

## REPORT

# Delayed patch test reading after 5 days: The Mayo Clinic experience

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**Background:** Some patients may have delayed allergic patch test reactions that are not identified with a typical 5-day reading protocol.

**Objective:** To identify allergens with delayed-positive reactions and to determine whether a late reading (day 7-9) can be substituted for the day-5 reading.

**Methods:** We retrospectively reviewed medical records of patients who underwent patch testing for suspected allergic contact dermatitis from October 1997 through December 2006 and returned for delayed readings between days 7 and 10 or beyond. (This cohort was predominantly patients with suspected allergies to metals and corticosteroids).

**Results:** A total of 36,064 individual reactions (471 allergens, 372 patients) were interpreted on day 5 and at least once during days 7 through 21. We analyzed the 170 allergens that were each tested in at least 50 patients. The 4 allergens with the highest percentage of delayed-positive reactions were gold sodium thiosulfate 0.5% (delayed-positive reactions in 22/353 patients), dodecyl gallate 0.25% (6/105), palladium chloride 2% (8/194), and neomycin sulfate 20% (10/253). We observed a low number of delayed-positive readings for *p*-phenylenediamine 1% (1/251) and for corticosteroids. Reactions to certain preservative and fragrance allergens dissipated after the day-5 reading. Most reactions that dissipated after day 5 were mild, whereas the reactions that became apparent after day 5 were strong.

**Limitations:** This was a retrospective study. Most patients had suspected allergies to metals and corticosteroids.

**Conclusion:** Late patch test readings (day 7 or beyond) were useful when interpreting reactions to metals and topical antibiotics, but it was not useful in the diagnosis of reactions to other allergens, including topical corticosteroids. Because reactions to certain fragrance and preservative allergens may dissipate after 5 days, patch test reactions therefore are optimally read at days 3 and 5, but an additional reading on day 7 or beyond is useful if patch tests to metals and topical antibiotics are performed. (J Am Acad Dermatol 10.1016/j.jaad.2008.04.022.)

## INTRODUCTION

Although different centers use different protocols for patch testing of allergens, most interpret results 48 hours after placement of allergens (when patches are removed) and again 3 or 4 days later. Commonly, patches are placed on a Monday (day 1), and reactions are examined on Wednesday (day 3) and Friday (day 5). Our institution generally uses this

5-day reading protocol. However, we questioned whether we were overlooking additional positive reactions by not examining patients more than 5 days after placement of patches. Some researchers suggest delaying readings for metals, corticosteroids,<sup>1</sup> and *p*-phenylenediamine (PPD) allergies,<sup>2-4</sup> but previous studies are confusing because different periods are used for patch test interpretation. For example,

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Geier et al<sup>4</sup> compared “late” day-6 readings with those from day 2 or 3, whereas the study by Isaksson and Bruze<sup>5</sup> compared readings on day 3 or 4 with readings on day 7.

We previously reported that readings after 5 days did not identify many additional corticosteroid allergies.<sup>6</sup> In this study, we retrospectively reviewed records in our clinical database to determine which allergens showed delayed-positive reactions (after day 5) and to measure the frequency of delayed-positive reactions. Our secondary objectives were to ascertain whether a later reading could replace the day-5 reading and to determine whether some positive reactions on day 5 dissipated by days 7 through 10.

## METHODS

### Patients

This study was approved by the Mayo Clinic Institutional Review Board. Patients underwent patch testing for suspected allergic contact dermatitis to metals and corticosteroids. Patients were tested at Mayo Clinic (Rochester, Minnesota) from October 1997 (when routine performance of patch test interpretation after day 5 was initiated for patients undergoing these tests) through December 2006. Some of these patients were described previously in a study of corticosteroid allergies.<sup>6</sup> Patients were identified from a clinical database, and patient characteristics and patch test results were extracted from medical records. No patients applied topical corticosteroids to patch test sites, were treated with immunosuppressive medication such as oral corticosteroids, or had medical conditions that could compromise the evaluation of skin responsiveness.<sup>7</sup> Twelve patients who denied research authorization were excluded from the analysis.

### Patch test application and interpretation of reactions

The method of patch test application, including chambers used, and the reading schedule were the same as that used by the North American Contact Dermatitis Group.<sup>7-9</sup> Testing was conducted with Finn Chambers on Scanpor tape (Epitest Ltd Oy, Tuusula, Finland). Most allergens were purchased from Chemotechnique Diagnostics (Vellinge, Sweden). Other allergens were compounded by the Mayo Clinic pharmacy (Rochester, Minn).

Allergens were applied to the upper back and removed after 48 hours. We asked patients to return for patch-test interpretation after day 5 because they were tested for allergies to metals and corticosteroids. Test results were interpreted for up to 7 to 10 days after placement of corticosteroids and up to 2 weeks after placement of metals. All patch-test

reactions were examined with each reading (not only reactions to metals or corticosteroids). For example, if a patient was tested with a metal series and a standard allergen series, all patch test reactions were read at days 3, 5, 7, and 14. Therefore our patient database included reactions to allergens that typically are not examined after day 5.

In this study, patch-test reactions of all patients were interpreted on day 3 (after removal of patch test material), day 5, and at least once during days 7 through 10. For patients tested for metal allergies, reactions again were interpreted at least once during days 10 through 14 and occasionally on day 21.

Patch-test reactions were interpreted by using criteria similar to those of the North American Contact Dermatitis Group. Possible outcomes were negative reaction, macular erythema, weak reaction (nonvesicular erythema, infiltration, and possibly papules), strong reaction (edematous or vesicular), extreme reaction (spreading, bullous, ulcerative lesions), and irritant reaction.<sup>7-9</sup> A positive patch-test result was defined as a weak, strong, or extreme allergic reaction. As previously described,<sup>10</sup> macular erythema reactions were considered positive if the results were relevant.

### Clinical relevance

Relevance of each reaction was recorded as follows: I, irritant; N, allergic, not relevant (no exposure to products containing the allergen); Q, allergic, questionably relevant (current exposure to products likely to contain the allergen); P, allergic, formerly relevant (past exposure to products likely to contain the allergen); and R, allergic, relevant (use test or patch test with the product containing the allergen is positive, or ingredient verified in patient's product and use of that product is verified).

### Statistical analysis

For each allergen, the percentage of positive patch-test reactions on day 5 was compared to that on days 7 through 21 by using an exact McNemar test for comparing correlated proportions. All calculated *p* values were two-sided, and *p* values less than .05 were considered statistically significant. Statistical analysis was performed using the SAS software package (version 9, SAS Institute, Inc, Cary, NC).

## RESULTS

During the 9.3-year study period, 36,064 individual reactions to 471 allergens from 372 patients were interpreted both on day 5 and during days 7 through 21. Of the 471 allergens, the mean number of patients tested per allergen was 76.6 (median, 25 patients/allergen). To avoid undue emphasis on percentages

**Table I.** Patch-test reaction rates among patients tested on day 5 and on day 7 or later\*

| Allergen <sup>†,‡</sup>                               | Patch test results, No. of patients |                             |                             |                             |                             |                   | <i>p</i> Value  |
|-------------------------------------------------------|-------------------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-------------------|-----------------|
|                                                       | Patients, No.                       | Neg day 5, neg day $\geq 7$ | Neg day 5, pos day $\geq 7$ | Pos day 5, neg day $\geq 7$ | Pos day 5, pos day $\geq 7$ | Irritant reaction |                 |
| 1,4-Butanediol dimethacrylate 2%                      | 122                                 | 120                         | 1                           | 0                           | 0                           | 1                 | ...             |
| 2-Bromo-2-nitropropane-1,3-diol 0.25%                 | 254                                 | 250                         | 0                           | 1                           | 2                           | 1                 | >.99            |
| 2-Hydroxyethyl methacrylate 2%                        | 148                                 | 143                         | 2                           | 2                           | 1                           | 0                 | >.99            |
| 2-Hydroxypropyl methacrylate 2%                       | 77                                  | 71                          | 1                           | 1                           | 2                           | 2                 | >.99            |
| 4- <i>tert</i> -Butylphenol formaldehyde resin 1%     | 253                                 | 245                         | 2                           | 2                           | 3                           | 1                 | >.99            |
| Amalgam 5%                                            | 195                                 | 191                         | 1                           | 0                           | 3                           | 0                 | >.99            |
| Amcinonide 1% in 70% EtOH                             | 161                                 | 153                         | 1                           | 1                           | 3                           | 3                 | >.99            |
| Amidoamine 0.1% Aq                                    | 122                                 | 119                         | 1                           | 0                           | 1                           | 1                 | >.99            |
| Ammonium tetrachloroplatinate 0.25% Aq                | 195                                 | 194                         | 1                           | 0                           | 0                           | 0                 | ...             |
| Anethole 5%                                           | 100                                 | 99                          | 0                           | 1                           | 0                           | 0                 | ...             |
| Bacitracin 20%                                        | 253                                 | 220                         | 6                           | 6                           | 21                          | 0                 | >.99            |
| <b>Balsam of Peru 25%</b>                             | <b>300</b>                          | <b>252</b>                  | <b>1</b>                    | <b>21</b>                   | <b>19</b>                   | <b>7</b>          | <b>&lt;.001</b> |
| Benzalkonium chloride 0.1% Aq                         | 253                                 | 231                         | 3                           | 11                          | 6                           | 2                 | .06             |
| Benzocaine 5%                                         | 87                                  | 86                          | 1                           | 0                           | 0                           | 0                 | ...             |
| <b>Benzoic acid 5%</b>                                | <b>292</b>                          | <b>272</b>                  | <b>1</b>                    | <b>10</b>                   | <b>4</b>                    | <b>5</b>          | <b>.01</b>      |
| Benzoyl peroxide 1%                                   | 144                                 | 140                         | 0                           | 2                           | 2                           | 0                 | .50             |
| Benzyl alcohol 1%                                     | 121                                 | 120                         | 1                           | 0                           | 0                           | 0                 | ...             |
| Beryllium sulfate tetrahydrate 1% Aq                  | 208                                 | 189                         | 6                           | 0                           | 11                          | 2                 | .03             |
| Betamethasone 17-valerate 1%                          | 161                                 | 154                         | 0                           | 2                           | 0                           | 5                 | ...             |
| Betamethasone dipropionate 0.5% in 70% EtOH           | 161                                 | 156                         | 0                           | 1                           | 0                           | 4                 | ...             |
| BIS MA 2%                                             | 98                                  | 95                          | 0                           | 1                           | 0                           | 2                 | ...             |
| Budesonide 0.1%                                       | 305                                 | 290                         | 4                           | 3                           | 3                           | 5                 | >.99            |
| <i>n</i> -Butyl methacrylate 2%                       | 137                                 | 136                         | 1                           | 0                           | 0                           | 0                 | ...             |
| Cadmium chloride 1% Aq                                | 195                                 | 192                         | 0                           | 1                           | 1                           | 1                 | >.99            |
| Caine mix III                                         | 214                                 | 204                         | 0                           | 5                           | 3                           | 2                 | .06             |
| Carba mix 3%                                          | 253                                 | 246                         | 1                           | 2                           | 1                           | 3                 | >.99            |
| Chloroxylonol (PCMX) 1%                               | 254                                 | 249                         | 0                           | 1                           | 4                           | 0                 | >.99            |
| Chromium chloride 5%                                  | 218                                 | 205                         | 1                           | 2                           | 8                           | 2                 | >.99            |
| Cinnamic aldehyde 1%                                  | 166                                 | 162                         | 1                           | 0                           | 1                           | 2                 | >.99            |
| Citric acid 1% Aq                                     | 83                                  | 81                          | 0                           | 1                           | 0                           | 1                 | ...             |
| Clobetasol-17-propionate 1%                           | 194                                 | 188                         | 0                           | 1                           | 0                           | 5                 | ...             |
| Cobalt chloride 1%                                    | 359                                 | 312                         | 6                           | 10                          | 27                          | 4                 | .45             |
| Cobalt sulfate 1%                                     | 195                                 | 177                         | 4                           | 2                           | 12                          | 0                 | .69             |
| Cocamidopropyl betaine 1% Aq                          | 145                                 | 141                         | 0                           | 3                           | 0                           | 1                 | ...             |
| Coconut diethanolamide (cocamide diethanolamine) 0.5% | 71                                  | 69                          | 2                           | 0                           | 0                           | 0                 | ...             |
| Colophony 20%                                         | 300                                 | 287                         | 1                           | 3                           | 6                           | 3                 | .63             |
| <i>Dermatophagoides</i> mix 0.1%                      | 108                                 | 99                          | 1                           | 2                           | 2                           | 4                 | >.99            |
| Desoximetasone 0.05%                                  | 156                                 | 152                         | 0                           | 1                           | 0                           | 3                 | ...             |
| Dexamethasone 21-phosphate disodium salt 1%           | 161                                 | 157                         | 0                           | 3                           | 0                           | 1                 | ...             |
| Diazolidinyl urea 1%                                  | 253                                 | 243                         | 0                           | 2                           | 7                           | 1                 | .50             |
| Diazolidinyl urea 1% Aq                               | 254                                 | 246                         | 3                           | 2                           | 2                           | 1                 | >.99            |
| Dimethylol dihydroxyethylene urea 4.5% Aq             | 63                                  | 62                          | 1                           | 0                           | 0                           | 0                 | ...             |
| Disperse blue #106 1%                                 | 240                                 | 223                         | 2                           | 7                           | 5                           | 3                 | .18             |
| <b>Disperse blue #124 1%</b>                          | <b>239</b>                          | <b>220</b>                  | <b>2</b>                    | <b>10</b>                   | <b>5</b>                    | <b>2</b>          | <b>.04</b>      |
| DMDM hydantoin 1%                                     | 247                                 | 242                         | 0                           | 2                           | 2                           | 1                 | .50             |
| DMDM hydantoin 1% Aq                                  | 210                                 | 207                         | 0                           | 3                           | 0                           | 0                 | ...             |
| Dodecyl gallate 0.25%                                 | 105                                 | 89                          | 6                           | 6                           | 4                           | 0                 | >.99            |
| Epoxy resin 1%                                        | 274                                 | 266                         | 2                           | 3                           | 3                           | 0                 | >.99            |
| Ethyl acrylate 0.1%                                   | 299                                 | 294                         | 0                           | 3                           | 1                           | 1                 | .25             |
| Ethyl methacrylate 2%                                 | 63                                  | 61                          | 0                           | 1                           | 1                           | 0                 | >.99            |
| Ethylenediamine dihydrochloride 1%                    | 256                                 | 248                         | 1                           | 3                           | 3                           | 1                 | .63             |
| Ethyleneglycol dimethacrylate (EGDMA) 2%              | 147                                 | 142                         | 1                           | 1                           | 2                           | 1                 | >.99            |

Continued

Table I. Cont'd

| Allergen <sup>†,‡</sup>                                  | Patch test results, No. of patients |                             |                             |                             |                             |          | Irritant reaction | p Value         |
|----------------------------------------------------------|-------------------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|----------|-------------------|-----------------|
|                                                          | Patients, No.                       | Neg day 5, neg day $\geq 7$ | Neg day 5, pos day $\geq 7$ | Pos day 5, neg day $\geq 7$ | Pos day 5, pos day $\geq 7$ |          |                   |                 |
| Ethyleneurea-melamine formaldehyde mix 5%                | 253                                 | 249                         | 0                           | 2                           | 1                           | 1        |                   | .50             |
| Fluocinolone acetonide 1% in 70% EtOH                    | 158                                 | 153                         | 0                           | 3                           | 0                           | 2        |                   | ...             |
| Fluocinonide 1%                                          | 221                                 | 214                         | 0                           | 3                           | 0                           | 4        |                   | ...             |
| Formaldehyde 1% Aq                                       | 254                                 | 238                         | 1                           | 4                           | 11                          | 0        |                   | .38             |
| <b>Fragrance mix 8%</b>                                  | <b>299</b>                          | <b>254</b>                  | <b>0</b>                    | <b>12</b>                   | <b>25</b>                   | <b>8</b> |                   | <b>&lt;.001</b> |
| Gold chloride 0.5% Alc                                   | 195                                 | 171                         | 4                           | 1                           | 18                          | 1        |                   | .38             |
| Gold sodium thiosulfate 0.25%                            | 90                                  | 77                          | 3                           | 2                           | 7                           | 1        |                   | >.99            |
| Gold sodium thiosulfate 0.5%                             | 353                                 | 248                         | 22                          | 13                          | 62                          | 8        |                   | .18             |
| Halcinonide 1%                                           | 161                                 | 158                         | 0                           | 1                           | 0                           | 2        |                   | ...             |
| Hexachlorophene 1%                                       | 222                                 | 218                         | 0                           | 2                           | 0                           | 2        |                   | ...             |
| Hexahydro-1,3,5-tris(2-hydroxyethyl)triazine 1%          | 252                                 | 241                         | 1                           | 4                           | 5                           | 1        |                   | .38             |
| Hexamethylenetetramine (methenamine 2%)                  | 74                                  | 70                          | 2                           | 0                           | 2                           | 0        |                   | .50             |
| Hexylresorcinol 0.25%                                    | 253                                 | 244                         | 0                           | 2                           | 6                           | 1        |                   | .50             |
| Hydrocortisone 17-butyrate 1% Alc                        | 289                                 | 285                         | 2                           | 1                           | 1                           | 0        |                   | >.99            |
| Hydrocortisone acetate 1%                                | 161                                 | 160                         | 0                           | 1                           | 0                           | 0        |                   | ...             |
| Imidazolidinyl urea 2%                                   | 249                                 | 243                         | 0                           | 2                           | 3                           | 1        |                   | .50             |
| Imidazolidinyl urea 2% Aq                                | 253                                 | 247                         | 0                           | 2                           | 3                           | 1        |                   | .50             |
| Isoeugenol 2%                                            | 96                                  | 94                          | 1                           | 0                           | 1                           | 0        |                   | >.99            |
| MCI/MI 100 ppm Aq                                        | 253                                 | 241                         | 1                           | 2                           | 6                           | 3        |                   | >.99            |
| Manganese chloride 2% Aq                                 | 194                                 | 189                         | 1                           | 1                           | 1                           | 2        |                   | >.99            |
| Menthol 2%                                               | 105                                 | 103                         | 0                           | 1                           | 1                           | 0        |                   | >.99            |
| 2-Mercaptobenzothiazole 1%                               | 254                                 | 249                         | 0                           | 1                           | 4                           | 0        |                   | >.99            |
| Mercuric chloride 0.1%                                   | 195                                 | 184                         | 2                           | 2                           | 5                           | 2        |                   | >.99            |
| <b>Mercury 0.5%</b>                                      | <b>193</b>                          | <b>165</b>                  | <b>1</b>                    | <b>8</b>                    | <b>13</b>                   | <b>6</b> |                   | <b>.04</b>      |
| Mercury ammonium chloride 1%                             | 195                                 | 184                         | 0                           | 3                           | 7                           | 1        |                   | .25             |
| Methyl salicylate 2%                                     | 89                                  | 87                          | 0                           | 1                           | 1                           | 0        |                   | >.99            |
| <b>Methyldibromo glutaronitrile/phenoxylethanol 1.5%</b> | <b>254</b>                          | <b>238</b>                  | <b>2</b>                    | <b>10</b>                   | <b>1</b>                    | <b>3</b> |                   | <b>.04</b>      |
| Molybdenum chloride 1%                                   | 208                                 | 205                         | 0                           | 1                           | 1                           | 1        |                   | >.99            |
| Mometasone furoate (ointment) 0.1%                       | 161                                 | 155                         | 0                           | 1                           | 1                           | 4        |                   | >.99            |
| <b>Natural fragrance mix 2%</b>                          | <b>295</b>                          | <b>278</b>                  | <b>1</b>                    | <b>10</b>                   | <b>5</b>                    | <b>1</b> |                   | <b>.01</b>      |
| Neomycin sulfate 20%                                     | 253                                 | 214                         | 10                          | 6                           | 22                          | 1        |                   | .45             |
| Nickel sulfate hexahydrate 2.5%                          | 355                                 | 274                         | 9                           | 14                          | 54                          | 4        |                   | .40             |
| <b>Octyl gallate 0.25%</b>                               | <b>83</b>                           | <b>72</b>                   | <b>0</b>                    | <b>7</b>                    | <b>1</b>                    | <b>3</b> |                   | <b>.02</b>      |
| Palladium chloride 2%                                    | 194                                 | 162                         | 8                           | 4                           | 19                          | 1        |                   | .39             |
| Paraben mix 16%                                          | 253                                 | 249                         | 0                           | 2                           | 2                           | 0        |                   | .50             |
| p-Phenylenediamine 1%                                    | 251                                 | 241                         | 1                           | 5                           | 4                           | 0        |                   | .22             |
| Phenol formaldehyde resion 1%                            | 256                                 | 252                         | 0                           | 2                           | 2                           | 0        |                   | .50             |
| Potassium dichromate 0.25%                               | 274                                 | 250                         | 3                           | 7                           | 12                          | 2        |                   | .34             |
| Potassium dichromate 0.5%                                | 190                                 | 168                         | 2                           | 6                           | 14                          | 0        |                   | .29             |
| Potassium dicyanoaurate 0.1% Aq                          | 195                                 | 151                         | 7                           | 2                           | 33                          | 2        |                   | .18             |
| Prednisone 5%                                            | 161                                 | 158                         | 0                           | 1                           | 0                           | 2        |                   | ...             |
| Propionic acid 3%                                        | 82                                  | 80                          | 0                           | 1                           | 0                           | 1        |                   | ...             |
| Propyl gallate 1%                                        | 104                                 | 100                         | 2                           | 1                           | 1                           | 0        |                   | >.99            |
| Propylene glycol 10%                                     | 254                                 | 253                         | 0                           | 1                           | 0                           | 0        |                   | ...             |
| Quaternium 15 1%                                         | 253                                 | 235                         | 1                           | 3                           | 13                          | 1        |                   | .63             |
| Resorcinol 1%                                            | 86                                  | 85                          | 0                           | 1                           | 0                           | 0        |                   | ...             |
| Sesquiterpene lactone mix 0.1%                           | 255                                 | 253                         | 1                           | 0                           | 1                           | 0        |                   | >.99            |
| Silver nitrate 1% Aq                                     | 195                                 | 184                         | 2                           | 3                           | 3                           | 3        |                   | >.99            |
| Sodium benzoate 5%                                       | 105                                 | 102                         | 0                           | 2                           | 0                           | 1        |                   | ...             |
| Sorbic acid 2%                                           | 140                                 | 139                         | 0                           | 1                           | 0                           | 0        |                   | ...             |
| Sorbitan sesquioleate 20%                                | 107                                 | 105                         | 0                           | 2                           | 0                           | 0        |                   | ...             |
| Spearmint oil 2%                                         | 98                                  | 95                          | 0                           | 1                           | 2                           | 0        |                   | >.99            |

Continued

**Table I.** Cont'd

| Allergen <sup>†,‡</sup>                        | Patch test results, No. of patients |                             |                             |                             |                             |                   | <i>p</i> Value |
|------------------------------------------------|-------------------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-------------------|----------------|
|                                                | Patients, No.                       | Neg day 5, neg day $\geq 7$ | Neg day 5, pos day $\geq 7$ | Pos day 5, neg day $\geq 7$ | Pos day 5, pos day $\geq 7$ | Irritant reaction |                |
| Stearyl alcohol 30%                            | 253                                 | 251                         | 0                           | 1                           | 0                           | 1                 | ...            |
| Tetrahydrofurfuryl methacrylate 2%             | 79                                  | 78                          | 0                           | 1                           | 0                           | 0                 | ...            |
| Thimerosal 0.1%                                | 57                                  | 49                          | 2                           | 3                           | 3                           | 0                 | >.99           |
| Thiuram mix 1%                                 | 252                                 | 246                         | 0                           | 1                           | 3                           | 2                 | >.99           |
| Tin 50%                                        | 195                                 | 194                         | 0                           | 1                           | 0                           | 0                 | ...            |
| Titanium alloy disc                            | 188                                 | 186                         | 0                           | 2                           | 0                           | 0                 | ...            |
| Tixocortol-21-pivalate 1%                      | 306                                 | 291                         | 0                           | 2                           | 13                          | 0                 | .50            |
| Tocopherol (vitamin E) 10%                     | 210                                 | 208                         | 0                           | 1                           | 0                           | 1                 | ...            |
| Triamcinolone acetonide 1%                     | 306                                 | 300                         | 0                           | 2                           | 0                           | 4                 | ...            |
| Triclosan 2%                                   | 301                                 | 300                         | 1                           | 0                           | 0                           | 0                 | ...            |
| Triethanolamine 2%                             | 255                                 | 250                         | 0                           | 2                           | 1                           | 2                 | .50            |
| Triethylene glycol dimethacrylate (TREGDMA) 2% | 147                                 | 144                         | 1                           | 1                           | 0                           | 1                 | >.99           |
| Zinc chloride 2% Aq                            | 195                                 | 182                         | 2                           | 3                           | 4                           | 4                 | >.99           |

*Alc*, Alcohol; *Aq*, aqueous; *BIS MA*, 2,2-bis(4-methacryloyloxyethoxy)-phenylpropane; *DMDM hydantoin*, 1,3-dimethylol-5,5-dimethyl hydantoin; *EtOH*, ethanol; *MCI/MI*, methylchloroisothiazolinone/methylisothiazolinone; *neg*, negative; *pos*, positive.

\*Reactions were examined on day 5 and on day 7 or later (up to day 21).

<sup>†</sup>Allergens were tested in 50 or more patients.

<sup>‡</sup>Boldface typeface designates allergens with day-5 positive reaction rates that were significantly higher from day-7 to day-21 positive reaction rates (two-sided exact McNemar test).

that were inflated by small sample sizes, we arbitrarily limited our analysis to the 170 allergens that had been tested in at least 50 patients (30,817 individual reactions). Of these 170 allergens, 117 had reactions that differed on day 5 when compared with days 7 through 21 (Table I).

For 14 allergens, the positive-reaction rate at days 7 through 21 was significantly higher than the rate during day 5 ( $p < .05$ ). Table II details the allergens with 2% or more newly positive reactions after day 5. Of the 30,817 individual reactions, 29,692 were negative on day 5, but 165 (0.6%) had a positive reading when examined during days 7 through 21. The allergen with the highest percentage of newly positive reactions (after day 5) was gold sodium thiosulfate 0.5%. Of the 353 patch test reactions to this allergen, 22 (6.2%) were negative on day 5 and positive at a reading during days 7 through 21.

Conversely, for 8 allergens, the positive-reaction rate at day 5 was significantly higher than the rate during days 7 through 21 ( $p < .05$ ). These allergens (identified by boldface type in Table I) were balsam of Peru 25%, benzoic acid 5%, disperse blue #124 1%, fragrance mix 8%, mercury 0.5%, methyldibromo glutaronitrile/phenoxyethanol 1.5%, natural fragrance mix 2%, and octyl gallate 0.25%.

We examined the reactions gained or lost after the day-5 readings to determine their strength. Most reactions that dissipated after day 5 were mild,

whereas the reactions that became apparent after day 5 were strong. Of the 456 positive reactions that dissipated after day 5 (117 allergens), 333 reactions (63.1%) were relevant macular erythemas, 98 (29.4%) were weak reactions, and 25 (7.5%) were strong or extreme reactions (see Table I). Of the 165 reactions that became apparent on day 7 or later (117 allergens), 51 (30.9%) were relevant macular erythemas, 99 (60%) were weak reactions, and 15 (9.1%) were strong or extreme reactions (Table I).

## DISCUSSION

This study confirmed that patch-test interpretation on day 5 was sufficient for detection of nearly all positive patch-test reactions. A few allergens, however, should prompt physicians to consider asking the patient to return for a later reading to detect delayed reactions; these allergens include metals (gold, palladium, beryllium, nickel, cobalt), topical antibiotics (neomycin sulfate, bacitracin), a few preservatives (dodecyl gallate, thimerosal, methenamine), and a surfactant (cocamide diethanolamine). Delayed-positive readings generally could be observed on days 7 through 9. Interestingly, after day 5, reactions to PPD and to corticosteroids rarely were observed.

Comparing our results with those of other studies is somewhat difficult because "late" readings are defined in different ways. Table III summarizes

**Table II.** Allergens with delayed-positive patch-test reactions

| Allergen*                                           | Patients tested (No.) | Pos day 5           |                                                          | Neg day 5, pos day $\geq 7^{\dagger}$ |                                                          |
|-----------------------------------------------------|-----------------------|---------------------|----------------------------------------------------------|---------------------------------------|----------------------------------------------------------|
|                                                     |                       | No. (%) of patients | No. (%) of patients with relevant reactions <sup>‡</sup> | No. (%) of patients                   | No. (%) of patients with relevant reactions <sup>‡</sup> |
| Gold sodium thiosulfate 0.5%                        | 353                   | 75 (21.2)           | 59 (78.7)                                                | 22 (6.2)                              | 14 (63.6)                                                |
| Dodecyl gallate 0.25%                               | 105                   | 10 (9.5)            | 9 (90.0)                                                 | 6 (5.7)                               | 6 (100.0)                                                |
| Palladium chloride 2%                               | 194                   | 23 (11.9)           | 17 (73.9)                                                | 8 (4.1)                               | 7 (87.5)                                                 |
| Neomycin sulfate 20%                                | 253                   | 28 (11.1)           | 27 (96.4)                                                | 10 (4.0)                              | 7 (70.0)                                                 |
| Potassium dicyanoaurate 0.1% Aq                     | 195                   | 35 (17.9)           | 29 (82.9)                                                | 7 (3.6)                               | 6 (85.7)                                                 |
| Thimerosal 0.1%                                     | 57                    | 6 (10.5)            | 5 (83.3)                                                 | 2 (3.5)                               | 1 (50.0)                                                 |
| Gold sodium thiosulfate 0.25%                       | 90                    | 9 (10.0)            | 6 (66.7)                                                 | 3 (3.3)                               | 3 (100.0)                                                |
| Beryllium sulfate tetrahydrate 1% Aq                | 208                   | 11 (5.3)            | 10 (90.9)                                                | 6 (2.9)                               | 4 (66.7)                                                 |
| Coconut diethanolamide (cocamide diethanolamine) 5% | 71                    | 0 (0.0)             | 0 (0.0)                                                  | 2 (2.8)                               | 1 (50.0)                                                 |
| Hexamethylenetetramine (methenamine) 2%             | 74                    | 2 (2.7)             | 2 (100.0)                                                | 2 (2.7)                               | 2 (100.0)                                                |
| Nickel sulfate hexahydrate 2.5%                     | 355                   | 68 (19.2)           | 58 (85.3)                                                | 9 (2.5)                               | 6 (66.7)                                                 |
| Bacitracin 20%                                      | 253                   | 27 (10.7)           | 26 (96.3)                                                | 6 (2.4)                               | 4 (66.7)                                                 |
| Cobalt sulfate 1%                                   | 195                   | 14 (7.2)            | 11 (78.6)                                                | 4 (2.1)                               | 3 (75.0)                                                 |
| Gold chloride 0.5% Alc                              | 195                   | 19 (9.7)            | 14 (73.7)                                                | 4 (2.1)                               | 4 (100.0)                                                |

Alc, Alcohol; Aq, aqueous; neg, negative; pos, positive.

\*Only allergens that caused delayed-positive reactions for at least 2% of patients are listed in this table.

<sup>†</sup>Tests were read within 21 days after application.

<sup>‡</sup>Percentages were calculated using the number of patients with positive reactions as the denominator.

studies of delayed-positive reactions and shows that late readings were taken on days 6 through 28, whereas early readings were taken on days 2 through 4.<sup>1,3-5,14</sup> Furthermore, different centers use different concentrations, vehicles, and allergens. For example, many European centers test nickel at 5% in petrolatum, whereas American centers test it at 2.5%. Some use the PPD base, and others use the salt. Corticosteroids have been tested in petrolatum, ethanol, and other vehicles.

The timing of a late reading makes a difference. Isaksson et al<sup>1</sup> reported that “without a reading on [day 7], 30.0% of contact allergy to corticosteroid would have been missed.” The data on which the statistics are based should be considered. Isaksson et al<sup>1</sup> compared readings on days 3 through 4 with readings on day 7 and concluded that the day-7 reading was necessary and important. In contrast, our group previously examined patients on day 5, compared those readings with readings from days 7 through 10, and detected only 1 new reaction.<sup>6</sup> However, these results are not necessarily discordant. One could postulate that had readings been performed on day 5 in the study by Isaksson et al,<sup>1</sup> such reactions might have been detected.

### PPD, metals, and topical antibiotics

In our group, PPD readings after day 5 identified only one additional reaction from 251 readings (0.4%). This was at variance with a previous report

from Hillen et al,<sup>2</sup> which described delayed reactions in 1.5% of those tested with PPD. Our results for detection of metal allergies substantiated the observations of others (see Table III)<sup>3,15</sup> and emphasized the importance of delayed readings. Topical antibiotics, including bacitracin (6 delayed-positive reactions of 253 tests) and neomycin (10 of 253), were associated with delayed patch-test reactions (interpreted during days 7 through 21). Others also have reported that delayed readings are necessary to detect allergic patch test reactions to topical neomycin (Table III).<sup>3</sup> To our knowledge, no others have reported delayed readings of bacitracin with outcomes that were similar to ours.

### Reaction strength of dissipating or delayed-positive reactions

Almost two thirds of the reactions that dissipated after day 5 were very mild (macular erythema). Whether these were irritant reactions or mild allergic reactions is impossible to determine (both were possible). However, the stronger reactions that dissipated by day 5 are more difficult to explain. Of reactions that became apparent only after day 5, less than one third were very mild (macular erythema). Because two thirds of the reactions were weak, strong, or extreme, they very likely were allergic patch-test reactions that required longer than 5 days to become apparent.

**Table III.** Review of the literature describing “late patch test readings” and “delayed patch test reactions”

| Study                                      | Allergens studied                                                                             | Patients tested (No.)                                       | Days of patch test interpretation | Findings                                                                                                                                                                                                                |
|--------------------------------------------|-----------------------------------------------------------------------------------------------|-------------------------------------------------------------|-----------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Hillen et al <sup>2</sup>                  | PPD<br>Epoxy resin<br>Nickel sulfate                                                          | 1748<br>1748<br>812                                         | 7, 14, 21                         | Delayed reaction observed in 1.5% of PPD reactions and 0.3% of epoxy resin. Reactions probably were due to patch test sensitization. No late readings were performed for nickel sulfate allergies.                      |
| Isaksson and Bruze <sup>5</sup>            | Budesonide,<br>tixocortol pivalate,<br>hydrocortisone<br>17-butyrate in pet.                  | 2                                                           | 3-4, 6-7, 10, 13                  | Reactions seen on days 6-7. Not all delayed reactions represent sensitization, at least not for budesonide.                                                                                                             |
| Jonker and Bruynzeel <sup>3</sup>          | European standard series, additional standard series                                          | 760                                                         | 2-3, 6-7                          | Late reactions were observed for nickel sulfate 2.6%, neomycin sulfate 0.9%, tixocortol-21-pivalate 0.5%, CI+Me—isothiazolinone 0.5%, p-tert-butylphenol formaldehyde 0.5%, potassium dichromate 0.5%, PPD, and others. |
| Davis, Richardson, and Farmer <sup>6</sup> | Corticosteroid series                                                                         | 135                                                         | 5, 7, 9                           | Two delayed reactions to 1656 corticosteroids; extended reading was of limited value.                                                                                                                                   |
| Lee et al <sup>11</sup>                    | Gold sodium thiosulfate                                                                       | 255 (pts had eczema)                                        | 4, 14, 21                         | Delayed reactions were observed for 54 pts (21.2%). However, not all reactions were read late.                                                                                                                          |
| Andersen et al <sup>12</sup>               | Isoeugenol                                                                                    | 27 (pts were isoeugenol sensitive)                          | 3, 7, up to 28                    | Dose-time relationship was investigated. Lower doses resulted in later reactions (0.2% concentration, mean reaction at day 7; 0.05% concentration, mean reaction at day 15).                                            |
| Isaksson et al <sup>13</sup>               | 2-Hydroxyethyl methacrylate, ethyleneglycol dimethacrylate                                    |                                                             | 3, 7, 10, 14, 21, 24, 28          | Readings on day 3 and day 7 failed to identify 16% reactions to 2-hydroxyethyl methacrylate and 5.3% of reactions to ethyleneglycol dimethacrylate because these reactions appeared more than 1 week later.             |
| Isaksson et al <sup>1</sup>                | Corticosteroid mix containing tixocortol pivalate, budesonide, and hydrocortisone 17-butyrate | 5432<br>3379                                                | 3-4<br>3-4, 7                     | Without a reading on day 7, 30% of contact allergies to corticosteroid markers were not identified.                                                                                                                     |
| Geier et al <sup>4</sup>                   | Standard series                                                                               | 1096<br>1243<br>1136                                        | 3-4<br>3 and 5<br>3 and 6         | More positive results for neomycin sulfate, cobalt chloride, and PPD were identified in the day 3–day 6 group.                                                                                                          |
| Hjorth and Thomsen <sup>14</sup>           | Neomycin                                                                                      | 139 (pts previously had positive test results for neomycin) | 2, 4, 6, 9, 10, 11, 13, 30        | A positive patch test was observed 7 days later for 27 pts. Of these, 7 were observed at close intervals—reactions developed on day 9 for 3 pts and on day 10, 11, 13, and 30 for others.                               |

Continued

Table III. Cont'd

| Study                          | Allergens studied                      | Patients tested (No.) | Days of patch test interpretation                                            | Findings                                                                                                                                                                                        |
|--------------------------------|----------------------------------------|-----------------------|------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Macfarlane et al <sup>15</sup> | Neomycin, potassium dichromate, cobalt | 403                   | 2, 4, 7, 9; compared paired readings from days 2 and 4 and from days 4 and 7 | Delayed-positive reactions (after day 4) were observed for neomycin, potassium dichromate, and cobalt. Paired readings from days 4 and 7 were of greater value than readings from days 2 and 4. |
| Mitchell <sup>16</sup>         | Large series of allergens              | 499                   | 2, 7                                                                         | One fifth of reactions that were negative on day 2 were positive on day 7.                                                                                                                      |

*pet.*, Petrolatum; *PPD*, *p*-phenylenediamine; *pts*, patients.

### Schedule of patch test interpretation

We questioned whether readings on days 7 through 10 (instead of on day 5) might maximize the detection of allergic patch test reactions. For example, it might be convenient to schedule patients to have patch tests applied on day 1, removed and evaluated on day 3, and reevaluated during days 7 through 10. However, our data showed that reactions to certain allergens, including balsam of Peru 25%, benzoic acid 5%, disperse blue #124 1%, fragrance mix 8%, mercury 0.5%, methyl dibromo glutaronitrile/phenoxyethanol 1.5%, natural fragrance mix 2%, and octyl gallate 0.25%, dissipated after day 5 (see Table D).

Reactions to some allergens may dissipate after day 5 for several reasons. These allergens may be borderline irritants that still give readings at day 5. They also could be the allergic patch-test reactions that disappear after day 5. Whatever the mechanism, it is important for clinicians to realize that reactions to many allergens may dissipate after day 5 and that some positive reactions would not be identified if readings were performed only on day 3 and on days 7 through 10. Therefore, we suggest that the day 5 reading should not be omitted.

### Could delayed reactions be due to patch test sensitization?

Hillen et al<sup>2</sup> showed that PPD (in 1% petrolatum) elicited delayed reactions in 1.5% of routine patch tests; in 5 of 7 patients, repeated patch tests with PPD disclosed patch-test sensitization as the cause of the delayed reaction. All delayed reactions, except for one, occurred in patients exposed to patch-test allergens for 48 hours. This finding raises the concern about whether delayed patch-test reactions might be caused by patch-test sensitization. We are unable to answer this question with the data presented herein because our patients did not have repeat patch

testing. This question should be addressed in future studies.

### Study limitations and strength

This was a retrospective study. Patients were tested because of suspected allergies to metals and corticosteroids (these patients were required to return after day 5). One strength of the study was the large number of patients who returned for patch-test interpretation on the stated days.

A potential limitation of this study is interperson variation in reading and interpretation of patch-test reactions. At our institution, interpretation of the reactions is performed by physicians (consultants and residents) under supervision of the Mayo Clinic Contact Dermatitis Group. A specialized patch-test nurse may assist with readings. This protocol is different from those used in other patch testing centers, where one physician will read and interpret patch-test results. The system of interpretation of patch tests at our institution is both a strength (permitting flexibility for patients and physicians) and a potential weakness (physicians with modest patch-testing experience can perform and interpret patch tests).<sup>17</sup>

### CONCLUSIONS

Patch-test interpretation on day 5 detected most allergic patch test reactions. If reactions to metals or topical antibiotics (neomycin and bacitracin) are suspected, consideration should be given to readings after day 5. Our experience showed that a reading on days 7 through 9 could detect most delayed-positive reactions. Unlike previous reports, our study showed that delayed readings (after day 5) for topical corticosteroids and PPD were of low value. Substituting a later reading (day 7 and after) for the day 5 reading might exclude reactions to some allergens such as fragrances.

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