodstuff, could be a source of occupational allergy. He reported five soybean mill workers with cough and asthma in whom symptoms were induced by exposure and in whom positive skin tests were obtained with soybean extract.

Tuft and Blumstein^{61, 62} associated clinical sensitivity to a variety of fruits

with wheal and flare responses obtained with the use of juice from the incriminated fresh or fresh-frozen fruit. Immunochemical studies showed the allergenic portion of the fresh fruit juice was associated with protein and that loss of allergenic activity on storage for a short period could be prevented by adjusting the pH of the preparation to 8.5.

Figley and Rawling⁸² (1950) reported that coffee workers with allergic symptoms had positive skin tests to both green coffee dust and castor bean and that their sera gave positive P-K tests when challenged with either allergen. The significance of this observation was perhaps clarified by Freedman and associates⁸³ and Siddiqi and Freedman⁸⁴ who detected the presence of chlorogenic acid in green coffee, orange, castor bean, and several other fruits and vegetables. Small quantities of this chemical were reported to induce large wheal and flare reactions in sensitive individuals and to neutralize P-K activity in sera from subjects sensitive to coffee, orange, and castor bean. Recent evidence suggests that quinic acid may be a dominant allergenic determinant in chlorogenic acid.⁸⁵ Reports by Layton and associates⁸⁶ have been at variance with those implicating chlorogenic acid as an important allergen. It is the belief of the latter group of investigators that protein constituents of coffee beans are at fault.

Although white potato sensitivity is not as common as many other food allergies, cases of atopy to this allergen have appeared in the literature. Pearson⁸⁷ reported 29 housewives who developed either bronchospasm or rhinorrhea when peeling potatoes. However, most of them were able to tolerate the ingestion of cooked potatoes without ill effects. Another study⁸⁸ indicated that juice from raw potato can induce positive wheal and flare responses in potato-sensitive subjects, whereas cooked potato and commercial extracts may be inactive. The latter workers fractionated potato juice by agar gel electrophoresis and obtained two cationic fractions which were active in eliciting skin reactions.

Recently, a subject with severe hypersensitivity to wheat gliadin has been studied.^{89, 90} The serum was found to contain skin-sensitizing antibody in a titer of 1:10,000 (by means of P-K testing), and minute quantities of α -gliadin allergen induced wheal and flare responses in passively sensitized volunteers. It was established that the reagins were heat labile (56° C.), inactivated by 0.1M 2-mercaptoethanol, eluted from DEAE-Sephadex over a range of buffer molarities, and emerged from a Sephadex G-200 column in a position intermediate between IgM and IgG. Skin-sensitizing activity in serum samples was neutralized in vitro by the addition of appropriate quantities of α -gliadin allergen. Further evidence for the specificity of the reagins was obtained in experiments in which the serum was mixed with an α -gliadin immunosorbent. There was significant loss of serum reaginic activity by exposure to this insoluble wheat allergen, whereas a control ragweed-sensitive serum mixed with the same immunosorbent displayed no such loss of P-K activity. Reaginic activity was closely associated with serum IgE antibodies and could be specifically removed by antiserum to the ϵ -chain. The subject under investigation had a plethora of IgG, IgA, IgM, and IgE antibodies to α -gliadin. IgE was detected in the

sputum, but this, in contrast to the serum IgE, was devoid of antigen-binding activity on radioimmunodiffusion.

The presence of a small quantity of reagin to a specific food substance is not necessarily of clinical significance. However, many of the studies enumerated suggest that an etiologic relationship between the reagins and clinical sensitivity to foods may exist when a strongly positive skin test to the food in question is associated with immediate symptoms upon ingestion of the food. The diagnosis of atopic sensitivity to a food is substantiated further by demonstrating IgE allergen-binding activity toward constituents of the food by radioimmunodiffusion.

Role of precipitins in food intolerance

A pathophysiologic role for either serum or stool precipitins to food proteins has not been established. It is still possible that such antibodies could serve a protective function, as originally suggested by Anderson and Schloss¹⁴ in 1923, or they could be of pathogenetic significance when they contact antigen *in vivo* by initiating a sequence of events leading to clinical symptomatology. Studies⁹¹ of certain pulmonary hypersensitivity diseases indicate that precipitins may be closely associated with human Arthus reactions and hence may cause symptomatology and tissue damage. It is attractive to postulate that certain antibodies present in optimum concentration may combine with food antigens, perhaps in the presence of complement, and produce an Arthus reaction. Under certain circumstances, circulating food antigens complexed to antibody could perhaps become lodged in blood vessel walls and cause tissue injury, as occurs in antigen-antibody complex-induced disorders. Food antigens reacting with specific antibodies might also initiate one or more of the complement-mediated reactions such as lysosomal disruption and the release of vasoactive substances and cathepsins.⁹² On the other hand, some precipitins to food antigens may well be innocent bystanders and have no particular function under ordinary circumstances. They might arise as a secondary phenomenon resulting from specific defects in the enzymatic digestion of food proteins or a failure of the body otherwise to prevent contact between antigenic food substances and immunologically reactive cells. Neither of these possibilities has been rigorously proved or disproved, and more sophisticated studies are needed to elucidate whether or not antibodies play a role in many instances of food sensitivity. At present, the finding of precipitating antibodies in unusual amounts in either the serum or stool may be considered of no more than ancillary aid to the clinician who already suspects food sensitivity, especially when milk or wheat proteins are involved. Except for severe acute reactions to ingested food, a firm diagnosis of food sensitivity is not justified until clinical improvement follows elimination of the specific food allergen from the diet and a reproducible recurrence of symptoms results from reintroduction of the food.

THE ROLE OF WHEAT INTOLERANCE IN GLUTEN-INDUCED ENTEROPATHY **Celiac disease and nontropical sprue—clinical and pathological features**

Intolerance to wheat may be manifested as celiac disease in childhood and idiopathic steatorrhea in adults. These conditions probably represent the same

disease, having almost identical clinical and pathological findings,⁹³ and the term celiac-sprue has been used by some⁹⁴ to denote this apparent identity. The hallmark of the disease is steatorrhea, which is frequently accompanied by bouts of diarrhea, bulky malodorous stools, and malabsorption of fats, carbohydrates, protein, and fat-soluble vitamins. Chronic gastrointestinal losses of essential substances contribute to weight loss, malnutrition, and vitamin-deficiency states.⁹⁵ Suction biopsies from the distal duodenum or proximal jejunum have revealed reduced epithelial surface area, relatively severe degrees of blunting and loss of villi, and round cell infiltration of the lamina propria.⁹³ In addition, the electron microscope has revealed a decreased size and number of microvilli which are in disorderly array in the brush border.⁹⁴ Studies^{96, 97} have indicated that the characteristic epithelial lesion may persist in the upper small bowel whether or not the patient is severely ill, and, if improvement does occur, the more mild distal lesions tend to recover first.

Gliadin—its role in pathogenesis of celiac disease and nontropical sprue

Most subjects with celiac disease or nontropical sprue may expect a clinical remission when placed on a diet free from wheat and rye gluten.⁹⁶⁻¹⁰⁰ Van de Kamer and associates¹⁰¹ established that the gliadin fraction of gluten contained the injurious portion of wheat causing symptomatology. Glutenin (the alcohol insoluble portion of gluten), ash, crude fibers, carbohydrate, and fat fractions from wheat did not produce steatorrhea in the celiac patients studied. The etiological role played by gliadin in producing clinical symptoms was confirmed histologically by Rubin and associates,¹⁰² who were able to produce a local exacerbation of disease with typical morphological changes by instilling gliadin into a normal area of ileum in a celiac subject.

Gliadin itself has been extensively studied and found to contain greater than 50 per cent of its peptide-bound amino acids as glutamic acid and proline.¹⁰³ Evidence has suggested that disulfide bonds in gliadin are largely intramolecular,¹⁰⁴ and it has been demonstrated that reduction and alkylation of these bonds destroy the ability of gliadin to precipitate with antibodies present in celiac sera.¹⁰⁵ By means of electrophoresis^{106, 107} and column chromatography,¹⁰⁸ gliadin has been separated into distinct fractions of similar molecular weight and amino acid composition (α_{1-2} , β_{1-4} , and γ). Alpha gliadin has appeared to contain the major precipitating antigenic activity as judged from studies with celiac sera.¹⁰⁵ This fraction has been found to have a molecular weight of 50,000.¹⁰⁹

Frazer and associates¹¹⁰ prepared a peptic-tryptic digest of gluten (fraction III) and found that this preparation was able to induce an exacerbation in celiac subjects, even after the digest had been autoclaved at 120° C. However, this peptide fraction could be inactivated by digestion with an extract of hog small intestinal mucous membrane.¹¹¹ It was concluded from these studies that a peptide fragment of gluten was not well tolerated by celiac patients. Other workers¹¹² confirmed that gliadin treated with pepsin or trypsin retained its noxious effect upon celiac patients, but papain digests were found to be inactive.

It was postulated that the celiac-activating fragment was a peptide composed of 6 to 7 amino acids, mainly glutamine and proline. Van de Kamer and Weijers¹¹³ postulated that the cause of gliadin toxicity in celiac subjects lay in the high content of glutamine. Further suggestive evidence for a role by glutamine was provided by Alvey and associates,¹¹⁴ who found abnormally high serum glutamine levels in celiac subjects following oral ingestion of gluten or gliadin. However, this response did not always occur, nor was it demonstrable in all laboratories, especially when testing mild or convalescent celiacs. Fingerprints prepared with the use of high-voltage electrophoresis and paper chromatography demonstrated a failure on the part of celiac jejunal mucosa to liberate proline from a peptic-tryptic digest of gliadin.¹¹⁵ However, this apparent enzymatic defect has since been shown to occur in other disorders and to revert to normal along with other jejunal enzyme activities in celiac patients following successful treatment with a gluten-free diet.¹¹⁶⁻¹²⁰ The return of peptidase activity while on therapy suggests a secondary enzymatic deficiency and a need to re-evaluate earlier theories of a primary intestinal inability to digest gliadin.

Immunological features of celiac sprue

No uniform acceptance has been given any explanation of the underlying mechanism for gluten intolerance in celiac disease. While early reports suggested that gluten or gluten fragments exerted a deleterious effect in the disease by a direct toxic action, equally plausible evidence suggested that immunological factors may play a role. A minority of celiac subjects have been noted to be exquisitely sensitive to gliadin and to respond following ingestion of small amounts with symptoms of forceful emesis, diarrhea, tachycardia, pallor, and shock.¹²¹ "Acute gliadin shock" resembles anaphylactoid reactions of the immediate hypersensitivity type both in clinical presentation and in the failure of suppression with corticosteroids. However, this degree of gliadin sensitivity is unusual in celiac disease, and ordinarily large amounts of wheat are required to produce acute symptoms.

Precipitins to gliadin antigens have been detected in sera from patients with celiac sprue,^{44, 105, 122} and hemagglutinating antibodies have also been found in higher incidence than in controls.^{45, 46} Katz and associates³⁹ have recently described the presence of precipitating antibody to a peptic-tryptic digest of gluten in the small intestinal secretions of 12 celiac subjects. They suggested that precipitins are produced and secreted by the gut and probably belong to the IgA class of immunoglobulins. Immonen and associates¹²³ have demonstrated that sera from celiac patients often contain an elevated level of IgA. Following institution of a gluten-free diet in their subjects, the elevation of the IgA rapidly returned to normal. Hobbs and Hepner¹²⁴ reported an isolated IgM deficiency in the sera of many celiac subjects, most of whom had a return to normal immunoglobulin levels after removal of gluten from the diet. Heiner and Rose¹²⁵ reported antibodies of the γ G, γ A, and γ E varieties to both gliadin and milk proteins in certain subjects with celiac disease and found that serum γ E levels were elevated in five of sixteen patients with this diagnosis.¹²⁶

The precise significance of specific antibodies in celiac disease and of abnormalities in immunoglobulin levels which may revert to normal in response to a gluten-free diet is unclear. They suggest a multifaceted involvement of the body's immunological apparatus in the disease and may indicate that a number of defense mechanisms contribute to normal processing of wheat gliadin in the intestinal tract, the malfunction of any of which might become particularly important in a subject who is predisposed to the development of celiac disease.

The descriptions by Crabbe and Heremans^{127, 128} and Hermans and associates¹²⁹ of a group of patients who have an absence or marked decrease of serum IgA and steatorrhea which may be responsive to a gluten-free diet illustrate another anomaly with immunologic implications which may be related to celiac disease. Some of these patients have nodular hyperplasia of intestinal lymphoid tissues and constitute a subgroup with a propensity for giardiasis and incomplete response to dietary management.¹²⁹ In addition to these patients, McCarthy and associates¹³⁰ have described four subjects with idiopathic steatorrhea who had small fibrotic spleens, atrophic lymphoid tissue, Howell-Jolly bodies in circulating red blood cells, and an impaired antibody response to typhoid-paratyphoid vaccine. The common occurrence of steatorrhea in both congenital and acquired agammaglobulinemia^{128, 131, 132} and its even more frequent presence in lymphopenic agammaglobulinemia¹³³ further attest to an intimate relationship between intestinal absorption and normal immunological responsiveness.

Winter and associates¹³⁴ noted that there is often a subnormal blastogenic response when lymphocytes from subjects with celiac disease are cultured in the presence of phytohemagglutinin. Their studies suggested that a serum factor rather than a defect in the lymphocytes may be responsible for this abnormal response. An attempt to identify antigen-binding activity in the small intestinal lymphoid cells of patients with celiac disease was made by Rubin and associates¹³⁵ with the use of immunofluorescent techniques. However, they failed to demonstrate binding of gliadin by the inflammatory cells or by immunoglobulins within cells of the intestinal lamina propria. Clearly, further studies will be needed before the pathogenesis of celiac disease can be fully understood.

OTHER CONDITIONS RELATED TO FOOD INTOLERANCE

Ulcerative colitis

Andresen,¹³⁶ Rowe,¹³⁷ and Truelove¹³⁸ have indicated that intolerance to one or several foods may contribute to gastrointestinal symptoms in a number of subjects with ulcerative colitis. They have recommended that clinical remissions be sought by systematic elimination of milk, fruits, and cereals from the diet. It should be stressed that clinical impressions have formed the basis for these reports, and at present there is no conclusive immunological evidence that hypersensitivity to foods plays a pathogenetic role in ulcerative colitis. Others^{139, 140} have detected elevated titers of serum hemagglutinins to various milk proteins in subjects with ulcerative colitis. As in celiac disease, there does not appear to be a consistent association between antibody titers, activity of

disease, and response to dietary manipulation, and the level of a particular antibody is seldom helpful in arriving at a diagnosis.

The significance of antibody levels to foods in sera of ulcerative colitis patients remains speculative. They may simply reflect a heightened but unrelated immunological response to ingested proteins. The fact that foods can normally elicit an antibody response is no longer questioned. One should also keep in mind that there may be an increased absorption of antigenically active food protein from the gastrointestinal tract in association with certain diarrheal diseases¹⁴¹ and that perhaps some of the circulating antibodies which may occur are useful in rapidly eliminating these foreign proteins from the circulation. Other antibodies might combine with antigens locally and retard their absorption from the gut.¹⁴² A certain proportion of antibodies might, however, induce the release of the chemical mediators, so that the balance established in each individual between the production of innocuous or protective antibodies and symptom-inducing antibodies is decisive in the occurrence or absence of symptoms. Certainly a possible role of cellular immunity in ulcerative colitis must be kept in mind, as must the oft-mentioned possibility of autoimmune mechanisms, a subject beyond the scope of this review.

Lactose intolerance

The relationship of intestinal lactase deficiency to milk intolerance is another problem which merits consideration. Methods have been developed for the assay of various small intestinal disaccharidases,^{143, 144} and two enzymes have been found in the human jejunum which are able to split lactose. The more important physiologically is a β -galactosidase (lactase) which is found in the brush border and hydrolyzes lactose rapidly.¹⁴⁵ The other is a less specific hetero- β -galactosidase (probably lysosomal) with weak lactase activity. Controlled studies by various investigators suggest an isolated hereditary lactase deficiency is prevalent among American Negroes and African Bantus.^{146, 147} Studies by Cook¹⁴⁸ demonstrated normal lactase activity in four Bantu neonates, but follow-up studies showed a decrease in lactose tolerance during the first few years of life. Cook and others feel that Bantus and their American Negro descendants probably have a genetic defect in lactase activity which becomes overt in early life.

Decreased small intestinal lactase activity does not necessarily imply a genetically controlled alactasia. Secondary lack of disaccharidase activity has been reported in celiac sprue by Plotkin and Isselbacher¹⁴⁹ and by Haemmerli and associates,¹⁵⁰ and similar enzymatic deficiencies have been found in subjects with other disorders including ulcerative colitis,¹⁵¹ tropical sprue,¹⁵² kwashiorkor,¹⁵³ and rosacea.¹⁵⁴ Therefore, despite the interest in primary lactase deficiencies,¹⁵⁵⁻¹⁵⁸ one should not lose sight of the fact that secondary deficiency is common and almost any condition predisposing to inflammatory changes in the intestine may result in a significant disaccharidase deficiency.¹⁵⁵ The deficiency is often proved to be secondary only after normal enzyme activity returns following successful treatment of the basic disease.

The relationship of milk intolerance and gastrointestinal symptoms has

already been discussed, and studies by Liu and associates¹⁵⁹ provide further evidence that milk protein-induced pathology, particularly in young children, should be considered in the differential diagnosis of patients with suspected or proved lactase deficiency. These authors demonstrated in convincing fashion that infants with lactase deficiency who are initially intolerant of both milk and lactose may subsequently be able to tolerate lactose ad lib following elimination of milk protein from the diet. Lactose intolerance may then reappear when milk protein is again ingested.

TREATMENT OF FOOD ALLERGY

Elimination of symptom-inducing constituents of an offending food or foods from the diet constitutes the major method of treatment of food allergy at the present time. Once this has been accomplished there may be some value in prescribing a diet which minimizes common food allergens while emphasizing foods which are less likely to be sensitizing. Rowe and associates^{137, 160-162} have reported that elimination diets are a successful form of treatment for a variety of chronic problems which may involve food intolerance and suggested a particularly important etiological role for cereal grains in many diseases. While such concepts have merit in the therapy of certain subjects sensitive to foods, it seems prudent at present to guard against presuppositions involving large numbers of patients and a wide range of symptomatology until more objective methods of evaluation are available. The use of empirically restricted diets composed of a limited number of foods may be ill advised for some subjects, because there is some danger of resulting undernutrition and patients with a tendency toward multiple sensitivities may develop new intolerances to foods which are introduced in large amounts and at frequent intervals. This is a particular problem in infants but also occurs in older patients. A more satisfactory diet may be one containing a variety of foods which are known to be reasonably well tolerated. At present the decision about what approach to follow is largely a clinical one depending on the experience and judgment of the physician and should include consideration of the need to alter or eliminate a restrictive diet if good health is not achieved and maintained.

The therapeutic success of a diet requires attention to several factors. The diagnosis and treatment of accompanying inhalant or contact allergies should proceed if indicated and ideally should precede initiation of a diet. In addition, the results of diet therapy must be interpreted with caution if the diet is given during a period of infection or at a time of year when offending pollens or spores are prevalent. We believe that a diet devoid of a specific food must be tried for a period of at least one week and in some instances for as long as four weeks. We have encountered no circumstances under which more than a month was necessary to determine the efficacy of a diet.

A number of factors may impair the success of an elimination diet. The patient may be unwilling to adhere to the restrictions imposed, or he may unwittingly partake of foods which contain small amounts of an offending antigen, sometimes in the form of by-products of the food, e.g., butter or cheese in subjects sensitive to milk. In addition, related foods may cause symptoms,

or the diet may fail due to an allergy to nonfood substances such as preservatives, tenderizers, dyes, antibiotics, molds, or pesticides.^{59, 163}

Certain patients who respond to complete dietary elimination of an offending ingestant may merit a trial of the same food after it has been boiled. This approach is suggested by the early work of Ratner and Gruehl¹⁶⁴ who were among the first to study the effect of moist high temperature on the allergenicity of certain foods. Their work demonstrated that certain grains after cooking showed a marked reduction in capacity to sensitize the guinea pig for anaphylaxis. More recent evidence^{43, 165} has shown that certain milk proteins after high-temperature treatment lose their ability to precipitate with specific antibody in gel diffusion. In the clinical setting, the use of heat-processed foods is particularly helpful in regard to cow's milk¹⁶⁵⁻¹⁶⁹ and occasionally in the case of other foods as well. Of the major antigens in milk, bovine serum albumin and gamma globulin are heat labile, α -lactalbumin is slightly less heat labile, β -lactoglobulin is intermediate in lability and is incompletely denatured by boiling, while α -casein is quite heat stable.

In the event that heat-processed foods provoke symptoms, the offending foods may usually be left out of the diet completely without detriment to the subject's nutritional status. For infants sensitive to cow's milk, a suitable substitute must be found to ensure normal growth and well-being. Soybean preparations have high nutritional value, have been used extensively,²⁶ and are well tolerated in the majority of infants. Nutramigen (a formula employing the products of enzymatic digestion of casein) and meat-base milks have also been employed successfully. In addition, poi has been found useful as a replacement for milk and cereals in the diet of allergic infants and children.¹⁷⁰

The concepts of parenteral and oral hyposensitization deserve brief mention. Early reports^{171, 172} suggested that either dietary elimination or subcutaneous hyposensitization was effective in controlling symptoms due to certain food allergies. However, injection therapy is often difficult, especially in highly sensitive individuals, and its value has seldom been substantiated over the years.

Ratner¹⁷³ suggested oral hyposensitization for treatment of milk-sensitive subjects, beginning with drop quantities diluted in water and gradually increasing to larger amounts. This approach also only rarely appears to be helpful and is seldom used at present. On the other hand it is common experience that tolerance to many allergenic foods may follow elimination of the food from the diet for a number of months, particularly in infants and young children. This seems to be the case in the majority of instances of milk intolerance in infancy and is seen as well in other food allergies. The sensitivity in some will disappear spontaneously within a few months or years²⁹ even if a diet is not strictly followed, presumably due to a maturational process involving the digestive and absorptive functions of the gastrointestinal tract or immunologic mechanisms or both.

At the present time, identification and elimination of allergenic foods must be the main concern of the physician who provides care for patients with food allergy. One can only hope that the time will come when it will be possible

to chemically block the expression of food allergy so effectively that offending foods may be eaten at will. Better still would be a capability to prophylactically modify or eliminate the basic pathophysiologic mechanisms which cause a person to become allergic upon normal exposure to foreign antigens.

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