

Treatment of delayed food allergy based on specific immunoglobulin G RAST testing

HAMILTON S. DIXON, MD, Rome, Georgia

This preliminary, descriptive study after extensive clinical experience demonstrates specific IgG food RASTs done in 114 consecutive patients with strong positive histories for delayed food allergy. Elimination of the positive foods was the sole means of treatment. The symptoms leading to the test are detailed, and the method of workup is reviewed. The overall results demonstrated a 71% success rate for all symptoms achieving at least a 75% improvement level. Of particular interest was the group of patients with chronic, disabling symptoms, unresponsive to other intensive treatments. Whereas 70% obtained 75% or more improvement, 20% of these patients obtained 100% relief. (Otolaryngol Head Neck Surg 2000;123:48-54.)

Food allergy has remained a very controversial subject, especially with pediatricians and traditional allergists. Whereas IgE was not discovered until 1969, thereby explaining immediate hypersensitivity, the exact mechanisms for delayed hypersensitivity remain in part theoretical.¹ The exact role of immune complexes, complement, and IgG in type III delayed hypersensitivity has not lent itself to a single reliable test for easy diagnosis. Furthermore, the prevalence of cyclic or delayed food allergy has never been well established in the literature.

From the clinical standpoint, delayed food allergy has no cause-and-effect relationship. Therefore the symptoms go unsuspected by both patient and physician. History, elimination diets, reintroduction of foods, and other conservative measures are usually not helpful.

For many years, traditional allergists have used scratch tests and now prick tests for foods, along with inhalant testing. Many false-positive and false-negative

results have made these tests unreliable, frequently only 20% accurate.²

Challenge feeding tests have been the gold standard for delayed food allergy and are accurate in trained hands.³ Even more difficult is the double-blind placebo-controlled food challenge. Unless exact rules are followed, reproducibility at challenge is low,⁴ and its impracticality has led to infrequent use in clinical practice.

Cytotoxic food testing has been shown to be accurate only in well-controlled laboratories with highly trained technicians. Results have often been equivocal, especially in office laboratories. The next generation test, the ALCAT, may hold more promise, but it is still not in general use.

Provocation-neutralization testing has also been shown to be efficacious in 6 published double-blind studies, with 75% to 80% accuracy demonstrated.^{5,6} I completed another double-blind study using videostroboscopy of vocal folds and provocation-neutralization testing in patients with allergic dysphonia.⁷ Internal medicine-pediatric allergists have been reluctant to accept this test because it is not immediately reproducible due to the nature of type III hypersensitivity. This time-consuming test is used by only a small number of otolaryngic allergists. Patient compliance in my practice has been poor because patients must make multiple visits and travel long distances to complete the necessary battery of skin tests. This problem has left many patients with incomplete workups and a continuation of troubling symptoms.

Thus there is currently no standardized, accepted test for delayed food allergy. Furthermore, the prevalence of delayed food allergy as a significant cause of illness has not been well reported.⁸ Even many traditional allergists are unaware of its importance, referring to this problem as food intolerance, which is regarded as nonallergic and is usually thought to be associated with chemical sensitivities caused by additives and food colors.

Specific IgG testing for foods has been controversial for several reasons: (1) IgG reflects exposure to the food; (2) IgG levels occur in the normal population⁹; (3) IgG is a protective antibody; (4) IgG₄ is thought by some to be more specific for clinical food allergy than total specific IgG^{10,11}; (5) some food reactions are non-immunologic; (6) there is little correlation between RAST classes (titers) and severity of symptoms; (7)

From the Department of Otolaryngology-Head and Neck Surgery, Vanderbilt University; AllerCare Laboratories; and private practice, Rome, GA.

Presented at the Annual Meeting of the American Academy of Otolaryngic Allergy, San Diego, CA, September 23, 1994.

Reprint requests: Hamilton S. Dixon, MD, 3268 Martha Berry Hwy, NE, Rome, GA 30165-9745.

Copyright © 2000 by the American Academy of Otolaryngology-Head and Neck Surgery Foundation, Inc.

0194-5998/2000/\$12.00 + 0 23/1/106402

doi:10.1067/mhn.2000.106402

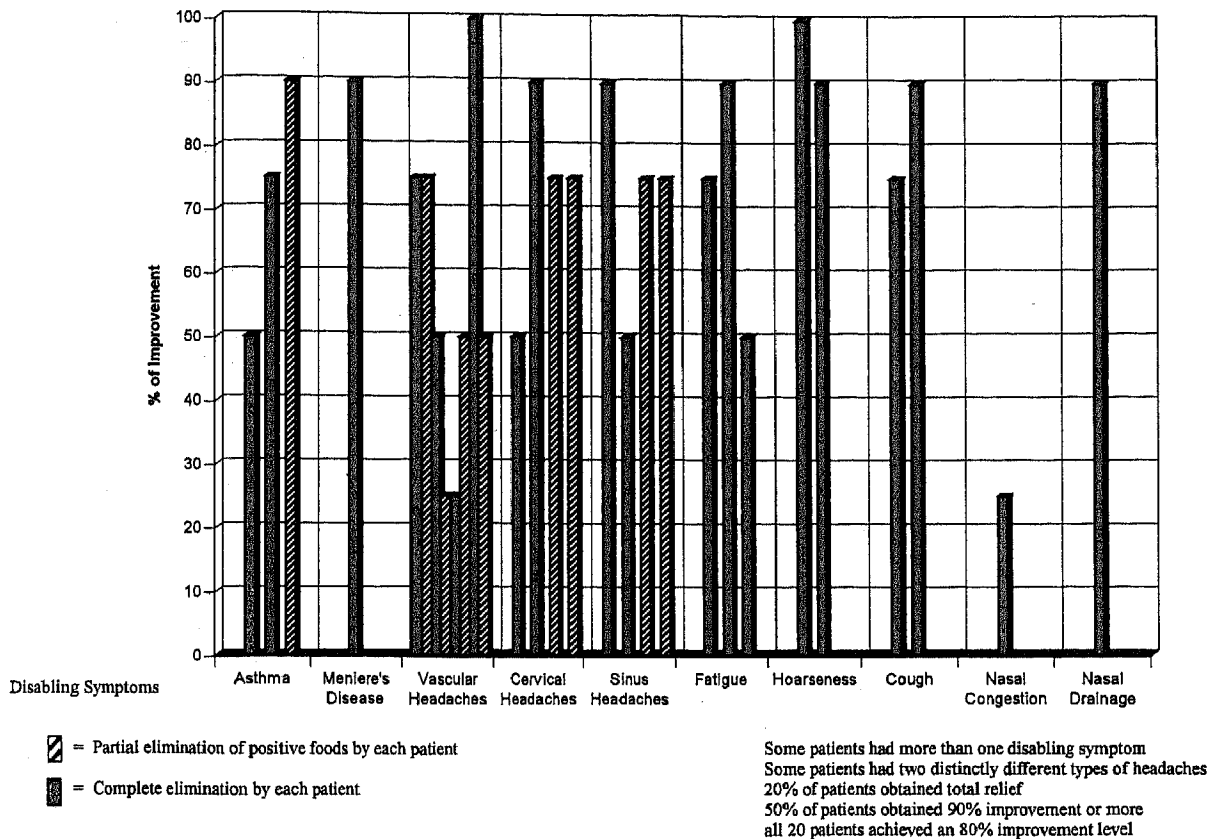


Fig 1. Symptom Improvement in 20 patients with disabling symptoms.

clinical tolerance may occur when IgE or IgG antibodies are still positive and skin tests are still reactive; (8) the RAST technology and scoring system for IgG have not been satisfactory in the past, causing previous preliminary studies to be equivocal¹²; (9) the highest score by IgG is only 10 times greater than the negative cutoff, compared with 80 times for IgE and IgG₄ RAST; (10) a positive result by IgG to a food does not confirm that this food is causing clinical symptoms; (11) the symptoms under consideration cannot be proven to be caused by food allergy by IgG testing; (12) IgG testing is considered for investigational use only by the Health Care Financing Administration and is thus not covered by most third-party payers; and (13) IgG testing is not yet an approved technique by the American Academy of Otolaryngic Allergy.

It is generally agreed that non-IgE immunologic hypersensitivity to foods exists¹³ and is able to cause considerable morbidity.¹⁴ The literature on cyclic or delayed food allergy has been growing for more than 60 years and has recently been compiled and brought up to date. Emphasis has been on the many symptoms possible and the fact that virtually any organ system can be

targeted.¹⁵ The cornerstone of symptoms for this problem lies in the gastrointestinal tract.¹⁶ Because otolaryngologists treat up to 60% of all illnesses, these problems are commonly seen but often go unsolved.

This preliminary, descriptive study was designed to clinically test the efficacy of specific IgG for foods as the sole test in patients with significantly positive histories of symptoms consistent with delayed food allergy. After 25 years' experience dealing with delayed food allergy and 3 years' experience with IgG tests for foods, I tested 114 consecutive patients by IgG RAST for foods. This followed a specific workup leading to the need for food diagnosis. No attempt was made to confirm by double-blind placebo-controlled food challenge that any positive food was specifically the cause of any symptom. The purpose of this study was to determine whether patients' symptoms would improve significantly with simple elimination of positive foods and to decide whether this test is worthy of more scientific study.

METHODS

All patients who seek treatment at my clinic undergo a comprehensive history regardless of the presenting symptom.

Table 1. Order of positive IgG food tests in 80 patients

Food	No. of tests	% Positive
Milk	73	82
Garlic	12	58
Mustard	12	58
Egg yolk	19	53
Tea	34	53
Chocolate	39	51
Banana	49	34
Whole egg	39	33
Black pepper	41	33
Wheat	69	32
Orange	18	28
Turkey	12	25
Oat	22	23
White potato	66	21
Carrot	24	20
Green bean	16	19
Cheddar cheese	16	19
Cabbage	12	17
Baker's yeast	25	16
Egg white	33	16
Cane sugar	40	15
Tomato	50	12
Peanut	42	12
Onion	34	12
Apple	25	12
Pork	30	11
Rice	30	10
Corn	67	9
Chicken	54	9
Lettuce	48	8
Coffee	38	8
Beef	51	2

Food not included if fewer than 10 tests.

If chronic symptoms of immediate or delayed allergy are elicited, additional specific and more detailed histories are obtained. The likelihood of allergy to a variety of inhalants, including foods, is generated. If functional gastrointestinal symptoms are present and the patient has one of the many typical delayed food allergy symptoms, a specific food questionnaire is completed (Appendix). Questions 9, 10, 16, and 23 are considered the key elements. For patients to be considered for food testing, answers to 3 of these 4 must be positive with significant frequency. Any other positive responses point to other target organs and lend further credibility to the need for testing. I personally spent considerable time with each patient reviewing the history in great detail to be certain that all questions were answered and that all responses were a true representation of the patient's condition. Because many patients have certain symptoms on an ongoing basis and consider them normal and thus answer no on the questionnaire, I made certain that each answer was a true reflection of actual symp-

Table 2. Reported symptoms in 80 patients

Symptom	No. reporting
Nasal congestion	40
Nasal drainage	36
Sinus headaches	33
Fatigue after meals	31
Throat clearing	29
Gas	26
Chronic fatigue	25
Dizziness	24
Dry cough	22
Sneezing	20
Hoarseness	20
Diarrhea	20
Migraine headaches	19
Itchy eyes	19
ringing in ears	18
Ear fullness	17
Nausea	17
Cervical headaches	15
Watery eyes	15
Itchy skin	14
Asthma	13
Burping	13
Cramps	13
Rash	12
Ear popping	11
Vomiting	7
Red eyes	7
Urticaria	6
Behavior problems	2

All symptoms were intermittent.

toms. Special attention was paid to grading each symptom before and after treatment to calculate the percent change.

Patients with significant inhalant allergy symptoms in whom pharmacotherapy had failed were tested with a total IgE (Prist) and specific IgE RAST, usually with a panel of 23 allergens. Five basic foods were included in this IgE panel. IgE foods of class II or higher were eliminated. It was generally expected that these IgE patients would be 80% better in 2 months.

If these patients receiving immunotherapy returned in 2 months and were only 50% better, foods were suspected, and the detailed food questionnaire was completed. However, if significant food symptoms were evident at the initial workup, the food questionnaire was completed initially, and IgG testing was considered, along with IgE RAST for inhalants.

At presentation, many patients have nasal obstruction, chronic or recurrent sinusitis, chronic secretory otitis, chronic otitis media and mastoiditis, and cholesteatoma. These conditions often require surgery, but underlying allergy is always suspected. If indicated by history, allergy testing is recommended after the surgery. Patients with nasal polyps and asthma are suspected for both immediate and delayed hypersensi-

tivity. Patients with headaches, both migraine¹⁷ and sinus-type, as well as patients with Meniere's disease¹⁸ and those with positional vertigo, are also suspected of having delayed food allergy.¹⁹

If the history suggested delayed food allergy, patients were asked to keep a 2-week diet diary. Only the foods eaten twice weekly or more were selected for testing (a delayed allergy cannot occur if a food is eaten less than twice weekly¹). The number of foods tested ranged from 10 to 15, keeping this a cost-effective approach. A specific IgG test for each suspected food was done by RAST.

Control comparisons were done with the many negative test results for each patient. For the purpose of this study, use of healthy control subjects without symptoms would serve no benefit. The presence of IgG levels to foods in nonatopic individuals is already established.⁹

The scoring system for this test is critical in achieving meaningful results, and its concepts are similar to those used in the development of the modified IgE RAST scoring system for inhalants by Nalebuff et al.²⁰ Whereas the current IgE scoring system has a class I cutoff of 750 counts, the IgG scoring system established by the manufacturer (Hycor Biomedical Inc, Garden Grove, CA) has a class I cutoff of 1670 counts, equivalent to 37.5 ng of allergen-specific IgG per milliliter. My experience combined with the experience of others indicates that this can lead to false-positive results and that the low-end cutoff should be raised. Rather than interfering with the counting parameters set by the manufacturer, I decided to modify the scoring system by diluting the serum sample 150 times (100 times is recommended). This effectively raised the low-end cutoff by a factor of one third. Now 1670 counts was equivalent to 50 ng of specific IgG antibody. This resulted in patient panels with only a few positive values in the range of 20% to 40%. Recognizing that I might still have a few low-end false-positive results, I decided to include class I and II foods in those to be eliminated, rather than missing true low-end positive values.

Follow-up was carried out in all cases with repeated personal interviews. No mail-in questionnaires or telephone interviews were done. Reports of symptom improvement after elimination were carefully evaluated for accuracy; all pre-treatment symptoms were reviewed, and all percents of change were confirmed for each.

This study was considered exempt by the institutional review board.

RESULTS

One hundred fourteen consecutive patients were tested for IgG foods. Five patients had totally negative test results, consistent with comprehensive patient selection. Sixteen patients were lost to follow-up. Fifteen patients did not eliminate the foods and continued to have the same problems. Eighty patients elimi-

Table 3. Order of symptom improvement in 80 atopic patients after elimination of positive foods by specific IgG tests

Symptom	No. reported	≥75% improvement	100% improvement
Diarrhea	20	90%	45%
Cramps	13	84%	38%
Cough	22	77%	36%
Cervical headache	15	73%	20%
Nausea	17	70%	24%
Burping	13	69%	15%
Hoarseness	20	65%	15%
Throat clearing	29	65%	28%
Nasal drainage	36	63%	17%
Fullness in ears	17	64%	29%
Nasal congestion	40	62%	20%
Asthma	13	61%	15%
Sinus headache	33	60%	24%
Gas	26	57%	12%
Itchy eyes	19	57%	26%
Sneezing	20	55%	20%
Ear popping	11	54%	27%
Watery eyes	15	53%	6%
Fatigue after meals	31	51%	23%
Dizziness	24	50%	21%
ringing in ears	18	50%	5%
Skin rash	12	50%	8%
Chronic fatigue	25	48%	0%
Migraine headache	19	47%	16%
Itchy skin	14	35%	7%

Symptom not included if reported fewer than 10 times.

nated the foods partially or completely and underwent follow-up of 6 to 22 months. One patient was followed up for only 4 months.

Of the 80 patients studied, 5 did not need IgE RAST testing for inhalants. Forty-six patients had been receiving immunotherapy for more than 2 months before undergoing testing for IgG foods. Eleven patients had entirely negative IgE RAST results. Nine of these 11 patients' symptoms improved by 80% after just 2 weeks' elimination of the positive foods.

Table 1 shows the order of the most frequently positive foods and lists the number of tests for each. Table 2 shows the frequency of symptoms reported. Table 3 shows improvement after elimination.

A successful outcome was selected at no less than a 75% improvement level. The average overall success rate was 71%, with all 80 patients considering all reported symptoms.

The elimination of positive foods was highly successful in relieving certain symptoms but was less so for others.

Cow's milk was the most commonly ingested food

and tested positive most frequently. This was followed by tea, chocolate, banana, and wheat when frequency of ingestion and positivity were combined.

Of special interest were 20 patients (25%) with disabling symptoms (Fig 1). For this group of patients, symptoms in 66% improved by 70% or more. However, there were 29 symptom groups in these 20 patients, with an 80% overall improvement level. Twenty percent of these patients had complete relief, and 50% obtained 90% or more relief.

DISCUSSION

The problem of entirely negative IgE RAST results for inhalants has increased since the sensitivity of the RAST has decreased somewhat (with increased specificity). RAST technology has improved, and the results now agree better with those of the Western blot test, the gold standard against which RAST is compared. Even results of skin titration testing agree well in patients with negative RAST results, again indicating that immunotherapy is not indicated. However, it is disconcerting to elicit a strong history of uncontrolled allergy in patients in whom pharmacotherapy has failed, only to obtain a negative IgE RAST result. It has been reassuring in this study to see that all 11 of the patients with negative IgE RAST results for inhalants had positive histories for delayed food allergy and have demonstrated positive IgG antibodies for commonly eaten foods. Even more reassuring is the 80% symptom improvement after elimination of positive foods in 9 of 11 patients. Thus 11% of the patients worked up for inhalant allergy had apparent delayed food allergy as the sole cause of their symptoms. Some positive foods are no doubt eliminated needlessly with this qualitative measure.

Further follow-up after the completion of this study has been continued, and IgG testing has been continued as the sole food test, with elimination as the sole treatment in my practice. The findings noted in this study have continued to be borne out with excellent outcomes.

Although this series of patients did not include any with secretory otitis, of special note are the many children with this problem who require tubes. Placing tubes a second time is rare in children who undergo this type of workup and cooperate with elimination of positive foods and any needed inhalant treatment. This is remarkable considering the cost of medical care for other children who have tubes placed many times. The cost of secretory otitis including tubes is more than \$2 billion per year. The cost of food elimination is free.

Success in total elimination requires strong discussion by the physician and a staff trained in effective diet manipulation. It is essential to find substitutes for main-

taining nutrition but especially for maintaining the fun of eating. To be successful in their elimination program, patients must be willing to study, shop at health food stores, look carefully at alternative foods, and obtain food allergy recipe books.²¹

Sublingual neutralization drops can be offered as an alternative to elimination, but this treatment was not used in this study because results are not uniformly reliable.

CONCLUSIONS

Specific IgG for commonly eaten foods can be considered when chronic food allergy symptoms are present and conservative treatment has failed. Delayed food allergy most often occurs in atopic patients who also have inhalant allergies. Delayed food allergy is highly suspect in allergic patients with negative IgE RAST or skin test results, which may explain their symptoms. Elimination of positive foods is successful in significantly decreasing symptoms. Twenty-five percent of those studied had incapacitating symptoms and achieved an 80% or greater improvement level, with 20% of those achieving 100% improvement and 50% obtaining 90% or more relief. In all 80 patients studied, 71% achieved a 75% or greater improvement level. Comprehensive history taking for careful patient selection is important in achieving these results.

REFERENCES

1. Trevino RJ. Food allergies and hypersensitivities. In: Trevino RJ, Dixon HS, editors. Food allergy. AAOA monograph series. New York: Thieme; 1997. p. 1-16.
2. Fadal RG. Introduction to food allergy and other adverse reactions to foods. *Res Staff Phys* 1988;34:23-3.
3. Dixon HS. The diagnosis of food allergy. In: Trevino RJ, Dixon HS, editors. Food allergy. AAOA monograph series. New York: Thieme; 1997. p. 64-7.
4. Dannaeus A. Food allergy in infants and children: state of the art. *Ann Allergy* 1987;59:124-6.
5. King WP, Rubin WA, Fadal RG, et al. Provocation-neutralization: a two-part study. Part I. The intracutaneous provocative food test: a multi-center comparison study. *Otolaryngol Head Neck Surg* 1988;99:263-71.
6. King WP, Rubin WA, Fadal RG, et al. Provocation-neutralization: a two-part study. Part II. Subcutaneous neutralization therapy: a multi-center study. *Otolaryngol Head Neck Surg* 1988;99:272-7.
7. Dixon HS. Dysphonia and delayed food allergy: a provocation-neutralization study with stroboscopy. *Otolaryngol Head Neck Surg* 1999;121:418-29.
8. Herr TM, Cook PR, Highfill G. In vitro testing in pediatric food allergy. *Otolaryngol Head Neck Surg* 1999;120:233-7.
9. Dockhorn RJ, O'Bryan JJ, Dockhorn DW, et al. Effect of diet on food IgG responses in healthy non-food allergic individuals. *Ann Allergy* 1991;66:104.
10. Awazuhara H, Kawai H, Maruchi N. Major allergens in soybean and clinical significance of IgG₄ antibodies investigated by IgE- and IgG₄-immunoblotting with sera from soybean-sensitive patients. *Clin Exp Allergy* 1997;27:325-32.
11. El Rafei A, Peters SM, Harris NS, et al. Diagnostic value of IgG₄

- measurement in patients with food allergy. *Ann Allergy* 1989;62:94-9.
12. Trevino RJ, Rapoport AS. Problems with in-vitro diagnosis of food allergy. *Ear Nose Throat J* 1990;69:42-6.
 13. Ortolani C, Bruijnzeel-Koomen C, Bengtsson U, et al. Controversial aspects of adverse reactions to foods. *Allergy* 1999;54:27-45.
 14. Marinkovich V. Specific IgG antibodies as markers of adverse reactions to foods. In: Wuthrich B, Ortolani C, editors. *Highlights in food allergy*. Monographs Allergy. Basel: Karger; 1996;32:221-5.
 15. Sampson HS. Food allergy [review]. *J Allergy Clin Immunol* 1989;4:1062-7.
 16. Bengtsson U, Hanson LA, Ahlstedt S. Survey of gastrointestinal reactions to foods in adults in relation to atopy, presence of mucus in the stools, swelling of joints and arthralgia in patients with gastrointestinal reactions to foods. *Clin Exp Allergy* 1996;26:1387-94.
 17. Mansfield LE, Vaughan TR, Waller SF, et al. Food allergy and adult migraine: double-blind and mediator confirmation of an allergic etiology. *Ann Allergy* 1985;55:126-9.
 18. Derebery MJ. Allergic and immunologic aspects of Meniere's disease. *Otolaryngol Head Neck Surg* 1996;114:360-5.
 19. Dixon HS. Food allergy—signs and symptoms. In: Trevino RJ, Dixon HS, editors. *Food allergy*. AAOA monograph series. New York: Thieme; 1997. p. 47.
 20. Nalebuff DJ, Fadal RG, Ali M. Development of the modified RAST. In: Fadal RG, Nalebuff DJ, editors. *RAST in clinical allergy*. Chicago: Year Book Medical Publishers; 1981. p. 35-48.
 21. Pilgrim D, Munger P. *Food allergies, what do I eat now?* Marietta (GA): Food Allergy Solutions; 1998.

APPENDIX: FOOD ALLERGY QUESTIONNAIRE

Name: _____

Date: _____

This questionnaire is designed to help determine whether some of your symptoms are related to delayed food allergy. Please read each question carefully, fill in all the blanks, and circle either *yes* or *no* on the left and the appropriate response on the right.

Note: for the symptoms asked, **none is normal**.

1. What foods do you eat more than once a day? (example: cola, tea, milk, bread, candy)

2. List any foods that make you sick or disagree with you:

- | | | | |
|-----|----|---|--|
| Yes | No | 3. Are you awakened between the hours of 1:00 AM and 5:00 AM with the following symptoms: headache, dizziness, stomach cramps, bloating, food cravings, or dry cough? | Circle your symptoms |
| Yes | No | 4. Does any member of your family have hay fever, asthma, hives, chronic skin condition, migraine headache, dizziness, stomach cramps, bloating, dry cough, or a sinus condition? | Circle the conditions |
| Yes | No | 5. During childhood, did you have any of the following: eczema, hay fever, asthma, or frequent earaches? | Circle the conditions |
| Yes | No | 6. Were you told that you had colic feeding problems as a baby? | |
| Yes | No | 7. Do you have itching of the skin, palate, or roof of the mouth?
How often does it occur? _____ | Daily Weekly Monthly |
| Yes | No | 8. Do you notice swelling of the ankles, feet, hands, or face on arising in the morning? | Circle area |
| Yes | No | 9. Do you ever have a full meal in the middle of the day?
(example: after church on Sunday or in a restaurant during the day) | |
| Yes | No | Do you ever experience fatigue 1 to 2 hours after that meal?
How often does this occur? _____ | Almost every time
Half the time Not very often |

- Yes No 10. Do you ever have a dry cough? _____ Daily Weekly Monthly
How many times might you cough in 24 hours? _____ Circle the number
5 10 20 30 40 50 75 100 >100
- Yes No 11. Do you eat snacks between meals?
List the foods: _____
- Yes No 12. Do you have excessive chilling when a sudden change in temperature occurs?
- Yes No 13. Do you have severe migraine headaches? Daily Weekly
How often? _____ Monthly Every several months
- Yes No 14. Do you have sinus headaches? Daily Weekly
How often? _____ Monthly Every several months
- Yes No 15. Do you have headaches in the back of your head? Daily Weekly
How often? _____ Monthly Every several months
- Yes No 16. Do you ever have gas, belching, bloating after meals, or cramps?
How often do you have this? _____ Daily Weekly Monthly
- Yes No 17. Have you noticed numbness of the face, arms, or legs at periodic intervals
for no apparent cause?
How often? _____ Daily Weekly Monthly
- Yes No 18. Do you have drowsiness, headache, or bloating after the ingestion of a
cocktail, beer, or wine?
- Yes No 19. Are you allergic to penicillin?
- Yes No 20. Do you ever have any diarrhea, even mild or intermittent?
How often? _____ Daily Weekly Monthly
- Yes No 21. Do you ever have repeated symptoms on awakening in the morning, such as headache?
List other recurring symptoms: _____
- Yes No Can you make the symptoms go away by eating or drinking any particular food,
such as coffee or cola?
List the foods that help improve the symptoms: _____
- Yes No 22. Are there any other reactions or problems that you notice with any other foods?
List these foods: _____
- Yes No 23. Do you ever clear your throat?
How often does this occur? _____ Daily Weekly Monthly
How many times per day? _____ Circle the number
1-2 5 10 20 30 40 50 75 100 >100
- Yes No 24. Do you ever have dizziness with a sense of motion?
Yes No Does this occur by spells?
Yes No When you move your head?
How long does the average spell last without stopping? 5-10 sec 1-2 min 15-30 min ≥1 hour
- Yes No 25. Does your weight increase or decrease 4-5 pounds in a 1-week period?