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CONCEPTS OF FOOD ALLERGY IMPORTANT IN SPECIFIC DIAGNOSIS

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ANY discussion of food allergy presupposes that the existence of inhalant allergy has been carefully appraised and controlled by means of adequate avoidance or therapy prior to and during the course of diagnostic measures designed to aid in the recognition of the etiologic roles of specific foods as allergens.

The incidence of specific food sensitivity is proportional to the relative frequency of ingestion of the various articles of the diet.^{1, 2} For instance, there is little doubt that the cereal grains constitute the basis of the American diet and that the more important members of this botanical group or fractions derived therefrom are ingested more frequently than any other foods. There is also agreement among physicians who have made a particular study of the role of food allergy by means of adequate diagnostic procedures that the commonly ingested cereal grains are the most common food allergens.^{2, 3} Rowe, who pioneered our clinical interest in food allergy, has emphasized for many years the importance of basic diagnostic diets eliminating the major cereal grains and, in his most recent works^{3, 4} lays greatest stress on a single cereal-free elimination diet which also omits eggs and milk as well as a group of several other foods. Rinkel's experience^{2, 5} as well as our own^{2, 6, 7} indicates that corn and wheat sensitivity are the two most important causes of chronic food allergy, there being no statistically significant difference between the incidence of sensitivity to these two cereal grains. There is also general agreement that multiple cereal sensitivity is either very common or is likely to be readily induced in an individual already specifically sensitized to one or more members of the cereal grain botanical family.

The clinical significance of food allergy as a cause of symptoms and the relative incidence of major foods as allergens depend upon the diagnostic measures employed; this necessitates a discussion of the relative merits of various diagnostic techniques.

The statement is frequently heard that one can tell by a carefully recorded history whether or not food allergy exists as a cause of symptoms. In general,

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this statement is true only in respect to those articles of the diet ingested at relatively infrequent intervals, or perhaps to those foods ordinarily ingested regularly in the diet but which at least intermittently are taken only once in 3 to 5 days. Sensitivity to the first group of foods, such as pineapple, rhubarb, lobster or walnut, for instance, is rarely ever a difficult diagnostic problem. The second group, including those foods ordinarily taken once in 3 days but at least occasionally taken at less frequent intervals, might include such items as tomato, chocolate, carrot, or apple. The individual patient may or may not be aware of sensitivity to such foods. Patients are rarely ever able to detect the presence of specific sensitivity to those articles of the diet eaten regularly at least once daily, such as corn, wheat, milk, eggs, or potatoes, providing they have not been placed on some prescribed or self-induced dietary program which happened to reduce the frequency of intake of these basic foods. In such a list of the relative incidence of food allergens, patients are least likely to suspect those at the top of the listing and become slightly more proficient in the matter of detection of specific reactors as one proceeds downward from the top of such a list arranged according to the probability of sensitization.

The best explanation of the patient's failure to recognize food allergens when ingested at frequent intervals has been given by Rinkel¹ in his description of the masking effect produced by the ingestion of a food when the patient is still in a reactive phase following previous ingestions of the same food. Under these circumstances one may not expect an immediate flare of symptoms after a meal containing the allergenic food in question but instead some immediate amelioration of chronic symptoms with a subsequent and delayed accentuation of his allergic manifestations.

Certain exceptions should be mentioned in respect to the general statement that the history cannot be relied upon to indicate specific sensitivity to the commonly ingested articles of the diet. At times, the massive ingestion of a food will break through this masking phenomenon; an example is the immediate accentuation of symptoms sometimes occurring in the wheat-sensitive patient following a spaghetti dinner.

At times, a common food will cause immediately detectable symptoms when consumed in the presence of an alcoholic beverage. Of greater importance, however, is the specific effects of alcohol indicating sensitivity to the foodstuffs from which the spirits were derived. A detailed history of intolerance to specific alcoholic beverages frequently affords clues pointing toward the allergenicity of the common offending foods. For instance, the adult individual who claims that a single drink of beer or whisky will precipitate symptoms interpreted as being allergic in type is usually sensitive to corn or wheat, or both.

Other helpful information obtained from the history is the quantitative food intake,⁷ indicating the number of times per day or week that the patient ingests the common food allergens. The same information may be obtained from the food diary. These data are important for, having no other reliable index in the new patient, one suspects specific sensitivity to those articles of the diet eaten most frequently; as a general rule, such a listing corresponds fairly

closely to the listing of food allergens based on probability. Exceptions in the patient's history which do not correspond to probability immediately become suspect. For instance, the individual drinking 20 cups of coffee daily is more likely to be coffee sensitive than the person taking 1 cup daily.

Rowe,⁸ Rinkel,⁹ Vaughan,¹⁰ and many others interested in the diagnosis of specific food allergy by means of clinical techniques have stressed the fallibility of skin tests with food allergens as diagnostic measures. Rinkel² has made the most exhaustive study of this problem and the interested reader is referred to the detailed investigation of this controversial point. The term "controversial" is used in a limited sense and refers to the popular conception apparently shared by many allergists in the reliability of such procedures. In the writer's opinion, the mechanical performance and literal interpretation of skin-test techniques have done more to retard the development and acceptance of the modern concept of food allergy than any other single point. I became convinced of this position 6 years ago and since that time have abandoned the use of both cutaneous and intracutaneous skin-testing techniques in the routine diagnosis of food allergy. Skin tests seem to be of slightly greater value in the detection of specific foods as inhalants than as ingestants.

Aside from the points in the history as mentioned and the limited information of diagnostic value which may be obtained from the food diary,² one may approach the diagnosis of specific food sensitivity by means of one of two recommended techniques; these consist of the individual food test as developed by Rinkel¹¹ or the basic type of elimination diet as first used by Rowe^{12, 13} and subsequently refined by him^{3, 4} or by combinations of these techniques.² Both procedures are in keeping with what is known of the dynamic nature and mechanism of food allergy and of the probability of sensitization based on the incidence of the major foods in the diet. Both techniques are cognizant of the all-important fact that the detection of specific food allergy is dependent upon the reproduction of clinical syndromes following the reintroduction of a specific food to the dietary after a preliminary short period of complete avoidance.

The most effective and widely used diagnostic diet is Rowe's cereal, milk, egg and fruit-free elimination diet.^{3, 4} In favor of such highly restricted elimination programs is the fact that a diet such as this may be applied as a routine procedure, thus saving time and effort in contrast to more individualized diagnostic clinical procedures. Rowe¹⁴ estimates that this diet is effective in the specific diagnosis of food allergy in 75 per cent of the cases of food allergy in which he applies it. In contrast to other diagnostic diets, this diet has the further advantage of eliminating all the cereals with the exception of cane,* an important point due to the high incidence of sensitivity to rye, oats, and rice existing in the individual already sensitive to wheat or corn. It should be emphasized that corn is eliminated completely in the form of this diet currently used by Rowe.¹⁴ The avoidance of milk, eggs, and fruit not only excludes the 4 most important food allergens but also handles the rather common problem of multiple fruit sensitivity.

*From the strict botanical sense, cane is a member of the graminæ and cane sensitivity is not as rare as formerly alleged.¹⁵

The Ralston wheat, milk and egg-free diet is to be criticized in that it does not eliminate corn which is at least tied with wheat for first place in the incidence of specific food allergens.^{2, 5, 6} Although this diagnostic diet is more applicable when used in conjunction with their restricted diet eliminating corn but the fact that rye is employed in both and the further fact that the majority of wheat-sensitive patients cannot tolerate rye materially limits the usefulness of the Ralston diets in specific diagnosis.

Although such sharply restricted elimination procedures are admirable for the individual who fortunately happens to have a relatively narrow base of sensitivity,⁷ unfortunately, even the experienced clinician cannot be certain which of his patients may be so categorized prior to instituting specific diagnostic measures. The individual with a current wide base of food sensitivities is also likely to have a low inherent tolerance for foods¹ which means that he is likely to develop new sensitivities readily. Such a patient may not only fail to have a significant degree of relief of his allergic symptoms from such a restricted diet but may develop one or more new sensitivities resulting from the oft-repeated ingestion of permitted foods. All such restricted standardized dietary programs employed in diagnosis are based on the presupposition that certain selected foods are relatively low in the incidence with which specific sensitivity is diagnosed; this presupposition does not preclude the fact that all foods are potentially allergenic. The so-called less important foodstuffs immediately become potentially important food allergens when their incidence in the diet is increased; this is particularly true of the individual who develops new sensitivities readily.

The other recommended approach in the specific diagnosis of food allergy is the performance of several individual food tests with the major articles of the diet based on the individual's eating habits and the probability of sensitization. The technique of this test was developed by Rinkel^{8, 11}; it consists briefly in the absolute avoidance of a particular food for 4 days prior to its experimental ingestion under observation. The incidence and severity of symptoms are recorded per unit of time by an observer trained in the technique of the test for one-half hour prior to the deliberate ingestion of the food in a fasting condition and for 3 one-half-hour periods thereafter. A second feeding is given 1 hour after the first, providing an acute symptom response has not developed. The test is considered positive if there is a doubling or tripling in the incidence of coughing, sneezing, or other symptoms found by experience to be associated with a positive reaction.² Total leucocyte counts (enumerating double the number of leucocytes usually counted) are performed prior to the initial feeding and at 20, 40, and 60 minutes thereafter. In the absence of clear-cut reactive symptoms, some emphasis is given to the interpretation of the leucocyte responses, an empirical association of fairly high correlation having been shown to exist between the development of a leucopenia of 10 per cent or greater occurring in the post-prandial blood observations and in the presence of delayed or cumulative types of food reactions.^{11, 16}

This diagnostic approach is advantageous in that it permits the direct observation of the patient immediately prior to and during the course of induced allergic reactions. When applied to the first 6 or 8 major allergenic foods in a patient's diet, the diagnostician learns something of the extent of involvement of the diet by the food allergy process.² In the event of a narrow base of sensitivity it is then safe and expeditious to proceed with highly restricted diagnostic diets. If more than fifty per cent of the first group of foods are incriminated, one then proceeds with further individual food tests without placing this type of patient on a highly restricted diet.

The chief disadvantage of this type of approach is the time and office space consumed in such tests.

Regardless of the exact methods employed, the complete avoidance of a major food for at least 4 days is an essential part of the diagnostic program, for otherwise the specifically sensitive patient may not react with clear-cut allergic symptoms when the food is reintroduced to the diet. This not only means the common forms of the foods but various fractions of the food as well. In view of the fact that this aspect of the avoidance of foods has recently been questioned,^{17, 18} the allergenicity of starches, sugars, alcohols, gelatins, and oils will be briefly reviewed.

As it has long been recognized that wheat starch (flour) and potato starch will cause symptoms when ingested by specifically sensitized individuals, it is not too surprising that cornstarch should act similarly in the corn-sensitive patient. The widespread use of cornstarch and certain heretofore unrecognized sources of exposure have recently been reported.^{2, 19 20}

The ingestion of corn sugar (glucose or dextrose) not only causes clinically demonstrable symptoms in the majority of corn-sensitive patients but also frequently results in more acute symptom responses than occur after the ingestion of corn as such. Both Rinkel and the author determined independently that the diagnostic accuracy of individual food tests with corn was increased if corn meal gruel and corn sugar were fed rather than testing with the gruel alone.^{2, 21} In selected circumstances the intravenous injection of corn sugar has been known to be associated with the production of allergic symptoms.²² In view of these observations it is not surprising to learn that clinical reactions may be induced by the ingestion or intravenous injection of cane sugar in certain cane-sensitive patients¹⁵ or by the ingestion of beet sugar or monosodium glutamate prepared from Steffan's waste (beet pulp following the extraction of the sugar) in at least some beet-sensitive individuals.²³

During the past 3 years a study to determine the specificity of alcoholic spirits in respect to the native foods from which the alcoholic beverages were derived has been in progress. Pure samples of corn, potato, and cane spirits were prepared* and tested in known sensitive patients as well as in individuals known not to be sensitive to the native food. In data as yet unpublished, it has been shown that alcoholic spirits exert a specific effect on allergic individuals in respect to the existence of sensitivity to the native food from which the spirits were derived. When comparable individual food tests were run on the same

*Prepared through the courtesy of Hiram Walker and Sons, Inc., Peoria, Ill.

individual with a large serving of the food and another time with an ounce of the specific spirits (100 proof), as a rule more acute allergic symptoms resulted from the alcohol.

Contrary to the common impression, certain patients highly sensitive to beef will have allergic symptoms following the ingestion of commercially available bovine gelatin,²⁴ although a similar allergenicity for the gelatin prepared for the pharmaceutical trade (Wilson) could not be demonstrated.

It is generally agreed that the oil fraction of a given food is less allergenic than other fractions. Nevertheless, there are unmistakable instances in which ingestion of the refined oil will cause allergic symptoms on certain individuals sensitive to the native food.^{2, 25} Sensitivity to cottonseed oil with or without the presence of positive skin tests with cottonseed extract may also exist.^{14, 26}

The general aim in the diagnosis of specific food allergy, whether by means of individual food tests with or without basic types of elimination diets, is to free the patient of current chronic allergic symptoms. In many instances this objective can be accomplished only by the elimination of the starches, sugars, alcohols, and sometimes the oils of specific foods as well as the avoidances of the food in its native or cooked state. The failure of clinicians to recognize these basic facts or the inability to instruct their patients adequately in the minutia required to accomplish the complete elimination of a food or the patient's reluctance to follow such instructions accounts for many of the apparent failures in specific allergic diagnosis. Such failures have not only reflected to the discredit of allergists but, unfortunately, commonly result in the most highly allergic individuals remaining undiagnosed. This would be bad enough, but even worse is the deduction under such circumstances that the patient is not even allergic when actually one is dealing with an advanced case of clinical allergy.

Once an individual has been freed of allergic symptoms on some type of diagnostic plan, the next stage is to return the previously omitted foods one by one and in such a timing as to note most effectively the relationship of the food to the production of symptoms. The evidence obtained may be confirmatory of points in the history or the results of earlier individual food tests. If the response upon reintroduction of a particular food to the diet is at all equivocal, it should again be omitted and subsequently returned to the diet in cumulative doses.

Once the specific diagnosis is made, then and only then should the role of the so-called "food fractions" be determined. It should be emphasized that not all corn-sensitive patients find it necessary to avoid all forms of corn and that not all milk-sensitive individuals find it necessary to avoid all traces of milk in order to have what the patient and his physician currently regard as a satisfactory degree of relief of symptoms. It is also recognized that some patients can continue on such a plan without any apparent ill effects, although it is difficult to tell in advance which individuals will take this particular course. Some patients will subsequently become intolerant to minor sources of such specific foods; an extreme illustrative case of this type has been reported by the author.²⁷ A more common course of events is for the patient to maintain an

active degree of sensitization to the food in question instead of gradually developing tolerance to it.

If the base of sensitivity permits, the ideal treatment of specific food allergy from the standpoint of an eventual gain of specific tolerance is the complete avoidance of the incriminated food. From a practical standpoint, this course of events is relatively easy when dealing with some foods and difficult to the point of being almost impossible with certain others. When the base of sensitivity is wide, the food-allergic individual profits by the avoidance of the most potent allergens and the use of all other foods on a rotating, diversified schedule of feedings as recommended by Rinkel.²⁸

REFERENCES

1. Rinkel, H. J.: Role of Food Allergy in Internal Medicine, *Ann. Allergy* 2: 115, 1944.
2. Rinkel, H. J., Randolph, T. G., and Zeller, M.: Food Allergy, Springfield, Ill., Charles C Thomas, Publisher, 1950.
3. Rowe, A. H.: Elimination Diets and the Patient's Allergies, Philadelphia, 1944, Lea & Febiger.
4. Rowe, A. H.: Nutrition in the Allergies, Wohl, Dietotherapy, Clinical Application of Modern Nutrition, Philadelphia, 1945, W. B. Saunders Company.
5. Rinkel, H. J.: Food Allergy, *J. Missouri M. A.* 37: 428, 1940.
6. Randolph, T. G., and Yeager, L. B.: The Incidence of Allergy to Major Foods, *J. Lab. & Clin. Med.* 32: 1547, 1947.
7. Randolph, T. G.: Food Allergy, *M. Clin. North America* Chicago Number, January, 1948, W. B. Saunders Company.
8. Rowe, A. H.: The Evaluation of Skin Reactions in Food Sensitive Patients, *J. ALLERGY* 5: 135, 1934.
9. Rinkel, H. J.: Food Allergy, *J. Kansas M. Soc.* 37: 177, 1936.
10. Vaughan, W. T.: Practice of Allergy, St. Louis, 1939, The C. V. Mosby Company.
11. Rinkel, H. J.: Food Allergy. II. Technique and Clinical Application of the Individual Food Test, *Ann. Allergy* 2: 504, 1944.
12. Rowe, A. H.: Abdominal Food Allergy; Its Treatment With Elimination Diets, *California & West. Med.* 29: 5, 1928.
13. Rowe, A. H.: Food Allergy; Its Manifestations, Diagnosis and Treatment, *J. A. M. A.* 91: 1623, 1928.
14. Rowe, A. H.: Personal communication.
15. Randolph, T. G., and Rollins, J. P.: Allergic Reactions From the Ingestion or Intravenous Injection of Cane Sugar, *J. Lab. & Clin. Med.* 36: 242, 1950.
16. Randolph, T. G., and Rawling, F. F. A.: Blood Studies in Allergy, V. Variations of Total Leucocytes Following Test Feeding of Foods; An Appraisal of the Individual Food Test, *Ann. Allergy* 4: 163, 1946.
17. Allergy to Refined Food Products (Editorial), *J. A. M. A.* 141: 847, 1949.
18. Lee, H. J., and Squier, T. L.: Provocative Diets in the Recognition of Food Allergy, *J. A. M. A.* 142: 318, 1950.
19. Randolph, T. G.: Cornstarch as an Allergen, Sources of Contact in Food Containers, *J. Am. Dietet. A.* 24: 841, 1948.
20. Randolph, T. G.: Allergy to So-called "Inert Ingredients" (Excipients) of Pharmaceutical Preparations, *Ann. Allergy* 8: 519, 1950.
21. Randolph, T. G., and Yeager, L. B.: Corn Sugar as an Allergen, *Ann. Allergy* 7: 651, 1949.
22. Randolph, T. G., Rollins, J. P., and Walter, C. K.: Allergic Reactions Following the Intravenous Injection of Corn Sugar (Dextrose or Glucose), *J. Lab. & Clin. Med.* 34: 1741, 1949 (abstract), *Arch. Surg.* 61: 554, 1950.
23. Randolph, T. G., and Rollins, J. P.: Allergic Reactions From the Ingestion of Beet Sugar (Sucrose) and Monosodium Glutamate of Beet Origin, *J. Lab. & Clin. Med.* 36: 407, 1950.
24. Randolph, T. G.: Gelatin as an Allergen, *J. Lab. & Clin. Med.* 32: 1548, 1947.
25. Rowe, A. H.: Clinical Allergy, Its Manifestations, Diagnosis and Treatment, Philadelphia, 1937, Lea & Febiger.
26. Randolph, T. G., and Sisk, W. N.: Cottonseed Oil Sensitivity, *Ann. Allergy* 8: 5, 1950.
27. Randolph, T. G.: An Unusual Case of Milk Sensitivity, *J. A. M. A.* 126: 430, 1944.
28. Rinkel, H. J.: Food Allergy. IV. The Function and Clinical Application of the Rotary Diversified Diet, *J. Pediat.* 32: 266, 1948.