# A comparison of six epicutaneous devices in the performance of immediate hypersensitivity skin testing

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*Six devices commonly used for immediate hypersensitivity epicutaneous skin testing were compared with regard to precision and diagnostic accuracy. Fifteen subjects were tested on the back to 10 mg/ml of histamine phosphate and 50% glycerosaline by prick technique with a smallpox needle (SN), bifurcated needle (BN), Greer "pen" (GP), and blood lancet, and by puncture with the Morrow-Brown needle (MB) and Multi-Test (MT). Five devices were tested in quintuplicate to histamine and once to glycerosaline in each subject; with MT, five histamine and three glycerosaline sites were used. Analysis of the wheal areas obtained with SN, BN, GP, and MB demonstrated comparable degrees of precision (coefficient of variation). The precision of MT was less than the other devices ($p < 0.05$). The blood lancet demonstrated intermediate precision. Twenty-two of 45 (49%) of the glycerosaline skin tests performed with MT were falsely positive, significantly more than the other devices ($p = 0.0001$). We conclude that MB, BN, GP, and SP are comparable devices for use in immediate hypersensitivity skin testing. The low precision and reliability of MT used for testing on the back would appear to make this device less than adequate for diagnostic or research studies. Its high rate of false positive reactions requires caution in interpretation of results when it is used in the clinical diagnosis of allergy. (J ALLERGY CLIN IMMUNOL 1989;84:168-74.)*

The use of immediate hypersensitivity skin testing as a diagnostic tool in clinical allergy dates to the studies on hay fever by Blackley[1] in the 1860s.[2] Since that time, it has become the standard clinical method for demonstrating the presence of allergen-specific IgE antibody in allergic diseases.[3] When skin testing is properly performed, it is also a sensitive bioassay.[4-6] It is useful in the standardization and comparison of allergen-extract potencies as well as evaluating the effects of medications or immunotherapy. The accuracy and precision of skin testing methods are of critical importance if meaningful information is to be obtained. Although a variety of devices are currently used to perform epicutaneous skin testing, few studies critically comparing the performance of such devices have been done.[7-13] The purpose of this study was to compare the response to histamine with six commercially available epicutaneous skin testing devices regarding precision and diagnostic accuracy.

*Abbreviations used*

| | |
|---|---|
| CV: | Coefficient of variation (standard deviation/mean × 100) |
| SN: | Smallpox needle |
| BN: | Bifurcated needle |
| GP: | Greer "pen" |
| L: | Lancet |
| MB: | Morrow-Brown needle |
| MT: | Multi-Test |

## MATERIAL AND METHODS

### Subjects

Fifteen healthy subjects, six male and nine female subjects, aged 29 to 57 years (mean 39), were studied. None were receiving medications known to inhibit immediate hypersensitivity skin tests.[14] The study was approved by the Institutional Review Board for the use of human subjects at National Jewish Center for Immunology and Respiratory Medicine, and all subjects gave informed consent before their participation.

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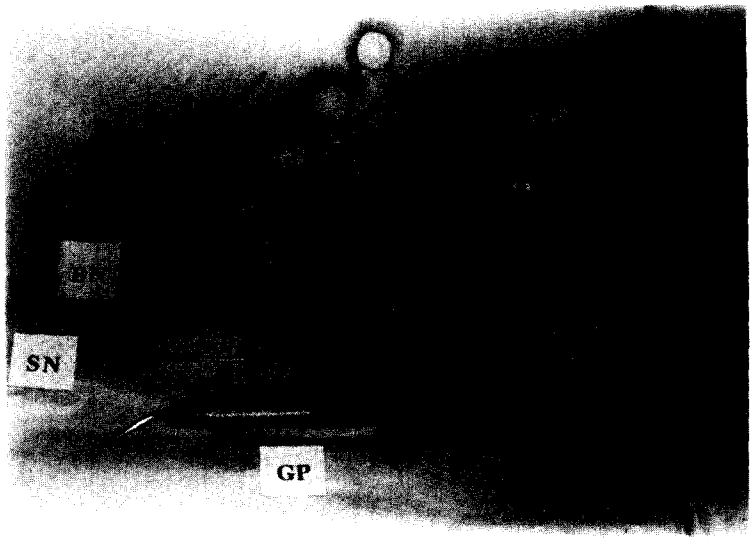


**FIG. 1.** Epicutaneous skin testing devices. The prick technique was used with the SN, BN, GP, and L. The puncture technique was used with the MT and MB.

## Skin testing devices

Six commercially available instruments for epicutaneous testing were used (Fig. 1).

1. The SN (Hollister-Stier Laboratories, Spokane, Wash.) is a straight, solid, stainless steel 41-mm long device. One needle was used for each subject and was then discarded.
2. The BN (Allergy Laboratories of Ohio, Columbus, Ohio) is a stainless steel 66-mm long device with a 0.7-mm distance between the two points. One needle was used for each subject and was then discarded.
3. The GP (Greer Laboratories, Lenoir, N.C.) device is a 54-mm long, solid, stainless steel needle with the tip bent 45 degrees to the shaft, which is grasped by a "pen" holder. One needle was used for each subject and was then discarded or sterilized for reuse.
4. The short-point blood microlance L (Becton Dickinson, Rutherford, N.J.) is a 32-mm long stainless steel device with a 2-mm point. One sterile device was used for each test and was then discarded.
5. The MB (AllerGuard, Topeka, Kan.) is a 27-mm long plastic device with a 1-mm point.[12] One sterile device was used for each test and was then discarded.
6. The MT (Lincoln Diagnostics, Decatur, Ill.) is a plastic multiple test–head applicator.[15] Test heads are 2 by 2 mm clusters of nine 2.4 mm long tines. Eight heads are available on each device in two rows separated by 3 cm. The four heads in each row are separated by 2 cm. One sterile device was used and was then discarded.

## Skin testing

Skin testing was performed with histamine phosphate (10 mg/ml histamine base; 0.05 mol/L)[6, 16] in 50% glycerosaline and with a similar 50% glycerosaline control. Subjects were tested on their backs by either of two highly experienced technicians (D. M. R. or L. L. M.). A template and porous felt-tip pen were used to mark the locations of skin testing sites 5 cm apart.[17] The location of histamine testing for each device was rotated among subjects to ensure equal distribution over the entire surface of the back and avoid possible variability as a result of different test sites.[11] For each device except MT, histamine was tested in quintuplicate and glycerosaline, once. Five sites on each MT were loaded with histamine and three with glycerosaline. The locations of histamine and glycerosaline on MT were randomized by one technician and were blinded to the testing technician. Both technicians performed skin testing on approximately an equal number of subjects. Because of limited room on the backs, each subject was tested with one MT and four of the other five devices. After the skin had been pricked or punctured, the drops were removed from the back.[18] Three hundred seventy-five histamine and 105 glycerosaline skin tests were applied on the 15 subjects.

The prick technique was used with SN, BN, GP, and L. A drop of material was placed on the skin and the device was passed through the drop, penetrating the skin at approximately a 45 degree angle. The skin was then gently lifted, creating a small break in the epidermis. To eliminate histamine "carryover," care was taken to wipe the SN, BN, and GP between each test with a water-saturated cotton ball. To eliminate any further histamine carryover in the prongs of the BN, it was first rinsed in 70% isopropyl alcohol and was then wiped.

The puncture technique was used with MB and MT. The MB was passed through a drop of liquid at an angle of 90 degrees to the skin. The skin was gently "stabbed" until resistance to further penetration was felt. Histamine and glycerosaline were carefully loaded onto the MT prongs

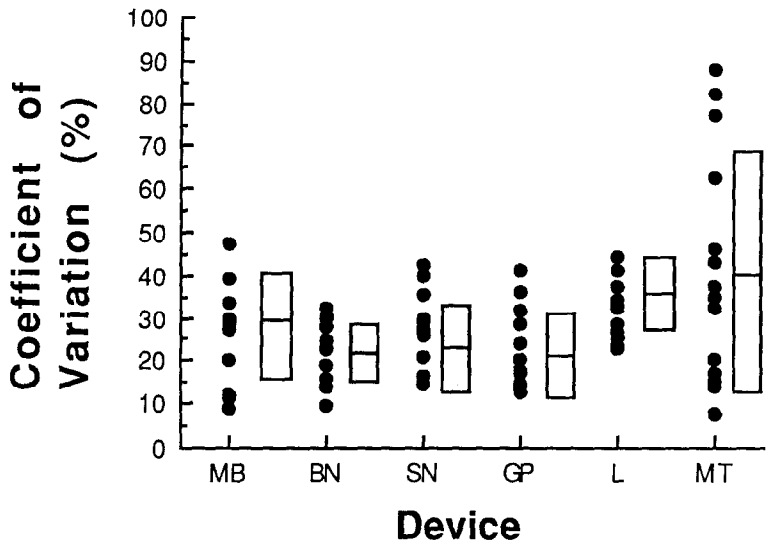


**FIG. 2.** Comparison of CV for skin test devices for individual subjects. The CV of MT (n = 15) was significantly greater than MB (n = 12), SN (n = 12), and GP (n = 12) ($p < 0.05$). *Boxes* indicate mean and 1 SD. *Each dot* may indicate more than one individual.

according to the manufacturer's recommendations. The device was then inverted and placed on the skin, and pressure was applied in a forward-backward and side-to-side fashion to leave a circular impression on the skin from each of the eight heads.

### Measurement of skin test reactions

Skin test reactions were recorded 10 minutes after placement.[19] The wheal reactions were carefully outlined with a fine porous-tip pen and tape-transferred onto paper. Wheals were magnified 10 times with an overhead projector. A graphics tablet interfaced to an Apple Macintosh Plus microcomputer (Apple Computer, Inc., Cupertino, Calif.) was used for computerized planimetry measurements of the wheal areas (square millimeter). The result was corrected by the magnification factor of 10.

For each skin test, three measurements were averaged and recorded. Since erythematous reactions were irregular and often confluent (especially with MT), only wheal areas were analyzed.[5, 7, 13]

### False-positive and false-negative reactions

Those reactions in which the wheal area of a histamine reaction was $<7$ mm$^2$ (diameter of approximately 3 mm) were considered false negative.[20] If the wheal-area reaction to glycerosaline was $\geq 7$ mm$^2$, it was considered falsely positive. The design of the study only allowed for one glycerosaline control per device per subject (except MT). Since each device (except MT) was tested in 12 of 15 subjects, only 12 glycerosaline controls per device were obtained. Therefore, to obtain a greater number of glycerosaline skin tests for each of the devices SN, BN, GP, and MB, four subjects (two male and two female subjects) who underwent testing in the precision component of the study had additional tests applied. These subjects each had 28 additional sites tested with each of the four devices (112 skin tests per subject). Skin tests to histamine (10 mg/ml) alternating with glycerosaline were placed 5 cm apart (total: 224 histamine and 224 glycerosaline skin tests). Therefore, in adding the 375 histamine and 105 glycerosaline skin tests performed in the precision component of the study, a total of 599 histamine and 329 glycerosaline skin tests were analyzed. Because its precision, cost, and subject preference were not comparable to the other four devices, additional skin testing with L was not done, and L was not included in this part of the analysis.

### Statistical analysis

Statistical analysis was performed with the StatView 512+ program (Calabasas, Calif.) on an Apple Macintosh Plus microcomputer. For each device, precision was expressed as the CV and was calculated for each subject. The CV "corrects" the standard deviation obtained for different sized mean wheal areas and is a commonly used statistical representation of precision. A one-way analysis of variance was used to determine overall significance for precision, and a post hoc analysis for multiple comparisons with the Fisher protected least-significant difference test established significance between individual devices. Rates of false positive and negative reactions were compared by chi-square analysis. Regression analysis for continuous measures was used to calculate correlation coefficients.

## RESULTS

The precision of the six devices represented by the CV obtained is illustrated in Fig. 2. The GP demonstrated the highest precision, and the MT demonstrated the lowest precision and a wider range of CV than other devices. When devices were compared in-

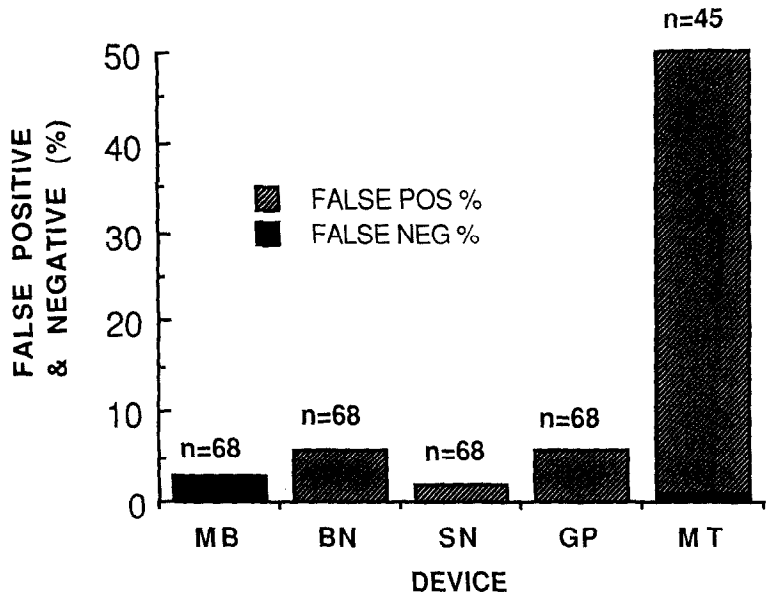


**FIG. 3.** Rates of false-positive and false-negative reactions for different devices. False-positive reactions were more common with MT than the other devices ($p = 0.0001$); *N*, number of glycerosaline skin tests applied.

dividually, the precision of MT was significantly less than SN, BN, MB, and GP ($p < 0.05$) but not statistically different from L. When devices were compared as a group, SN, BN, MB, GP, and L were significantly more precise than MT (CV, 26.5 ± 9.3 versus 39.5 ± 26.6, respectively; $p < 0.001$; data not presented). The precision of SN, BN, MB, and GP did not differ significantly. There was no correlation between the mean wheal areas obtained for each device for each subject and the CV ($r = 0.08$; $p > 0.5$; data not presented). The area measurements of MT wheals and CV were examined in relationship to their placement on the back (upper, middle, and lower). Wheals were somewhat larger in the lower back, and CV was somewhat higher in the upper back, although these differences were not significant ($p = 0.23$ and $p = 0.87$, respectively). The precision of each device was examined as regards the technician who performed the skin testing. No significant differences were found.

The rates of false-positive and false-negative reactions are illustrated in Fig. 3. False-negative reactions to histamine were not observed with SN, BN, or GP, were only rarely found with MT, L, and MB (1% to 3%), and did not significantly differ between devices. False-positive reactions to glycerosaline were observed with the BN in 4/68 (6%); GP, in 4/68 (6%); SN, in 2/68 (3%); and MB, in 0/68 (0%). The differences between these four devices were not significant. Twenty-two of 45 (49%) of the glycerosaline skin tests performed with MT were positive, significantly more than any other device ($p = 0.0001$; df, 5; chi-square, 102). The results of skin testing with MT obtained on one subject are illustrated in Fig. 4. All three glycerosaline tests were positive and were not distinguishably different from results obtained from the five histamine reactions. Three of the 12 glycerosaline skin tests applied with the L were positive, although because of the small number of tests, the results were not included in this analysis (see Material and Methods).

The subjects were asked to blindly rank their preferences for each of the devices as regards pain or discomfort. Devices were ranked in decreasing order of preference: BN > SN > GP > MB > L > MT. Only L produced occasional bleeding at the skin test sights. The current device costs for placing 32 tests per patient were SN, $0.03; BN, $0.12; GP, $0.16; MB, $1.50; L, $1.92; and MT, $5.16.

## DISCUSSION

We have performed an analysis of the performance of six commercially available epicutaneous devices used for immediate hypersensitivity skin testing. The results with MT were significantly different from results with MB, BN, SN, or GP, demonstrating the least precision and greatest number of false-positive reactions. The L generally produced values intermediate to MT and the other devices. The MB, BN, SN, and GP were all comparable in all the analyses.

The precision of epicutaneous skin testing has been examined by a number of investigators and is usually

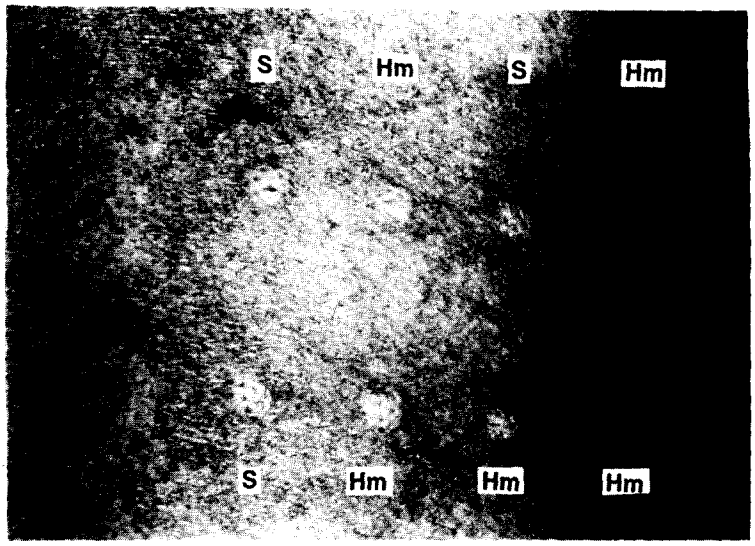


**FIG. 4.** Results of skin testing with MT obtained on one subject. The three glycerol saline *(S)* tests were positive (>7 $mm^2$) and not distinguishably different from results obtained from the five histamine *(Hm)* reactions.

expressed as the CV. CV for histamine reactions, measuring the diameters of the wheals, ranges from 5% to 115% with greater precision obtained (5% to 15%) for diameters >5 to 7 mm.[7, 9, 10, 12, 13, 21, 22] A CV of histamine wheal diameters of 20% has been recommended by the Nordic Society of Allergology.[23] Measurements of wheal area would be expected to produce CV approximately twice that of diameters.[24] The precision of our results is therefore in agreement with precision of results previously reported with a mean CV for wheal areas of 29.1% (range 22.6 to 39.5 for the different devices).

Relatively few studies have compared the precision of different devices used for epicutaneous skin testing. Most studies have not statistically compared the CV obtained[7-9, 11, 12] or have not found significant differences.[10, 13] Aas[7] found the CV with histamine for MT to be 30% (wheal diameters) compared with 8% with a short-bevelled needle and 10% with the MB. Interestingly, the precision of a single MT applicator head was similar to that of the other two devices.[7] In a well-controlled study, Sullivan[13] compared MT to the prick method using a 26-gauge needle. CV averaged 32% (diameter measurements) for histamine dihydrochloride, 0.01 mol/L (equivalent to approximately 10 mg/ml of histamine phosphate base), with MT on the forearm, and was not significantly different from the prick technique. Although Sullivan[13] did not demonstrate different degrees of precision between MT and prick method, the CV of 32% (equivalent to approximately twice that value with wheal area calculations) obtained for both methods is markedly greater than the precision we obtained with MB, BN, SN, or GP (22% to 28%).

Determinations of precision are useful when skin testing is to be used for scientific work; however, this calculation may not be relevant when it is used for clinical diagnostic work. It was for this reason that we chose to also compare the devices as regards false positive and negative reactions. No device produced a large number of false-negative reactions. However, nearly half (49%) the skin tests to glycerosaline with the MT were positive, significantly greater than any of the other devices. Other investigators have reported MT producing positive reactions to diluent controls.[25, 26] Our initial trials with the BN suggested a high rate of false-positive reactions to glycerosaline, which we attributed to "carryover" of histamine between the device prongs. False-positive reactions were largely eliminated when the prongs were rinsed in 70% isopropyl alcohol and wiped with a water-saturated cotton ball. Similar experience has previously been reported.[27]

In this study, MT produced the lowest precision. The reasons for this are speculative. Although MT is not used in the skin test laboratory of the National Jewish Center, practice trials with all devices were done to familiarize the technicians with their use. In particular, care was taken to load each MT head with an equal amount of testing material according to the manufacturer's recommendations. Inconsistency with MT may be due to its use on the back instead of the

forearm. It is possible that the irregular bony understructure of the back would make even distribution of pressure difficult with the relatively large rigid MT, whereas this would not matter with individual inoculation by the other epicutaneous methods. Support for this view is found in a recent study comparing MT delayed-hypersensitivity testing on the back and forearm.[28] Quantitative cell-mediated immunity scores were significantly less on the back than on the forearm, suggesting the diagnostic criteria established on the forearm could not be used to interpret results obtained on the back. Further study with immediate hypersensitivity skin testing comparing the back and forearm with MT should be done.

Most likely false-positive reactions with MT are a result of the close spacing of testing heads (2 to 3 cm) allowing one skin test reaction to effect an adjacent testing site. This was visually appreciated by the confluence of erythematous flares that occurred only with MT. It has been demonstrated that positive prick skin tests can dramatically effect the results of adjacent testing sites,[29] often causing negative tests to become positive. For this reason, placement 5 cm apart has been recommended[6, 17] and is the method of prick skin test placement in the laboratory of the National Jewish Center. Additionally, the precision of MT was found to equal that of MB when a single MT applicator was used.[7] These observations, combined with our findings, suggest that the close proximity of the MT heads also may affect the reliability of the reaction. Moderately sized wheal reactions to allergen ($\geq$6 to 7 mm diameter) could be expected to produce similar results.

In conclusion, we have compared six epicutaneous skin testing devices with regard to precision and diagnostic accuracy. MB, BN, GP, and SN were all similar. The low precision of MT used for testing on the back would appear to make this device less than adequate for diagnostic or research studies. Its high rate of false-positive reactions require caution in interpretation of results when it is used in the clinical diagnosis of allergy. Nevertheless, because of its wide use, further comparative studies of MT in immediate hypersensitivity skin testing should be performed.

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# Cross-reactivity of IgE antibodies to caddis fly with arthropoda and mollusca

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*We investigated the possibility that subjects with IgE antibodies to an inhalant insect allergen, such as caddis fly, might also have antibodies to cross-reacting carbohydrate determinants (CCDs). IgE antibodies to cross-reacting allergens in caddis flies, mussels, oysters, shrimps, crabs, honeybee, and yellow jacket venoms were determined by RAST, RAST inhibition, and immunoblot studies with sera from three different sources: (1) sera of patients with well-defined inhalant atopy to caddis fly, (2) sera with IgE anti-CCD antibodies from subjects without known exposure to caddis fly, and (3) hyperimmune antisera with IgG anti-CCD antibodies raised as a result of immunization of rabbits with grass-pollen extract, buckwheat glycoprotein, or with honeybee venom. Sera from groups 2 and 3 reacted with Sepharose-coupled caddis fly extract in a RAST-type assay and elicited virtually identical patterns on immunoblots of caddis fly extract separated on sodium dodecyl sulfate-polyacrylamide gel electrophoresis, whereas the sera from group 1 atopic patients did not react with CCD-rich material. However, indications for other types of cross-reacting antibodies were detected. The IgE antibodies of one of the patients studied (who was allergic not only to caddis fly but also to shellfish) were found to detect a cross-reacting homologous protein in extracts of mussel, oyster, shrimp, crab, honeybee, and yellow jacket venom. Preliminary results suggest that this cross-reacting 13 kd protein, the most prominent caddis fly allergen, is an invertebrate hemoglobin (erythrocruorin)-like molecule. These studies suggest the possibility that patients sensitized by exposure to caddis fly antigens could develop allergic reactions during their first exposure to shellfish or to their first bee sting. (J ALLERGY CLIN IMMUNOL 1989;84:174-83.)*

Aquatic and terrestrial arthropods and mollusks are common causes of both inhalant and ingestant allergic disease. Inhalant allergy to caddis fly was one of the first well-documented causes of inflammatory airway disease.[1] After initial studies by Parlato in 1929, subsequent clinical studies confirmed the prevalence of caddis fly atopy with symptoms varying from allergic conjunctivitis and rhinitis to life-threatening status asthmaticus. Allergy to various inhaled insect allergens has been known for several decades[2-4] involving insects, such as caddis flies, cockroaches, moths, and chyronomid larvae. A widespread IgE-mediated hypersensitivity of insect origin has been reported from Sudan,[5, 6] Japan,[7, 8] and the United States.[9-11]

When we started our serologic investigations regarding the incidence of sensitization to nonstinging and nonbiting insects, we were surprised to find positive caddis fly RASTs with sera from patients without known exposure to caddis flies. We had found, previously,[12, 13] that IgE antibodies in some human sera

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