

- sponse to histamine in human skin: identification of doxepin as a potent in vivo inhibitor. *J ALLERGY CLIN IMMUNOL* 1982;69:260-7.
15. Rao KS, Menon PK, Hilman BC, Sebastian CS, Bairnsfather L. Duration of the suppressive effect of tricyclic antidepressants on histamine-induced wheal-and-flare reactions in human skin. *J ALLERGY CLIN IMMUNOL* 1988;82:752-7.
16. Lin RY, Erlich ER, Don PC. Skin prick test responses to codeine, histamine, and ragweed utilizing the Multitest device. *Ann Allergy* 1990;65:222-6.
17. Hamburger RN, Berger WE, Quiwa NB, Terrazas V, Casillas R, Miller SP. Skin testing compared with in vitro testing for screening allergic patients. *Ann Allergy* 1991;67:133-7.

Comparison of the sensitivity and precision of four skin test devices

David B. Engler, MD, Alan C. DeJarnatt, MD, Tommy C. Sim, MD,
Jana L. Lee, RN, and J. Andrew Grant, MD Galveston and Houston, Texas

*Twenty volunteers were skin tested with seven concentrations of histamine phosphate and a glycerosaline control to determine the relative sensitivity and precision of four skin test devices. Greer Pen (GP), Greer DermaPIK (DP), Center Multi-Test (MT), and Morrow Brown needle (MB). The end points of the study were (1) wheal and flare response of each device, with a dose-response curve, (2) the time required to apply each set of eight tests, and (3) the volunteers' subjective assessment of each device. On a different day, 10 of the volunteers were tested to determine the precision of each device. Dose-response curves for half-log dilutions of histamine phosphate were produced with a glycerosaline control. The DP and GP induced wheal and flare responses discernible from that of the glycerosaline control at a lower concentration of histamine phosphate than the MB and MT. The DP took a shorter time to apply eight samples than any other device. The MB was preferred by the most volunteers, but any device tested on the upper half of the back was usually preferred over that tested on the lower half. When 5 mg/ml histamine phosphate was used, coefficients of variation for each device demonstrated that for wheals the precision of the DP, GP, and MT was similar (mean, 21.1%, 23.1%, and 24.5%, respectively). The MB was larger (mean, 59.9%). For flares, the precision of GP and DP was similar (mean, 22.0% and 23.5%, respectively), with the MT and MB larger (mean, 35.5% and 58.2%, respectively). Repeating the analysis for the MB with 10 mg/ml histamine phosphate, we found a mean coefficient of variation of 16.5% for wheals and 19.6% for flares. We conclude that the DP is equal to the GP in precision and sensitivity for wheal and flare, but it has the advantage of allowing allergy skin testing to be performed more quickly. The MT has similar precision for wheals but has less precision for flares. The MB device is more precise only with higher concentrations of histamine phosphate than those routinely used in the clinical practice of allergy. (*J ALLERGY CLIN IMMUNOL* 1992;90:985-91.)*

Key words: Skin testing, allergy testing, histamine

From the Division of Allergy and Immunology, Department of Internal Medicine, The University of Texas Medical Branch at Galveston.

Supported by a grant from Greer Laboratories, Lenoir, N.C.

Received for publication May 23, 1991.

Revised Jan. 2, 1992.

Accepted for publication Feb. 7, 1992.

Reprint requests: David B. Engler, MD, The Allergy Clinic, 7707 Fannin, Suite 100, Houston, TX 77054-1918.

For more than a century, skin testing has been the standard procedure for diagnosing inhalant allergies. Most authors recommend use of positive and negative controls with the testing.^{1,2} Recently several new devices have become available to perform immediate skin testing. They are claimed to be disposable, easy to use, comfortable, and more accurate. We examined the sensitivity, time necessary to apply material, volunteers' preference of the devices, and the precision of four of these devices.

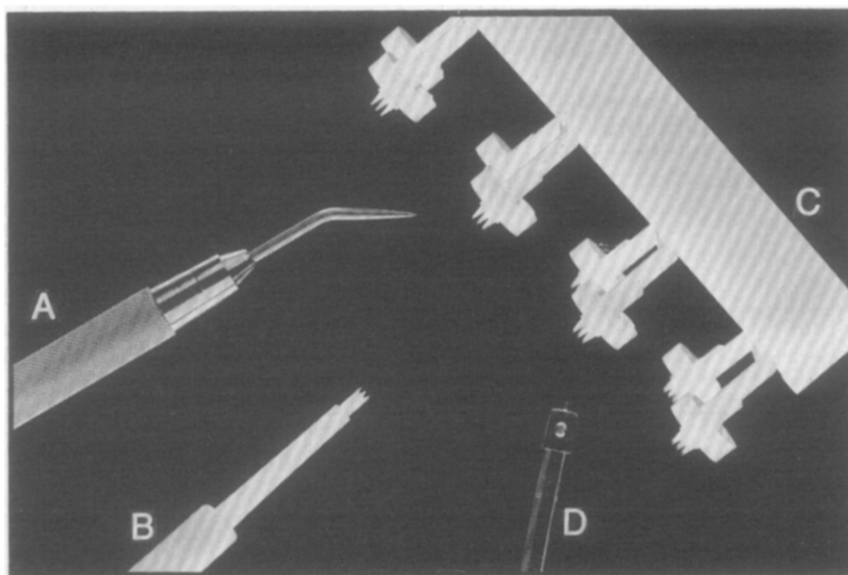


FIG. 1. *A*, Greer Pen, a 54 mm long, solid stainless steel needle with an angled tip, is used with a "pen" to hold the tip in place. One needle is used for each subject, wiped off between tests, and then discarded. *B*, DermaPIK, a 41 mm long device with six points arranged in a 2 mm circular fashion, is used once per antigen, then discarded. *C*, Center Multi-Test, a sterile, multiple test head applicator, can apply eight different tests at once. Tines are in groups of nine, each 1.9 mm long, grouped in two rows separated by 3 cm. The four heads in each row are 2 cm apart from each other. *D*, Morrow Brown needle, a 27 mm long device with a single 1.25 mm point is used once per antigen then discarded.

Abbreviations used

GP:	Greer Pen
DP:	DermaPIK
MT:	Multi-Test
MB:	Morrow Brown
HP:	Histamine phosphate

METHODS

Subjects

Twenty volunteers, 10 men and 10 women, 22 to 49 years of age, were studied. None was taking antihistamines or tricyclic antidepressants that might induce false-negative skin test results.^{3,4} The protocol was approved by the Institutional Review Board of The University of Texas Medical Branch at Galveston. Informed consent was obtained from each volunteer. We examined each volunteer's back to confirm an adequate area to perform skin testing and to confirm a lack of skin disorders. The back was divided into four quadrants, one for each device. Skin testing was performed by one nurse (J.L.L.).

Skin testing devices

The following four commercially available devices for percutaneous testing were used (Fig. 1):

1. The Greer Pen ([GP] Greer Laboratories, Lenoir, N.C.) is a 54 mm long, solid stainless steel needle

with an angled tip. It is used with a "pen" to hold the tip in place. One needle is used for each volunteer, wiped off between each test, and then discarded.

2. The DermaPIK ([DP] Greer Laboratories, Lenoir, N.C.) is a 41 mm long device with six points (each 0.81 mm long) arranged in a 2 mm circular fashion. It is used once per antigen and then discarded.
3. The Center Multi-Test ([MT] Center Laboratories, division of EM Pharmaceuticals, Port Washington, N.Y.) is a sterile, disposable, multiple test head applicator that can apply eight different tests at once. The tines are in groups of nine, each 1.9 mm long, grouped in two rows separated by 3 cm. The four heads in each row are 2 cm apart from each other.
4. The Morrow Brown needle, ([MB] Aller/ Guard, Topeka, Kan.) is a 27 mm long device with a single 1.25 mm point. It is used once per antigen and then discarded.

Skin testing

Sensitivity. On each of 20 volunteers skin testing was performed with a glycerosaline control and half-log dilutions of histamine phosphate (HP) (5.0, 1.67, 0.5, 0.167, 0.05, 0.0167, and 0.005 mg/ml) prepared in glycerosaline. Each of the four devices was used with each of the eight dilutions, for a total of 32 pricks or punctures on each volunteer (Fig. 2). Each test was placed 5 cm away from the next, except for the Multi-Test, where all eight tests were applied at once,

2 cm apart from each other. The quadrant used for a particular device was rotated counterclockwise for each volunteer so that no one device would be used in only a single quadrant.

Time. The time to place the eight tests was measured. For the GP we measured the time to unscrew each vial, place a drop of material on the skin, screw each cap back onto the vial, and prick the skin. The GP needle was wiped with isopropyl alcohol between each prick to prevent carryover. The DP testing device rests in a well of material. The time was measured to remove the DP from the well, place it on the skin with a puncture and twist technique, and place a new DP in the well. For the MB, time was measured to remove the lid from the MultiWell extract tray, put the eight MB devices into the wells, use the eight devices on the volunteer, and close the lid. For the MT, time was measured to unscrew each cap from the vial of material, place the material onto the MT prongs with the Dip-n-Touch system, screw each cap back onto the bottle, and apply the single device to the volunteer.

Preference. Each volunteer was asked to rank each device for comfort. The scale was from 1 to 4, with 4 being the most uncomfortable.

Precision. On a separate day, 10 of the volunteers (5 women and 5 men) underwent testing with these four devices to determine their respective precision. The 5 mg/ml strength of HP was used eight times with each of the four devices on each volunteer. Because we got a poor result with the MB using the 5 mg/ml strength, we repeated the procedure with this device with a 10 mg/ml strength.

Measurement of skin-test reactions. Reactions were measured at 15 minutes. Wheals and flares were traced with a thin felt-tip pen by an investigator (D.B.E.) who was not involved with placing the skin tests, and then they were transferred onto paper by laying tape over each mark. The wheals were then measured by calculating the arithmetic mean of the longest diameter and its perpendicular. The flares were measured by the same technique except with the MT device, which often had confluence of its flares. All measurements were performed by two investigators who were blinded to the results. With the MT, the longest radius was measured from the center and then multiplied by two to achieve a diameter.

Statistical analysis

Statistical analysis for the dose-response and precision studies was performed with the Epistat program (Round Rock, Texas) on an IBM (IBM Corp., Armonk, N.Y.) computer. For each device, precision was expressed as coefficient of variation, calculated from the means and standard deviations as follows:

$$\text{Standard deviation/mean} \times 100\% = \text{coefficient of variation}$$

Then the coefficients of variation for each volunteer were averaged to result in a mean coefficient of variation for each device. A one-way analysis of variance (ANOVA) was used to compare the dose-response curves with the reactions ob-

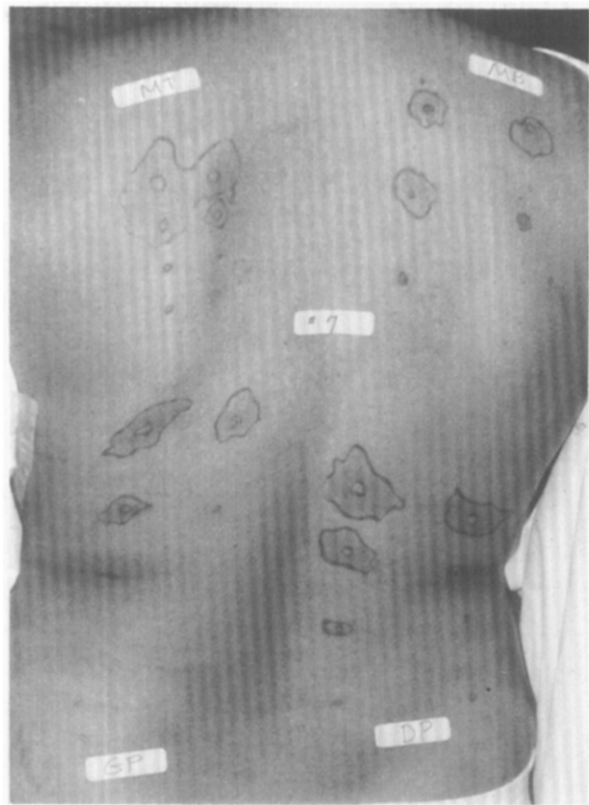


FIG. 2. Each volunteer was tested with each device on a separate quadrant of the back. The quadrant used for a particular device was rotated counterclockwise for each volunteer so that no one device would be used in only a single quadrant.

tained with glycerosaline. A significant change in reaction size from baseline was defined as $p < 0.05$. Data are expressed as mean $\pm$ SD.

RESULTS

Sensitivity

A dose-dependent response for each of the four devices was recorded for both wheals (Fig. 3) and for flares (Fig. 4) by use of half-log dilutions of HP between 5.0 and 0.005 mg/ml. One-way ANOVA showed that the GP and DP devices both produced wheal and flare responses that were significantly different from the glycerosaline control at 0.05 mg/ml. The MT and MB devices did not produce responses significantly different from those of the glycerosaline control until 0.167 mg/ml for wheal or flare. However, the DP and MT devices consistently produced a larger baseline with glycerosaline.

Time

The DP took an average of 31.7 seconds to apply eight samples; the MB took 48.7 seconds;

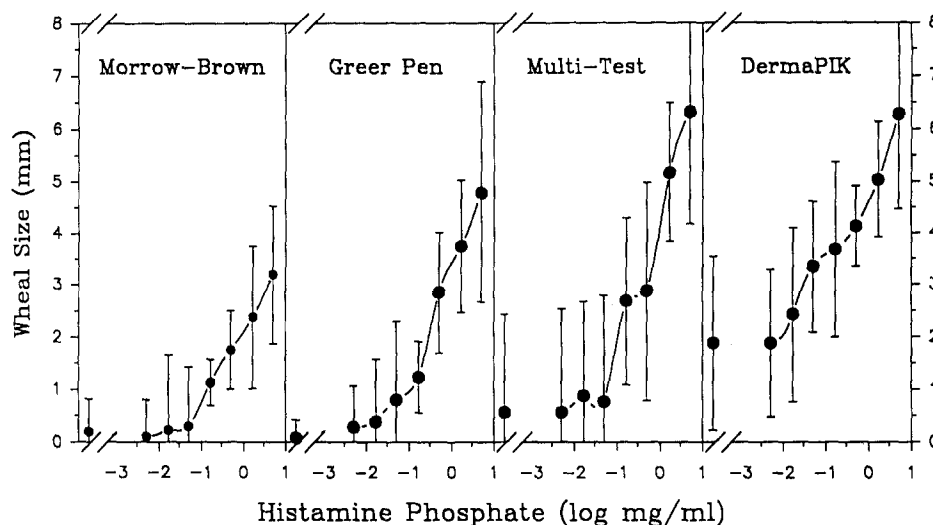


FIG. 3. Dose-response curves were produced for wheals by use of the four devices with 20 volunteers. The DermaPIK and Greer Pen produced wheal responses discernible from glycerosaline control at lower concentrations of histamine (0.05 mg/ml) than the Morrow Brown and Multi-Test (0.167 mg/ml). Data presented as mean $\pm$ SD.

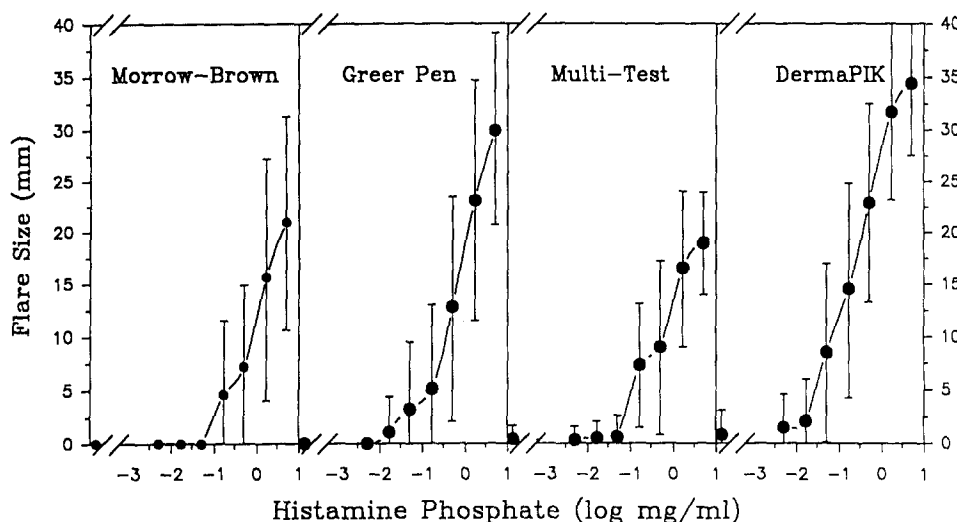


FIG. 4. Dose-response curves were produced for flares by use of the four devices with 20 volunteers. The DermaPIK and Greer Pen produced flare responses discernible from glycerosaline control at lower concentrations of histamine (0.05 mg/ml) than the Morrow Brown and Multi-Test (0.167 mg/ml).

the MT took 54.3 seconds; and the GP took 61.7 seconds.

Preference

The MB was ranked "least uncomfortable" by 11 of 20 volunteers, making it the most desirable by the volunteers. The MT was preferred by 9 of 20 (Fig. 5). However, any device placed on the upper half of the back was usually preferred over a device placed on the lower half of the back.

Precision

Coefficients of variation for each device were recorded with 5 mg/ml HP: For wheals, the precision of the DP, GP, and MT was similar (mean 21.1%, 23.1%, and 24.5%, respectively). Mean for the MB was 59.9% (Fig. 6). By ANOVA, the values for MB were greater than the others ($p < 0.05$), which were not significantly different. For flares, the precision of GP and DP was similar (mean, 22.0% and 23.5%, respectively), with the MT and MB higher (mean,

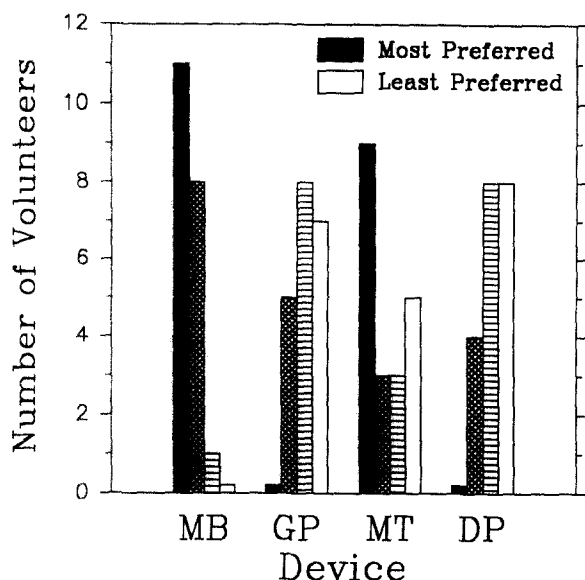


FIG. 5. Preference of volunteers by device. MB was preferred by most volunteers.

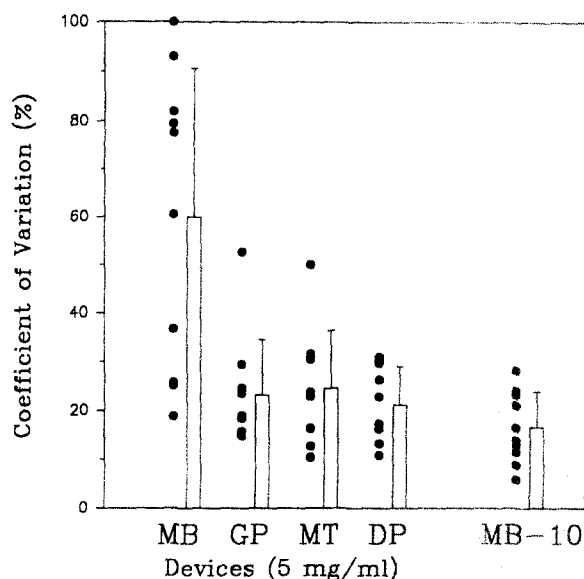


FIG. 6. Comparison of coefficients of variation of wheals for skin test devices for individual volunteers. Coefficients of variation of MB were higher than for MT, GP, and DP.

35.5% and 58.2%, respectively) (Fig. 7). By ANOVA, the values for MB were again greater than the others ($p < 0.05$), which were not significantly different. Mean coefficients of variation for the MB device with use of a higher concentration of HP, 10 mg/ml, were 16.5% for the wheal and 19.6% for the flare (Figs. 6 and 7). These values were not significantly different from those obtained with the other devices at 5 mg/ml.

DISCUSSION

Over the dose range we tested all four devices produced predictable dose-response curves for wheals and for flares. The one-way ANOVA showed the DP and GP to be more sensitive than the MB and MT; they induced wheal and flare responses discernible from glycerosaline control at lower concentrations of HP. The DP and MT induced higher background wheal and flare responses; thus an investigator must compare responses with a well-placed glycerosaline solution control. This higher background response may be attributable to increased dermal abrasion because these two devices both use multiple prongs. Although most clinicians measure only wheal size, the flare response has been shown by Turkeltaub et al.^{5,6} to be more responsive to allergen concentration than the wheal reaction.

The time required to place the samples varied widely. Of all the devices, the DP required the least

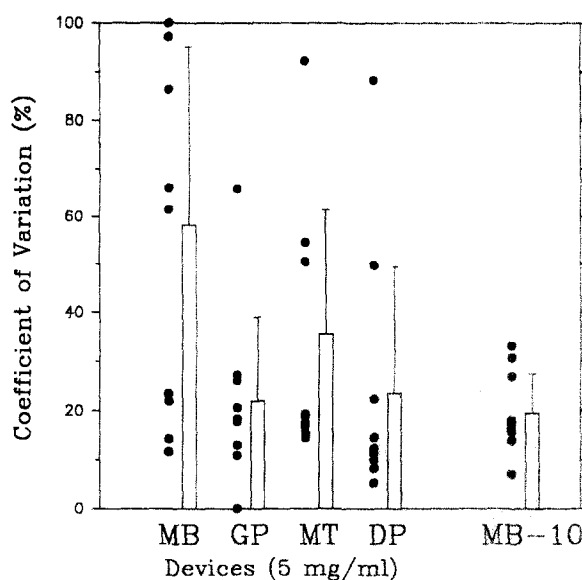


FIG. 7. Comparison of coefficients of variation of flares for skin test devices for individual volunteers. Coefficients of variation of MT and MB were higher than for GP and DP.

time by far, probably because the entire system is set up to test before it is used. The MB device took longer to apply the tests, although both of these systems have wells in which the testing device rests. Not having to unscrew and screw a bottle cap was a time advantage. However, our nurse stated that removing the MB de-

vices from the central branch on which they were packed was more difficult than removing the DP device.

That most volunteers preferred the MB is not surprising because it contains only one point to penetrate the skin. The MT was also preferred by many volunteers who said they appreciated having all the tests done at once. The top half of the back was usually preferred over the bottom half of the back, regardless of the device used.

Coefficients of variation are an accurate assessment of precision or reproducibility.^{4, 7, 8} Adinoff et al.⁷ found the GP, along with the MB, the smallpox needle, and the bifurcated needle the most precise instruments for immediate hypersensitivity testing. We found the GP and DP achieved the best results. Our results for the MB and MT devices differ widely from those of Adinoff et al. In fact, we used these two devices differently. For the MB, we used the Aller//Guard MultiWell extract tray, which allowed the testing device to rest in a well, similar to that of the DP system. With use of this system, however, we found many false-negative reactions at the 5 mg/ml strength. For this reason, and because this device induced smaller wheals and flares than any other we studied, the MB has the highest coefficients of variation for wheal and flare. Basomba et al.,⁸ also found a higher coefficient of variation with the MB needle. The MB we used, provided by Aller//Guard in July 1990, had a four-sided point. This four-sided device, when used in the MultiWell system, might not hold a drop of testing material as well as the newer MB needle with three sides, released early in 1991 (personal communication, Harry Morrow Brown). We repeated the reproducibility study using 10 mg/ml HP for this device to determine whether larger skin reactions would result in smaller coefficients of variation. It is interesting to note that the 10 mg/ml strength gave excellent results with the MB, but this concentration is stronger than that used in clinical practice. In fact, 10 mg/ml HP is not commercially available in the United States, and was prepared in our laboratory. For the MT our coefficients of variation were much better than those obtained by Adinoff et al.,⁷ possibly because we used a newer version of the MT, with smaller (1.9 mm) prongs instead of 2.4 mm prongs used in their study. Garibaldi and Slavin⁹ point out that the shorter points have less entrance into the dermis, thus causing fewer irritant responses for negative controls. With use of the MT, we did find less precision with the measurement of flares, although this difference was not significantly different from the GP and DP. Between the various test sites often a

confluence of flares occurred, which we believe was because of the short distance between the testing prongs on the MT. Many authors recommend placing skin tests at least 5 cm apart to decrease the chance of one reaction spreading into the next.^{1, 2, 10} The MT, as described, has its prongs 2 cm apart.

The current cost of placing eight tests for each device is as follows: GP, \$0.17; DP, \$0.72; MT, \$1.37; and MB, \$0.48. These prices do not include the one-time cost to purchase the time-saving testing systems necessary for the DP, MT, or MB that we used in our study.

All of these devices performed well under the appropriate circumstances. However, one must interpret flares from the MT with caution, since the points are so close to each other, and overlap reactions occur with the flares. One must also interpret negative results with the MB device with caution. It may be useful to use stronger concentrations of antigen with this device if it is to be used with the MultiWell system. We recommend that a clinician always perform positive and negative controls to properly interpret skin tests regardless of the device they use. Negative controls are especially important with the MT and DP because they tend to produce higher background responses. The DP is equal in precision and sensitivity for wheal and flare to the GP, but it has the advantage of allowing skin testing to be performed more quickly.

Many authors believe that the allergic skin reaction occurs chiefly because of the liberation of histamine.^{2, 11, 12} However, because this study was performed with HP, not with allergens, a definite conclusion cannot be made with regard to the precision and reproducibility of these devices for testing with allergens. Further studies with allergens will be helpful.

We thank Harold Nelson, MD, for help in developing the methods and James A. Hokanson, PhD, for advice regarding statistical analysis. We also thank Alice Cullu for critically reviewing this manuscript, Center Laboratories for providing the Multi-Test devices, Aller//Guard for providing the Morrow Brown devices, and Greer Laboratories for providing the DermaPIK devices.

REFERENCES

1. VanArsdel PP, Larson EB. Diagnostic tests for patients with suspected allergic disease. *Ann Intern Med* 1989;110:304-12.
2. Voorhorst R, van Krieken H. Atopic skin test reevaluated. I. Perfection of skin testing technique. *Ann Allergy* 1973;31:137-42.
3. Nelson HS. Diagnostic procedures in allergy. I. Allergy skin testing. *Ann Allergy* 1983;51:411-8.
4. Sullivan TJ. Pharmacologic modulation of the whealing re-

- sponse to histamine in human skin: identification of doxepin as a potent in vivo inhibitor. *J ALLERGY CLIN IMMUNOL* 1982;69:260-7.
5. Turkeltaub PC, Rastogi SC, Baer H, et al. A standardized quantitative skin-test assay of allergen potency and stability: studies on the allergen dose-response curve and effect of wheal, erythema, and patient selection on assay results. *J ALLERGY CLIN IMMUNOL* 1982;70:343-52.
 6. Turkeltaub PC. Biological standardization of allergenic extracts. *Allergol Immunopathol* 1989;17:53-65.
 7. Adinoff Ad, Rosioniec DM, McCall LL, Nelson HS. A comparison of six epicutaneous devices in the performance of immediate hypersensitivity skin testing. *J ALLERGY CLIN IMMUNOL* 1989;84:168-74.
 8. Basomba A, Sastre A, Pelaez A, et al. Standardization of the prick test. A comparative study of three methods. *Allergy* 1985;40:395-9.
 9. Garibaldi E, Slavin RG. Multi-Test false-positive readings can be observed after deviation from product use instructions [Letter]. *J ALLERGY CLIN IMMUNOL* 1990;86:137.
 10. Voorhorst R. Perfection of skin testing technique. *Allergy* 1980;35:247-50.
 11. Aas K. Some variables in skin prick testing. *Allergy* 1980;35:250-2.
 12. Havnen J. Prick test and intracutaneous test. Variability in histamine tests between different individuals and in the same individual. *Acta Allergol* 1974;29:225-7.

Bound volumes available to subscribers

Bound volumes of THE JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY are available to subscribers (only) for the 1992 issues from the Publisher, at a cost of \$54.00 for domestic, \$75.78 for Canadian, and \$72.00 for international subscribers for Vol. 89 (January-June) and Vol. 90 (July-December). Shipping charges are included. Each bound volume contains a subject and author index, and all advertising is removed. Copies are shipped within 30 days after publication of the last issue in the volume. The binding is durable buckram with the journal name, volume number, and year stamped in gold on the spine. *Payment must accompany all orders.* Contact Mosby-Year Book, Inc., Subscription Services, 11830 Westline Industrial Dr., St. Louis, MO 63146-3318; phone (800) 325-4177, ext. 4351, or (314) 453-4351.

Subscriptions must be in force to qualify. Bound volumes are not available in place of a regular journal subscription.