Letters to the editor

ALLERGY DIAGNOSIS

To the Editor:

We here wish to clarify some points made by William K. Dolen in his interesting Guest Editorial[1] in which he discussed our paper.[2] We agree that the measurement of specific IgE is not an alternative to a clinical history and physical examination of patients, but it is complementary to these procedures. Nor did we suggest IgE measurement as a screening method for allergic diseases. Our aim was to evaluate the clinical usefulness of in vitro and in vivo testing in an innovative way, in the search for a new gold standard, by utilizing both techniques and the expertise of well-trained and experienced clinicians in our Department. As Dolen himself states, we cannot claim that the skin prick test is a definitive tool for establishing a diagnosis.

Other authors[3,4] have attempted to define a new gold standard and have proposed the concordance between the clinical history and the skin prick test. They have reported a clinical efficiency of over 95% with the Pharmacia CAP System. This percentage is greater than the 70% to 80% found when comparing Pharmacia CAP System with prick testing, and this discrepancy may depend on the fact that some skin prick negative/CAP positive patients are not, as observed by Kelso,[5] "false positives," but "true positives," as already demonstrated by Leimgruber with the CRIE technique.[6] To our knowledge, no study has compared the skin prick test with a positive history and in vitro results.

Another point made by Dolen is that there is a lack of standardization in skin prick tests. He has well demonstrated the difference between the extract potency of allergens used in the USA and those of allergens used in European countries. There are few data on the reproducibility and accuracy of in vivo tests while extensive intra- and inter-laboratory quality assurance schemes have been applied on "second generation" in vitro tests, namely the Pharmacia CAP System. Regarding the possible bias in our study, supposedly caused by the enrollment procedure used, our patients and controls were referred consecutively to our outpatient clinic without an "a priori" diagnosis of allergy. The choice of allergens to be tested was suggested by anamnestic data, and we stress that many of our "negative" results were obtained in the sera of symptomatic patients.

We agree, however, that our study has an inherent limitation in that it was performed over a short period of time in a confined geographic area (Northeast Italy). We are now conducting further studies searching for decisional levels and a more reliable threshold for in vitro testing by using receiver operating curve (ROC) analysis.

We, moreover, stress that the comparison of in vitro against in vivo results is not an effective goal since neither technique has a 100% clinical efficiency. Nor, in our experience, is there a statistically significant difference between them.

According to the position statement approved by the Executive Committee of the American Academy of Allergy and Immunology,[7] in vitro techniques are recommended in selected groups of patients (those with extensive dermatitis or dermographism, who cannot be withdrawn from medications that interfere with proper skin testing, and occasionally, patients who otherwise refuse skin testing). It is inconceivable that these in vitro techniques should be considered as having lower clinical efficiency than in vivo tests. We believe that this misconception depends on the fact that most of studies in the literature are based on the "first generation" in vitro test, the so-called RAST. Finally, we should devote our efforts to enhancing cooperation between clinic and laboratory, as this is the key to better understanding of diagnostic testing in allergic diseases.

MARIO PLEBANI
FRANCO BORGHESAN
DIEGO FAGGIAN
Department of Laboratory Medicine
University-Hospital, 35128 Padova
Italy

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Response:

In our busy academic allergy-immunology practice at the Medical College of Georgia, diagnostic allergy testing is considered a laboratory service, with the skin testing laboratory, allergen extract laboratory, and clinical laboratory working together with faculty, fellows (in allergy-immunology and clinical laboratory immunology), residents, medical students, nurses, and others in the evaluation of patients. All faculty and fellows are directly involved in the evaluation and management of patients.

We agree that studies performed with "first generation" in vitro test methods should not define the present state of the art. Based on a detailed analysis of results of both European and American studies, we chose the Pharmacia CAP System (PCS) as the method to be used for specific IgE measurement in our laboratory. The laboratory is certified by the College of American Pathologists (CAP) and has performed consistently well in the CAP Diagnostic Allergy Survey. While all allergy-immunology physicians order in vitro tests, the PCS has not replaced skin testing in our laboratory for several reasons:

1. No comparative study of skin testing and the PCS performed in the patient population of an allergy-immunology practice in the United States has demonstrated that the PCS has equivalent or better sensitivity in the detection of allergen specific IgE.
2. In our practice setting, a skin test costs substantially less (as billed to a patient or insurance company) than an in vitro test. Although we are an academic practice, we are and have been concerned about cost effective care.
3. In some allergy practices, the initial history and examination are performed in one visit, with testing and a summary conference at another visit. Because many of our patients drive several hours for outpatient visits, we try to do a complete workup in one morning or afternoon; having results of skin tests available within a few minutes is an important advantage.

For dermographic patients, we employ Pepys' modified prick skin test, which can produce clearly negative test sites when carefully performed. We have only rarely encountered a patient who refuses skin testing. The most common reasons for ordering in vitro tests (as an alternative to skin tests) are:

1. Patient taking a beta blocker that can't be withdrawn.
2. Need for testing with a substance not available as an allergen extract for skin testing.
3. History of marked sensitization or anaphylaxis. Titrated skin testing (as is routinely done with insect venoms) is a clear alternative, however.
4. A patient who is taking an antihistamine at the first visit and needs only limited testing.
5. Extensive dermatitis that can't readily be cleared. In our experience, this is uncommon.
6. In a patient with a convincing history of sensitization, a skin test result that is negative or equivocal. In nearly all comparison studies, there has been an occasional clearly positive in vitro test in the light of a clearly negative skin test.

Allergy-immunology practice standards in the United States differ from those in other countries. There is considerable disagreement as to what is the optimal concentration of allergen extracts for skin testing; likewise, while some clinicians in Europe feel that the 0.35 kU/L cutoff used in the PCS is too *high*, many of us in the United States feel that it's too *low*. Because of these and other differences, results of studies performed in the United States are not always applicable to clinical practice elsewhere, and

vice versa. The oceans that separate us are narrowing, however, and continued discourse and research collaborations will enhance our specialty and our understanding of each other. However, we still await the development of an in vitro testing system with sensitivity, cost profile, and turnaround time equivalent to skin testing.

WILLIAM K DOLEN, MD
Associate Professor, Pediatrics and Medicine
Laboratory Director, Allergy-Immunology
Medical College of Georgia, Augusta, GA

ANAPHYLAXIS FOLLOWING INGESTION OF CARMINE

To the Editor:

We read with interest the article by Beaudouin et al.[1] The authors provide clear evidence for an IgE-mediated mechanism in anaphylaxis following ingestion of carmine contained in a fruit yogurt. The patient had positive skin prick and histamine release tests to carmine.

Recently we described a case of a severe anaphylactic reaction to carmine used in the manufacturing of Campari. In this case we were able to demonstrate specific IgE to carmine.[2] The patient suffered from a severe systemic reaction after drinking Campari-Orange. Skin prick and intracutaneous tests to Campari were strongly positive suggesting carmine as the cause of the reaction. In order to characterize further the component to which the patient was reacting, the producer of Campari (Campari SA, Milano, Italy) kindly provided us with the red dye added in the manufacture of Campari, correctly declared on the label of the bottle to be carmine. A strongly positive skin prick test to the dye (0.1% in water) occurred in the patient, whereas ten healthy atopic controls were negative. A disk was prepared with carmine in order to detect serum anti-carmine IgE antibodies by radioallergosorbent test (RAST). Serological analysis initially was negative but revealed specific IgE to carmine (class 2 positive, 0.8 PRU) after a one-year-period during which the patient repeatedly suffered from minor allergic reactions to food containing red dyes (eg. ice cream).

To our knowledge, this is the first documented case of an immediate-type reaction to carmine dyed food in which in addition to a positive skin prick test, specific IgE antibodies to carmine could be demonstrated. The episode highlights the importance of a detailed allergological assessment, especially by means of skin prick tests with the natural allergen or fresh food. These tests easily allow identification of the causative agent in cases of sudden anaphylactic reactions. Knowing the relevant allergen, the patient is able to eliminate the allergen from his diet and avoid recurrent fatal anaphylaxis. In addition, he can be provided with an emergency kit in case of a dietary indiscretion.

MARTIN K KÄGI AND BRUNELLO WÜTHRICH
Allergy Unit, Department of Dermatology
University Hospital, CH-8091
Zürich, Switzerland

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2. Kägi MK, Wüthrich B, Johansson, SG. Campari-Orange anaphylaxis due to carmine allergy (Letter). Lancet 1994;344:60–1.

Response:

We thoroughly agree with the need for a detailed allergological assessment whenever a food induced reaction is suspected. This includes a detailed history, the checking of the labels of the suspected food, an informed inquiry for hidden allergens at workplaces, skin prick tests of the incriminated food and its components such as dyes or preservatives. Newly suspected allergens deserve to be well identified by in house radioimmunoassays or immunoblots. In any case a double blind placebo controlled challenge is highly advisable. The diagnosis and need for subsequent avoidance should be recorded on a medical identity card. An emergency kit is mandatory in the case of the most severe reactions.

We should insist on informative labelings of any manufactured food.

Our own manuscript had been written just before the publication from Kägi in *Lancet* and its publication in *Annals of Allergy, Asthma, and Immunology* , was pending during this period at the time of the other publication.

PROFESSEUR DA MONERET-VAUTRIN
Docteur Etienne Beaudouin
Centre Hospitalier Universitaire
Nancy, France

DIAGNOSIS OF LATEX ALLERGY

To the Editor:

I received my July *Annals* today and hasten to write concerning two points with which I disagree in an otherwise important position statement article on "Latex Allergy."[1] First I wish to endorse with enthusiasm the cautionary notes and the five proposals.

The opening paragraph states: "Allergy to natural rubber latex. . .(was) uncommon before 1980 and the origin of the current proliferation of cases **remains unknown**." The current epidemic of allergy to latex is, to my knowledge, due indirectly to the AIDS epidemic which caused a marked increase in the demand for rubber. This caused the "curing" process to be speeded up with insufficient time for digestion of naturally occurring allergenic proteins. The uncured proteins are easily leached from the latex products (tubing, sheets, catheters, gloves, etc.) and in addition can become airborne. Once an individual is sensitized to latex, even with proper curing, there is still enough undigested protein to trigger an allergic reaction.

With regard to "Diagnostic Testing": the statement regarding skin testing is misleading in that the "homemade" nonstandardized reagents for skin tests has nothing to do with the fact that there will be **severe reactions**. If appropriate skin test allergens are utilized there will be some severe reactions. The statement then goes on to mislead regarding **in vitro allergy tests** stating that "they are less sensitive and may involve substantial time delay in obtaining results." The evidence that we have obtained clinically and through the IBT Laboratory in Lenexa, Kansas, is that in vitro latex tests are at least as sensitive (and in some cases more sensitive) than skin tests, and they are certainly totally safe with regard to anaphylactic or other severe reactions.

Thank you for publishing this correction of statements.

ROBERT N HAMBURGER, MD
Professor of Pediatrics, Emeritus
Head, Pediatric Immunology and Allergy Division
University of California
San Diego, California

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1. Charous BL, Banov C, Bardana EJ, et al. Latex allergy—an emerging healthcare problem. Ann Allergy 1995;75:19–21.

Response:

Dr. Hamburger argues that the "current epidemic of allergy to latex is. . .due indirectly to the AIDS epidemic which caused a marked increase in the demand for rubber" with resultant changes in the manufacturing process that allowed allergenic proteins to remain in the finished product. We do not disagree with the broad outlines of this argument. We agree that the epidemic of human immunodeficiency virus infection and the advent of "universal precautions" is responsible for changes in rubber manufacturing, but would point out that these events also served to increase markedly latex exposure and consequent allergic sensitization.

This explanation, however, fails to explain the significant prevalence of latex allergy observed in some European studies by the mid-1980s, well before the advent of "universal precautions." Furthermore, to claim that "changes" in the manufacturing process are responsible begs the question. What remains unknown is which of the many changes in rubber manufacturing is chiefly responsible for creating a "new" allergic disease that has assumed epidemic proportions in highly exposed workers and patients.

Dr. Hamburger takes issue with the position paper's statement that "in vitro tests are less sensitive. . ." and maintains that in his hands they are "at least as sensitive (and in some cases more sensitive)." The original statement was based on experience with a variety of other well studied antigens, such as stinging insect venoms and penicillin, where reproducible studies using a single antigen and endpoint titration techniques have demonstrated the superior sensitivity of in vivo skin testing. We are unaware of any published study using latex antigen that contradicts these findings. However, given the complex nature of latex antigen, it is certainly possible that different methodologies may yield different, perhaps complementary results. We would encourage Dr. Hamburger to submit his findings for review and publication since they may prove to be a significant addition to our understanding of latex allergy.

Lastly, we certainly welcome Dr. Hamburger's endorsement of the ACAAI Position Paper and are pleased to work with him on promoting measures designed to increase the safety of patients and healthcare workers.

On behalf of the Latex Allergy Committee of the ACAAI,

B LAUREN CHAROUS, MD
EMIL J BARDANA, MD
ROBERT G HAMILTON, PHD
TIMOTHY SULLIVAN, MD