

February 6, 1984. Because such a stay affects not only OTC human drugs, but also cosmetic products and contact lens solutions and tablets, the Commissioner of Food and Drugs made the petition response an advisory opinion. Therefore, this response may be relied on by manufacturers and packers of all affected products. A copy of this advisory opinion is on file at the Dockets Management Branch. Elsewhere in this issue of the *Federal Register*, the agency is amending the tamper-resistant packaging regulations with regard to the stay of the effective date.

*B. Availability of Information on Tamper-Resistant Packaging Technologies*

In the preamble to the tamper-resistant packaging and labeling regulations published in the *Federal Register* of November 5, 1982 (47 FR 50444), the agency listed 11 technologies which at that time it considered suitable to meet the intent of the regulations. The agency also stated that the technologies listed were merely intended to be examples, and that the list was not intended to preclude technological innovation that might result in totally different but equally acceptable systems for providing protection to the consumer.

In response to the final tamper-resistant rule, several comments requested that a "new" method of packaging be included in the FDA list of acceptable technologies. In the April 19, 1983 clarifying amendments, the agency discussed these comments but declined to revise the list because the list was not intended to be inclusive. The agency emphasized again that the list of technologies was never intended to be complete, that the agency did not intend that technological innovation be precluded, and that manufacturers and packagers are free to adopt any packaging system, whether or not listed in the preamble to the final rule, if it meets the definition of tamper-resistant packaging provided in the regulations. Further, the agency indicated that the use of a technology listed in the preamble does not, by itself, constitute compliance with the requirement for the use of a tamper-resistant packaging system, because the performance characteristics of some technologies vary widely.

Although the agency has concluded that the list of 11 technologies in the preamble should not be revised, it does recognize that there is a need to make available a document that contains the current agency thinking on acceptable tamper-resistant technologies as well as those technologies for which the agency

has identified a problem. It is important that such information be communicated to FDA investigators as well as to the affected industry. The agency has concluded, therefore, that the most appropriate procedure for communicating this information is to make it a part of the "Tamper-Resistant Packaging Compliance Program," No. 7356.838, originally issued on June 1, 1983. The agency will supplement this compliance program as necessary. Setting forth this information in the compliance program will both disseminate this information to FDA field investigators and, because compliance programs are available under the agency's freedom of information regulations (21 CFR Part 20), provide a mechanism whereby the information will be available to other interested persons. A copy of the Tamper-Resistant Compliance Program and the current supplements will be available for review in the Dockets Management Branch under the docket numbers found in brackets in the heading of this document. Requests for single copies of the Tamper-Resistant Compliance Program or the supplement concerning packaging technologies should be sent to the Dockets Management Branch.

Dated: August 11, 1983.

Joseph P. Hile,  
Associate Commissioner for Regulatory Affairs.

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BILLING CODE 4160-01-M

### Health Care Financing Administration

#### Medicare Program; Exclusion From Medicare Coverage of Certain Food Allergy Tests and Treatments

**AGENCY:** Health Care Financing Administration (HCFA), HHS.

**ACTION:** Proposed notice.

**SUMMARY:** This notice proposes to exclude certain food allergy testing and treatment techniques from Medicare coverage. The procedures that would be excluded from coverage are the cytotoxic leukocyte test, sublingual, intracutaneous and subcutaneous provocative and neutralization testing, and neutralization therapy for food allergies. The Medicare statute and regulations preclude reimbursement for items or services that are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. Available evidence does not show that these tests and therapies for food allergies are safe and effective.

Therefore, we are proposing to exclude these techniques from Medicare coverage and provide a uniform Medicare policy concerning these exclusions.

**DATES:** To assure consideration, comments should be received by September 19, 1983.

**ADDRESSES:** Address comments in writing to: Health Care Financing Administration, U.S. Department of Health and Human Services, Attn: BERC-231-PN, P.O. Box 26676, Baltimore, Maryland 21207.

If you prefer, you may deliver your comments to Room 309-G Hubert H. Humphrey Building, 200 Independence Avenue, SW., Washington, D.C., or to Room 132 East High Rise, 6325 Security Boulevard, Baltimore, Maryland 21207.

Comments will be available for public inspection as they are received, beginning approximately three weeks after publication in Room 309-G of the Department's office at 200 Independence Ave., SW., Washington, D.C. 20201 on Monday through Friday of each week from 8:30 a.m. to 5:00 p.m. (202-245-7890).

Response to comments: Because of the large number of comments we receive, we cannot acknowledge or respond to them individually. However, we will respond to the comments and make any necessary changes to this proposal when we publish the final notice in the *Federal Register*.

**FOR FURTHER INFORMATION CONTACT:** Mary Louise McIntyre, (301) 594-8558.

#### SUPPLEMENTARY INFORMATION:

##### I. Background

The Medicare statute prohibits payment for any expenses incurred for items or services "which are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member" (section 1862(a)(1) of the Social Security Act). HCFA has interpreted this statutory provision to exclude from Medicare coverage medical and health care services and items that are not demonstrated to be safe and effective by acceptable clinical evidence. HCFA's source of medical advice on issues of medical safety and efficacy of services and items is the Public Health Service (PHS).

The National Center for Health Care Technology (NCHCT) in PHS announced in the *Federal Register* on September 23, 1980 (45 FR 63143), that it was evaluating several cytotoxic food testing procedures that are used in the diagnosis and treatment of allergies,

including, among others, the cytotoxic leukocyte test, sublingual, intracutaneous and subcutaneous provocative and neutralization testing, and neutralization therapy for food allergies. The notice invited relevant information from any person or group wishing to respond. The NCHCT also solicited comments from 22 medical associations and societies with an interest in food allergies. On June 16, 1981, the NCHCT provided HCFA with recommendations concerning Medicare coverage policy for the tests specifically mentioned above, based substantially on the information and advice it received in response to its solicitation. The NCHCT recommends that these procedures should not be covered by Medicare because their effectiveness has not been demonstrated by acceptable clinical evidence.

This recommendation is consistent with earlier advice from the PHS, received in February 1978, recommending against coverage of these cytotoxic food tests because of insufficient clinical data to establish their effectiveness. In accordance with that advice, HCFA issued instructions to Medicare contractors in July 1978, withdrawing Medicare coverage from the tests effective August 1, 1978. Those instructions, however, were rescinded in February 1979, retroactive to August 1, 1978, because of objections from some physicians and medical specialty organizations that the PHS recommendation had been based upon commentary from only one side of a controversy, with the other side insufficiently considered. Because it became clear that there was a wide range of conflicting views regarding the efficacy of cytotoxic food testing, the PHS agreed to restudy the evidence concerning these procedures.

## II. Discussion

Medicare has continued to pay for the procedures in question, pending development of additional medical and scientific evidence and new advice from the PHS study. That new information and advice was provided to HCFA in June, 1981, as noted in section I. above. The new information supports the earlier position that the cytotoxic techniques at issue should not be covered under Medicare. The complete NCHCT recommendations, with references to sources in the medical literature, are given in the appendices to this notice.

Since the cytotoxic leukocyte test, sublingual, intracutaneous and subcutaneous provocative and neutralization testing, and neutralization therapy for food allergies are not

established as safe and effective, we propose to exclude them from Medicare coverage under the authority of section 1862(a)(1) of the Social Security Act. Because Medicare has been paying for these procedures and beneficiaries have relied on Medicare payment for them, we would not exclude them until 30 days after the date that the final notice is published. We welcome any public comments that would have an impact on this proposal.

## Cross-References

Part A Intermediary Manual, Chapter II, Coverage of Services Appendix, Coverage Issues section 50-2; Medicare Carriers Manual, Chapter II, Coverage Issues Appendix, section 50-2; Hospital Manual, Coverage Issues Appendix, section 50-2.

## Appendices

I: National Center for Health Care Technology Evaluation of Cytotoxic Leukocyte Test for the Diagnosis of Food Allergy—1981.

II: National Center for Health Care Technology Evaluation of Sublingual Provocative Testing and Neutralization Therapy for Food Allergies—1981.

III: National Center for Health Care Technology Evaluation of Intracutaneous (Intradermal) and Subcutaneous Provocative and Neutralization Testing and Neutralization Therapy for Food Allergies—1981.

(Section 1862(a)(1) of the Social Security Act; 42 U.S.C. 1395y(a)(1))

(Catalog of Federal Domestic Assistance Program No. 13.773, Medicare—Hospital Insurance and No. 13.774, Medicare—Supplementary Medical Insurance)

Dated: August 5, 1983.

Carolyn K. Davis,  
Administrator, Health Care Financing  
Administration.

## Appendix I—National Center for Health Care Technology Evaluation of Cytotoxic Leukocyte Test for the Diagnosis of Food Allergy; 1981

### Description

The cytotoxic leukocyte test was first described by Black as an *in vitro* method for diagnosing allergy to food, pollen, epidermal and inhalant allergens (Black, 1956). The test was based on the earlier findings of Squier and Lee that ragweed antigen caused lysis of sensitized polymorphonuclear leukocytes (Squier and Lee, 1947). Bryan and Bryan modified the technique and advocated its use in diagnosing food allergies (Bryan and Bryan, 1960; Bryan and Bryan, 1967; and Bryan and Bryan, 1969).

The procedure involves the slow centrifugation (1½ hours) of citrated venous blood to produce a buffy coat of leukocytes and platelets. The buffy coat is mixed with

serum and water and exposed to food antigens on silicated microscope slides. Control slides of the cell mixture without antigens are made at the same time. A 60X high dry objective lens is recommended for observing the reactions which consist of rouleaux formation by erythrocytes, platelet agglutination, and loss of pseudopods with streaming of cytoplasmic granules by the neutrophilic leukocytes. In marked reactions, the leukocytes disintegrate. The leukocyte reactions are the easiest to evaluate and the cytotoxic test is based on them. If there is no reaction after two hours, the test is considered negative. The food antigens used are the partially purified food extracts from commercial laboratories used in skin tests (Bryan and Bryan, 1967). The test is used as a screening procedure for patients with suspected food allergies and as many as 70 potential allergens can be screened with this method (Ulett and Perry, 1974).

## Rationale

The cytotoxic leukocyte test is based upon the observed toxic effects of antigen-antibody reactions on the polymorphonuclear leukocytes (Bryan and Bryan, 1960). This appears to be a multifaceted process which is effected by unknown factors (Holopainen, et al., 1980). The immunologic mechanism of this effect and its relationship to food allergies remains unclear (Benson and Arkins, 1976; and Breneman, 1978).

## Review of Available Information

There has been some controversy about using the cytotoxic leukocyte test as a screening and diagnostic test for food allergies. Its reliability, validity, and reproducibility have been questioned (Lieberman, et al., 1975; Golbert, 1975; and Holopainen, et al., 1980). Following Squier and Lee's report of *in vitro* lysis of sensitized leukocytes by ragweed antigen (Squier and Lee, 1947), Franklin and Lowell were unable to reproduce this observation and were unable to account for the discrepancy (Franklin and Lowell, 1949). When Black described his new test for diagnosing allergic diseases, he presented 10 case reports but provided no clinical correlations for the test results (Black, 1956). Chambers, Hudson, and Glaser tried to validate Black's method testing 13 children (aged 1½ to 11 years) with "clear-cut clinical sensitivities to foods, animal danders, or pollen and who had not received hyposensitization injections." They found the test clearly identified only 1 of 24 known patient sensitivities (4 percent) and 4 patient sensitivities were completely missed (17 percent). Definite interpretation could not be made in approximately 70 percent of the tests and there was agreement between independent observers on only two thirds of the tests. They concluded that the test was time consuming and its validity was seriously questioned (Chambers, et al., 1958).

Bryan and Bryan modified Black's technique by using silicated glassware and used the test to diagnose food allergies in 107 patients aged 9 to 80. They reported improvement in 80 percent of symptoms after elimination of the reacting food but provided no criteria for measuring these outcomes. They found some false positive reactions and

some errors possibly due to faults in the technique (Bryan and Bryan, 1980).

This report was followed by subsequent reports of the Bryans (Bryan and Bryan, 1967; Bryan and Bryan, 1969; and Bryan and Bryan, 1971) but not controlled clinical trials were reported. In 1972, Lowell and Heiner asserted that the validity of the cytotoxic leukocyte test had not been proven and called for double-blind evaluations of the procedure (Lowell and Heiner, 1972). Randolph reported on the findings of an unpublished pilot study of 50 patients and stated that the cytotoxic tests did not correlate well with results of his comprehensive environmental control program (Randolph, 1974).

Ulett and Perry found the cytotoxic leukocyte test to be an efficient, reproducible, and reliable method for screening individuals for sensitivity to a large number of foods. They observed a near perfect correlation of this test with the *in vivo* leukocytosis response following consumption of sensitizing foods but concluded that the method needed further study (Ulett and Perry, 1974). In another report, they again found an excellent agreement between these two methods especially when the cytotoxic tests were done near the time of maximum leukocytosis to avoid false negative cytotoxic tests (Ulett and Perry, 1975).

The first report of a controlled, blinded clinical trial of the cytotoxic test appeared in 1975. Using the Bryan's method, 45 volunteers aged 4 to 45 years old were tested for 50 food allergies and divided in to 3 groups: 20 with no history of food allergy or other complaints; 15 atopic individuals with well-documented allergic reactions to foods; and 10 with less well-documented untoward reactions to food such as headache, fatigue, dyspnea, maculopopular rash, nasal congestion, and diarrhea (non-atopic group). The interpretation of the tests was found to be highly subjective with very little inter- and intra-observer concordance. The test had little sensitivity in the evaluation of the atopic group (73 percent false negatives) and non-atopic group (80 percent false negatives). It also lacked specificity with all 15 atopic patients having false positive tests to an average of 5.5 foods (with a range of 1 to 11) (Lieberman, et al., 1975).

Another study evaluated the cytotoxic test for diagnosing food allergy in a double blind fashion. Nine atopic patients and five controls (with no history of food allergy) were tested 6 times by one examiner for each of 10 food antigens. The atopic group had 73 percent reproducible results (at least 5 out of 6 test gave the same result) and the controls had 68 percent. Considering only these reproducible results, the atopic group had an incidence of 70 percent false positives and the controls had 57 percent. Two of the nine atopic patients had reproducible, false negative tests (Benson and Arkins, 1976).

An uncontrolled, unblinded evaluation of the cytotoxic food test by patient questionnaire led Boyles to conclude that his results "unequivocally" validated the use of cytotoxic food tests as a clinical tool. "Approximately" 50 percent of the study group (N=239) attended a two hour lecture program on food allergy and dietary therapy. 118 (49 percent) of the questionnaires were

returned. The return rate was 65 percent for those who attended the lecture and 38 percent for those who did not. No clinical information or objective evaluation of improvement was provided (Boyles, 1977).

In an uncontrolled, unblinded study comparing cytotoxic food testing with intracutaneous food allergy testing, 300 patients with presumed food allergies were screened for 34 foods. 6,967 (88.3 percent) of the cytotoxic tests were interpreted as positive for food allergy. 5,119 (73.5 percent) cytotoxic test positives were retested using intracutaneous serial dilution titration testing and intracutaneous provocation testing. 5,110 (99.8 percent) of them had positive serial dilution titration tests and 2,918 (57 percent) had positive provocation tests. 693 (21.5 percent) of negative cytotoxic tests were rechecked with these tests because of a suspicion of false negativity based on dietary history or other factors. 669 (96.4 percent) and 374 (54 percent) of these had positive tests on serial dilution titration and provocation, respectively. Additional negative cytotoxic reactors were rechecked in a similar manner with similar results. The author concluded that no correlation existed between the cytotoxic test and either of these intracutaneous testing methods and that cytotoxic screening was valueless (King, 1978).

A recent study of the reliability and reproducibility of the cytotoxic leukocyte test revealed 78 percent interobserver agreement on 1,127 tests. Intraobserver agreement on reading the same tests over three consecutive days was found to be about 81 percent. The authors concluded that the cytotoxic leukocyte test is reproducible, provided the technicians are properly trained; however, they felt the significance of this test in the diagnosis of food allergies is yet to be elucidated (Holopainen, et al., 1980).

Lehman also found the cytotoxic test to be reproducible, but, because the results fluctuated extensively from day to day and from week to week, he felt the test should be regarded as useless in the diagnosis of food allergies. He found elimination diets and sublingual food drop therapy had no apparent influence on the cytotoxic test results. He concluded that elimination—rechallenge diets and observation of patient symptoms remains the standard and most reliable means of testing for food allergies (Lehman, 1980).

#### Discussion

The cytotoxic leukocyte test for food allergy screening and diagnosing lacks an acceptable rationale based on current knowledge of allergy and immunology. While the procedure may yield reproducible results, the validity of these results has not been supported in controlled, double blind studies and there is a lack of correlation with clinical evidence of food allergy. The test is plagued with a large number of false negative and false positive results indicating that it lacks specificity and sensitivity. The test is time-consuming, requires well-trained and supervised technicians, and is dependent on subjective interpretation.

However, the cytotoxic leukocyte test has been incorporated into the medical practice of many otolaryngologic allergists, clinical

ecologists, and others. A wide variety of medical specialty societies and associations were contacted for assistance with this evaluation. The American Council of Otolaryngology—Head and Neck Surgery and the American Society of Ophthalmologic and Otolaryngologic Allergy (ASOOA) suggested that the test may have some value. ASOOA did not, however, recommend it as a primary testing technique at this time. Individual members of the Pan-American Allergy Society and the Society for Clinical Ecology expressed opinions about this test and some use and endorse it. The American Osteopathic College of Allergy and Immunology said the cytotoxic test is of some benefit but not highly accurate. The American Academy of Allergy, the American College of Allergists, the American College of Physicians, the Federation of American Societies for Experimental Biology, and the Council of Medical Specialty Societies all found the cytotoxic leukocyte test to be lacking scientific evidence of effectiveness in diagnosing food allergies and that this test should be considered experimental.

#### Summary

The cytotoxic leukocyte test for diagnosing food allergies lacks an acceptable scientific rationale, lacks specificity and sensitivity, and lacks evidence of clinical effectiveness. It is a time consuming, highly technical test which is dependent on subjective interpretation. The cytotoxic leukocyte test should be considered experimental at this time.

#### Acknowledgement

This assessment is based on a search of the medical literature with assistance from the Food and Drug Administration and the National Institute of Allergy and Infectious Diseases (National Institutes of Health). The American Academy of Allergy, the American Academy of Dermatology, the American College of Allergists, the American College of Physicians, the American Council of Otolaryngology-Head and Neck Surgery, the American Osteopathic College of Allergy and Immunology, the American Society of Ophthalmologic and Otolaryngologic Allergy, the Federation of American Specialty Societies for Experimental Biology, the Joint Council of Allergy and Immunology, the Pan American Allergy Society, and the Society for Clinical Ecology provided assistance with this evaluation either directly or through their members. This assessment is based on information available at this time. It will be revised, as appropriate, when additional information warrants a revision.

Anyone wishing to submit additional information regarding this evaluation should contact: Director, Office of Health Technology Assessments, Room 310, Park Building, 12420 Parklawn Drive, Rockville, Maryland 20857, (301) 443-4990.

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Ulett, G. A., and Perry, S. G. Cytotoxic Testing and Leukocyte Increase as an Index to Food Sensitivity II. Coffee and Tobacco. *Annals of Allergy*. 1975; 34:150-60.

## Appendix II—National Center for Health Care Technology, Evaluation of Sublingual Provocative Testing and Neutralization Therapy for Food Allergies; 1981

### Description

Sublingual provocative testing for food allergies consists of administering diluted food antigens sublingually and observing the patient for clinical symptoms over a period of 10 to 20 minutes. If no symptoms develop, another food antigen may be tested. If a food antigen provokes a reaction, a more dilute solution of the same antigen is applied sublingually in an attempt to "neutralize" these symptoms. If the offending food(s) can not be easily eliminated from the patients diet, neutralizing drops (of the same dilution which neutralized the provoked symptoms) can be prescribed for the patient to take regularly before or after a meal which includes the offending food(s) thereby avoiding or relieving the food allergy symptoms (Morris, 1969).

### Rationale

The sublingual route of absorption has been used for over a century as a rapid and effective route of absorption of medications, most notable of which is nitroglycerine for angina pectoris. This route provides an access to the systemic venous circulation that bypasses the portal circulation avoiding modifications due to digestion and hepatic transformation (Dickey, 1978). Hansel was the first to suggest the sublingual route for administering antigens (Hansel, 1953). Dickey and Pfeiffer modified Rinkle and Lee's intradermal method of provocative testing for allergy by administering the extracts sublingually (Dickey and Pfeiffer, 1964).

It has been suggested that the provocative reaction is an anaphylactic end-organ reaction produced by substances (proteoses, peptones, and others) that somehow bypass the usual protective mechanisms of the gastrointestinal tract and liver and that lymphocytes are necessary to continue the reaction. The neutralization of the reaction by a weaker concentration of the antigen has been theorized to be a modification or inactivation of the lymphocytes by the smaller amount of antigen (Morris, 1969).

### Review of Available Information

There have been a number of positive anecdotal reports of the clinical application of sublingual provocative testing and neutralization therapy for food allergy over the past two decades; however, there have been no well controlled studies which have demonstrated the safety and effectiveness of these technologies. Despite a lack of supportive evidence from well designed studies, these procedures have been adopted and have become widely practiced by otolaryngologic allergists, clinical ecologists, and others.

Kailin and Collier reported on a double-blind study of the neutralizing dose method of therapy for food and pollen allergies. They allowed five physicians with a minimum of seven years of experience using provocative and neutralization techniques to select patients previously tested and known to react to allergenic extracts. The neutralizing treatments were applied sublingually or

intracutaneously using either an actual extract identified as an allergen for the patient by prior provocative testing or a saline placebo. In 24 of 34 trials (70.6 percent), the actual active extract was correctly identified by symptom relief, but in 28 of 40 trials (70 percent), saline was also judged to be an active extract by symptom relief. The authors concluded that there was no discrimination between the active extract and saline and that the neutralizing dose was not related to the allergen content of the dose (Kailin and Collier 1971).

In 1974, the Food Allergy Committee of the American College of Allergists reported on a two year, nationwide double-blind, cross-over study of the sublingual provocative testing method for diagnosing food allergy. 61 patients and 732 tests were analyzed in 1973 and 20 patients and 240 tests were analyzed in 1974. The extracts used in 1974 were four times more concentrated than those used in 1973, but there was no change in the percentage of positive reactions (30.6 vs. 30.8 percent). No significant statistical deviation from chance expectation of the number of subjective and objective positive tests was found. The committee concluded that the test does not discriminate between control and food extracts; the four fold increase in extract concentration between 1973 and 1974 had no effect; the test is neither reliable nor sensitive; there is no statistical evidence of validity of the tests; and the sublingual provocative test is not a satisfactory method of diagnosis of food allergy (Breneman, et al, 1974).

Hosen compared sublingual provocative testing with therapeutic fasting and subsequent challenge feedings in a controlled but non-blinded study of 126 patients. He observed that the correlation of these two testing methods ranged from 0 to 100 percent and that the average diagnostic efficiency of sublingual testing after therapeutic fasting was 49 percent. He found therapeutic fasting followed by food challenge the most efficient method of diagnosing food allergy (Hosen, 1976).

Rapp reported one case of milk sensitivity that was repeatedly demonstrated by non-blind and double-blind dietary challenges and successfully treated with sublingual milk therapy (Rapp, 1978).

Recently, Lehman reported on a double-blind study of sublingual provocative food testing in 15 patients with food allergies. Positive reactions were observed as frequently when a placebo was given as when sublingual food drops were given; therefore, the test did not differentiate between placebo and food drops. He considered the test to be unreliable for the diagnosis of food allergy (Lehman, 1980 a and b).

### Discussion

Sublingual provocative testing and neutralization therapy for food allergy have been sources of controversy among various groups of allergists.

Advantages of sublingual therapy have been suggested by proponents to include:

1. Sublingual drops obviate the need for repeated injections;

2. Patients can self-administer the drops;  
3. Continuity of treatment may be enhanced by patient willingness to take the drops;

4. Lower total dosage of antigen seems to be needed; and,

5. Adverse hypersensitivity reactions are apparently rare (Baker, 1976).

However, none of the controlled, double-blind clinical trials have shown sublingual provocative testing and neutralization therapy to be effective for diagnosing and treating food allergies. Therefore, despite widespread clinical application, these methods should be considered experimental.

The rationale for sublingual provocative testing and neutralization therapy has been questioned. From what is currently known of the time sequence of verified immunological events, there is no basis to support an immunologic therapeutic response from the neutralizing dose of an allergenic food extract applied sublingually (communication to the National Center for Health Care Technology from the American Academy of Allergy, 1980).

#### Summary

Sublingual provocative testing and neutralization therapy for food allergy are widely used but lack scientific evidence of effectiveness. No known immunologic mechanism can account for the neutralization of provoked symptoms by dilute solutions of food antigens. Sublingual provocative testing and neutralization therapy for food allergy should be considered experimental at this time.

#### Acknowledgement

This assessment is based on a search of the medical literature with assistance from the Food and Drug Administration and the National Institute of Allergy and Infectious Diseases (National Institutes of Health). The American Academy of Allergy, the American Academy of Dermatology, the American College of Allergists, the American College of Physicians, the American Council of Otolaryngology—Head and Neck Surgery, the American Osteopathic College of Allergy and Immunology, the American Society of Ophthalmologic and Otolaryngologic Allergy, the Federation of American Specialty Societies for Experimental Biology, the Joint Council of Allergy and Immunology, the Pan American Allergy Society, and the Society for Clinical Ecology provided assistance with the evaluation either directly or through their members. This assessment is based on information available at this time. It will be revised, as appropriate, when additional information warrants a revision.

Anyone wishing to submit additional information regarding this evaluation should contact: Director, Office of Health Technology Assessments, Room 310, Park Building, 12420 Parklawn Drive, Rockville, Maryland 20857, (301) 443-4990.

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Rapp, D. J. Double-blind Confirmation and Treatment of Milk Sensitivity. *The Medical Journal of Australia*. 1978; 1:571-2.

#### Appendix III—National Center for Health Care Technology, Evaluation of Intracutaneous (Intradermal) and Subcutaneous Provocative and Neutralization Testing and Neutralization Therapy for Food Allergies; 1981

##### Description

Intracutaneous and subcutaneous provocative and neutralization testing and neutralization therapy for food allergies are adaptations of the serial dilution titration technique used in inhalant allergies. As originally described by Lee and Rinkel, the procedure involves intracutaneous injections of 0.05 cc of a 1:5 dilution of an extract concentrate of a suspected food into two separate sites above the elbow on the lateral side of the arm. The patient is observed for allergic signs and symptoms resembling his or her original complaint(s), usually to a lesser degree than when challenged directly with the food by oral feeding. The types of symptoms provoked include: headache; nasal symptoms; chest symptoms (coughing, wheezing, dyspnea, etc.); ear reactions (blocking and itching); gastrointestinal reactions; skin eruption or itching; and general symptoms (fatigue, chilling, muscle pain, and drowsiness) (Rinkel, et al., 1964). Miller gave a more extensive list of symptoms (Miller, 1972).

If there is no change in the symptom pattern or no symptoms are induced after ten minutes, 0.02 cc of a 1:125 dilution of the extract is injected and the patient is observed again. As soon as symptoms are provoked, one attempts to neutralize the reaction with weaker dilutions of the same antigen. Lee and Rinkel recommended starting with 0.01 cc of a 1:1,953,125 (5<sup>6</sup>) dilution and observing the patient for ten minutes. If there is no

change in symptoms, the dose is considered ineffectual and stronger dilutions are applied until the symptoms are relieved. If the 1:1,953,125 dilution provoked an increase in symptoms, they recommended trying a 1:48,828,125 (5<sup>11</sup>) dilution and then proceeding with increasingly stronger dilutions until the symptoms are relieved. The dilution which provides relief of the symptoms is called the "neutralizing dose." When the symptoms provoked by one food are neutralized, other suspected foods can be tested in a like manner (Lee, 1961; Lee and Rinkel, 1962; and Rinkel, et al., 1964).

Subsequently the procedure has undergone some modifications and has been adapted to screening and treatment as well as diagnosis. Some advocate the subcutaneous route of administering the test doses and there have been variations in the volume of the injections from 0.01 to 0.02 cc (Williams, 1965). As a screening test for food allergies, 0.01 cc of 1:500 dilutions of extracts of each of four suspected foods are injected intracutaneously simultaneously. If no symptoms are provoked, another battery of four foods is tested. If symptoms are provoked, provocative testing of the four antigens (one at a time) is recommended (Lee, et al., 1969).

Neutralization therapy for food allergies involves regular intracutaneous injections of the "neutralizing dose" either before or after meals containing the offensive food(s). These injections are usually given twice weekly but the frequency can vary from daily to once weekly. After a period of time, tolerance to the particular food(s) may develop and the injections will no longer be needed (Lee, et al., 1969). Some recommend the subcutaneous route to administer the neutralizing doses (Miller, 1972). Another variation is the use of the sublingual route for testing and therapy which is the subject of a separate evaluation.

Whealing of the skin at the injection sites was initially dismissed as an objective sign of food allergy because of very high rates of false positive (60 percent) and false negative (80 percent) results when compared to the allergy history (Willoughby, 1965). Others advocate observation and measurement of the wheal for additional guidance as to whether one needs to go to a stronger or weaker dilution of the food extract (Lee, et al., 1969; and Miller, 1972).

##### Rationale

It has been suggested that the provocative reaction is an anaphylactic end-organ reaction produced by substances (proteoses, peptones, and others) that somehow bypass the usual protective mechanisms of the gastrointestinal tract and liver and that lymphocytes are necessary to continue the reaction. The neutralization of the reaction by a weaker concentration of the antigen has been theorized to be a modification or inactivation of the lymphocytes by the smaller amount of antigen (Morris, 1969).

##### Review of Available Information

Following the initial description of the technique, intracutaneous provocative testing and neutralization therapy for food allergies became widely practiced by otolaryngologic allergists, clinical ecologists, and others

before their safety and clinical effectiveness had been demonstrated by well designed clinical trials.

Rinkel, et al., presented a table which compared skin tests, deliberate feeding tests, and the provocative food test; however, it is impossible to discern any correlation (or lack thereof) between the three methods because the data was aggregated by food and no patient specific test results were given. They went on to report that all patients reacting to the deliberate feeding test (the number of patients was not given) were subjected to the provocative test and that they found no discrepancy between the two tests (Rinkel, et al., 1964).

Willoughby reported that the intracutaneous provocative test was 85 percent accurate for incriminating specific food sensitivities on routine screening but he presented no data on which to base this statement. He also reported on the relative safety of the procedure having observed no fatal anaphylactic reactions after approximately 200,000 tests (Willoughby, 1965).

Bronsky, et al., reported in abstract on an evaluation of the provocation-neutralization skin test technique employing 20 children hospitalized for intractable asthma with a history of food allergy. They found significant fluctuations of the pulse and white blood cells to a comparable extent in both the control and test periods. They found the provoked subjective symptoms to be infrequent and these symptoms fluctuated spontaneously or could not be neutralized. They concluded that the validity of the provocation-neutralization technique was not established by their study (Bronsky, et al., 1971).

Kailin and Collier briefly reported on a double-blind study of the neutralizing dose method of therapy for food and pollen allergies. They allowed five physicians with a minimum of seven years of experience using provocative and neutralization techniques to select patients previously tested and known to react to allergenic extracts. The neutralizing treatments were applied sublingually or intracutaneously (treatment wheals were covered immediately) using either an actual extract identified as an allergen for the patient by prior provocative testing or a saline placebo. In 24 of 34 trials (70.6 percent), the actual active extract was correctly identified by symptom relief, but in 28 of 40 trials (70 percent), saline was also judged to be an active extract by symptom relief. The authors concluded that there was no discrimination between the active extract and saline and that the neutralizing dose was not related to the allergen content of the dose (Kailin and Collier, 1971).

Draper compared the intradermal provocative test to the deliberate feeding test for diagnosing food allergy in 121 patients. A total of 1,500 provocative tests were performed yielding 264 (17.6 percent) positives (some patients reacted to more than one food). One hundred ninety-three of these positives were checked with deliberate feeding tests and 120 (62.2 percent) of these were positive. He concluded that because of the high false positive rate (37.8 percent) the intradermal provocative test could not be

relied solely upon for diagnosing food allergy and questioned the accuracy of negative in intradermal tests as well (Draper, 1972).

In 1973, the Ad Hoc Committee on Provocative Food Testing of the American College of Allergists reported on their findings of a double blind crossover study of subcutaneous provocative food testing of 70 patients with and without history of food allergy. They concluded that subcutaneous provocative food testing was unquestionably able to provoke symptoms in some patients by some unknown mechanism; however, the test was not reproducible and could not be recommended as a valid procedure because positive responses were not reliable and negative responses were not predictive of feeding test results. Correlation of responses to the subcutaneous provocative test and the feeding test yielded a phi coefficient of 0.15 (not significant) (Caplin, 1973).

In 1976, the Food Committee of the American Academy of Allergy presented in an abstract the results of its double-blind study of subcutaneous food testing.

Sixty-one patients were subjected to two series of subcutaneous injections of five food antigens and two blanks yielding 110 positive tests on the first trial. Only 41 tests were concordantly positive on the second trial and concordance patterns for food tests and controls were similar. They found the subcutaneous provocative food test to be both a poor positive and poor negative predictor and that they were unable to confirm its reproducibility and validity (Crawford, et al., 1976).

Miller presented a preliminary report on a double-blind, crossover study of food extract injection therapy (subcutaneous neutralization therapy) using eight patients selected for having symptoms and syndromes of food sensitivity and having responded well to food injection therapy. He developed a symptom improvement scoring system with five discrete gradations of improvement from "0" (baseline level of symptom) through "4+" (complete relief of symptoms). The symptoms evaluated were wide ranging and varied from patient to patient. They included headache, vertigo, tinnitus, nausea, abdominal cramps, depression, hyperactivity, insomnia, shiners, frequent urination, day wetting, enuresis, photophobia, acne (adult), diarrhea, aphthous stomatitis, syncope, laryngeal edema, flatulence, eczema, urticaria, nasal congestion, eustachian tube blockage, eye itching, paroxysmal nocturnal dyspnea, irritability-fatigue, hemorrhagic proctitis, perennial allergic rhinitis (food caused), and asthma. The relative advantage of the active treatment over the placebo ranged from 0.44 to 2.41 (mean 1.33) using this symptom improvement scoring system. This advantage of the active treatment over the placebo was found to be significant at the 99.8 per cent level of confidence by paired comparison t test (Miller, 1977).

King compared the *in vitro* cytotoxic food allergy testing with serial dilution titration and intracutaneous provocative food allergy testing in 300 consecutive food allergy patients. The study was not designed to evaluate the validity of any of the procedures; however, some of the findings are of interest for this evaluation. Of the 5,119

positive cytotoxic test results which were retested, 5,110 (9.8 percent) were concordantly positive with serial dilution titration, and only 2,918 (57.0 percent) were concordantly positive with intracutaneous provocative testing. Of the 693 negative cytotoxic test results which were similarly rechecked (because of a suspicion of false negativity based on food allergy history or other tests), 689 (96.4 percent) and 374 (54.0 percent) were discordantly positive on retesting with serial dilution titration and intracutaneous provocative testing, respectively. Because of this discrepancy, further comparisons were made utilizing 30 patients who were retested to 230 foods. One hundred twenty-six of 129 (97.7 percent) positive cytotoxic tests were concordantly positive on retesting with serial dilution titration and 90 (69.8 percent) on retesting with intracutaneous provocative testing. Ninety-three (92.1 percent) and 58 (57.4 percent) of 101 negative cytotoxic tests were discordantly positive on retesting with serial dilution titration and intracutaneous provocative testing, respectively. The author concluded that no correlation existed between these food allergy testing techniques (King, 1978).

#### Discussion

Intracutaneous and subcutaneous provocative testing and neutralization therapy for food allergy have been sources of controversy among various groups of allergists.

Advantages of these procedures in diagnosing and treating food allergies have been suggested by proponents to include:

1. Serial titration and symptom provocation testing are combined and compliment each other by providing a double end point involving both wheals (objective) and symptoms (subjective), each confirming the other;

2. Neutralization provides rapid symptom relief (within minutes); and,

3. Neutralization therapy is the only treatment of food allergies which allows the patient to eat most or all of his or her allergenic foods without symptoms (Miller, 1978).

These procedures seem to be relatively safe. To our knowledge, no serious complications (such as fatal anaphylaxis) have been reported. Rinkel, et al., reported no violent reactions and only 12 reactions which required medication for relief of induced symptoms (Rinkel, et al., 1964).

The clinical effectiveness of these procedures has not been conclusively demonstrated. The only double-blind, crossover study (Miller, 1977) which supported the validity of these procedures relied on a symptom scoring system of questioned validity. The wide variety of symptoms attributed to food allergies in the eight patients studied seems implausible and, therefore, the subsequent statistical analysis of the improvement in these symptoms is open to criticism. Several other double blind studies of these procedures have found them to lack accuracy, reproducibility, and validity for the diagnosis and treatment of food allergies.

The rationale for intracutaneous and subcutaneous provocative and neutralization testing and neutralization therapy for food allergies has been questioned. From what is currently known of the time sequence of verified immunological events, there is no basis to support an immunologic therapeutic response from the neutralizing dose of an allergenic food extract applied intracutaneously or subcutaneously. (Communication to the National Center for Health Care Technology from the American Academy of Allergy, 1960).

#### Summary

Intracutaneous and subcutaneous provocative and neutralization testing and neutralization therapy for food allergies are widely used but lack scientific evidence of effectiveness. No known immunologic mechanism can account for the neutralization of provoked symptoms by dilute solutions of food antigens. Intracutaneous and subcutaneous provocative and neutralization testing and neutralization therapy for food allergies should be considered experimental at this time.

#### Acknowledgement

This assessment is based on a search of the medical literature with assistance from the Food and Drug Administration and the National Institute of Allergy and Infectious Diseases (National Institutes of Health). The American Academy of Allergy, the American Academy of Dermatology, the American College of Allergists, the American College of Physicians, the American Council of Otolaryngology-Head and Neck Surgery, the American Osteopathic College of Allergy and Immunology, the American Society of Ophthalmologic and Otolaryngologic Allergy, the Federation of American Specialty Societies for Experimental Biology, the Joint Council of Allergy and Immunology, the Pan American Allergy Society, and the Society for Clinical Ecology provided assistance with this evaluation either directly or through their members. This assessment is based on information available at this time. It will be revised, as appropriate, when additional information warrants a revision.

Anyone wishing to submit additional information regarding this evaluation should contact: Director, Office of Health Technology Assessments, Room 310, Park Building, 12420 Parklawn, Drive, Rockville, Maryland 20857, (301) 443-4990.

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#### Office of Human Development Services

#### Federal Council on the Aging; Meeting

Agency holding the meeting: Federal Council on the Aging.

Time and date: Meeting begins at 9:30 AM on Wednesday, September 14, 1983 and ends at 3:00 PM on Thursday, September 15, 1983.

Place: Room 800 (top floor), Hubert H. Humphrey (HHH) Building, 200 Independence Avenue, SW, Washington, DC 20201 on September 14 from 9:30 AM-5:00 PM; Room 405A, HHH Building, September 15 from 9:00 AM-3:00 PM.

Status: Meeting is open to the public. Contact person; Rita Lowry, Room 309D, HHH Building, 245-2451.

The Federal Council on the Aging was established by the 1973 Amendments to the Older Americans Act of 1965 (Pub. L. 93-29, 42 U.S.C. 3015) for the purpose of advising the President, the Secretary of Health and Human Services, the Commissioner on Aging and the

Congress on matters relating to the special needs of older Americans.

Notice is hereby given pursuant to the Federal Advisory Committee Act (Pub. L. 92-453, 5 U.S.C. App. 1, Sec. 10, 1976) that the Council will hold a meeting September 14 and 15, 1983, from (9:30 AM to 5:30 PM and from 9:00 AM to 3:00 PM respectively in Room 800 (September 14) and Room 405A (September 15) of the Hubert H. Humphrey Building, 200 Independence Avenue, SW, Washington, DC 20201.

The agenda will include a fact-finding session on the impact of proposed legislation on elderly homeowners and investors regarding tax laws on the sale/leaseback home equity conversion mechanism by a panel of experts and subsequent discussion. This fact-finding session will take place on September 14 from 9:30 AM-12:30 PM. A substantial amount of time has also been set aside for FCA committee discussions on the afternoon of September 14 and on September 15.

Dated: August 16, 1983.

Adelaide Attard,  
Chairperson, Federal Council on the Aging.

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#### Social Security Administration

#### Proposed Availability of Funding for Mainstream English Language Training Projects for Refugees

AGENCY: Office of Refugee Resettlement (ORR), SSA, HHS.

ACTION: Notice of availability of funding for Mainstream English Language Training Demonstration Projects for Refugees.

SUMMARY: This announcement governs the award of social service grants to state and local governments, public and private non-profit agencies, or any combination thereof, which are currently providing and/or coordinating refugee English language training programs. Grants will be awarded for the implementation of Mainstream English Language Training (MELT) demonstration projects designed to test, refine, and validate (1) the proposed set of ESL student performance levels and test instruments, and (2) a proposed core curriculum for domestic refugee English language training programs. The expected results of these grants will be the identification of program elements (with respect to assessment, placement, curriculum and program design) standards necessary for the establishment of domestic adult refugee