Determinants of Airway Response to Challenge with Distilled Water in a Population Sample of Children Aged 7 to 10 Years Old*

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We challenged 446 schoolchildren and measured the percent decrease in FEV, following 10 min of tidal inhalation of UNDW. Assessment tools for respiratory symptoms and atopy were questionnaire and skin testing, respectively. A previous diagnosis of asthma was most strongly associated with a positive airway response (defined as a fall in FEV, ≥10 percent. A positive response was also associated with atopy, presence of cough, cough during night, or any respiratory symptom. A child’s age and the prechallenge FEF75% also explained response to distilled water indicating less responsiveness for older children and those with relative greater airway diameter. For the previous diagnosis of asthma, a positive distilled water challenge test had a sensitivity of 36 percent and a specificity of 92 percent. We conclude that a significant relationship between airway response to distilled water, asthma and symptoms suggestive for asthma exists for a childhood population sample.

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In 1980 inhalation of an aerosol of distilled water was reported to increase airway resistance in symptomatic asthmatic subjects.1 Inhaling such an aerosol was concluded to be a useful test to identify bronchial responsiveness. Since then repeated clinical studies on challenge with ultrasonically nebulized distilled water (UNDW) have been performed,5-18 and have suggested that responsiveness to distilled water is consistent with moderate to severe asthma.17

Although the mechanism by which UNDW elicits bronchoconstriction is not known precisely, it is thought that a change in osmolarity of the airways causes the release of inflammatory mediators from mast cells.9 Hence an indirect cell-mediated rather than a direct action on bronchial smooth muscle is believed to occur.18 Therefore bronchial response to UNDW has been postulated to more closely parallel bronchial mucosal inflammation than challenge with methacholine.14 Further the airway response induced by UNDW can be thought to be similar to naturally occurring stimuli provoking asthmatic attacks, such as exercise or weather changes, where variation in osmolarity of airway epithelial fluid also occurs.

Given the postulated mast-cell mediated mechanism, response to distilled water would be an attractive tool to identify bronchial asthma and related risk factors. However, to our knowledge no population study has been reported to date. To examine the interrelation between UNDW response and respiratory disease and to overcome selection bias limiting clinical data, we set up a population-based study. For a childhood sample, the distribution of response to distilled water and the determinants of a positive test (defined as an UNDW-induced fall in FEV, ≥10 percent) are presented.

METHODS

Study Population

In Lower Austria, an exposure-stratified sample of four towns was chosen on the basis of existing air pollution records. Public schools were visited and all pupils in grades 2, 3, and 4 invited to participate. Approval to conduct the study was given by the local ethics committee. The schools were visited between January and March 1989. The parents of 530 children were contacted and written consent was given for 512 children to participate in the study and have a challenge test performed. Thirty-two children were absent when their school was visited.

Questionnaire and Skin-Prick Testing

A self-administered questionnaire was completed by the parents of each child. Questions were derived from a standardized World Health Organization questionnaire* and translated into German. We asked the parents about the presence of respiratory symptoms apart from colds in the previous 12 months. Included were the following: cough, cough during the night, cough when playing, breathlessness when playing, breathlessness during the night,
wheeze, and breathlessness associated with wheeze. Whether there was a previous diagnosis of asthma and wheezy bronchitis also was requested. A recent upper respiratory tract illness was assumed if the child had suffered from a cough during the four weeks preceding the challenge and/or showed rales on physical examination when tested. For each child, the last 12 months of exposure to maternal smoking also was assessed and classified as absent or present.

Skin-prick tests for seven common allergens (cat dander, dog dander, Dermatophagoides pteronyssinus, birch, timothy grass, ragweed and alternaria; ALK Laboratories, Denmark) were performed on 214 children. Atopy to any allergen was considered positive when wheal diameter was equal to or greater than that of a histamine control. Three strata of skin-test positivity were determined (stratum one: negative skin-test for all allergens; stratum two: positive test for one allergen; stratum three: positive test for at least two allergens).

Spirometric Protocol

Before the recording of lung function, each child's height in stocking feet (to the nearest centimeter) was measured and a physical auscultation of the chest completed. Subjects performed forced expiratory maneuvers in the standing position with a nose clip. Spirometric recordings were made with a linear heated pneumotachograph (Jaeger, Würzburg, Germany) and judged according to standard American Thoracic Society criteria for curve acceptability and flow measurements.12 Measures derived from the best of three acceptable tracings were corrected to BTPS and transferred to a microcomputer. A second prechallenge spirometric reading was recorded after a 5-min interval. Lung function parameters investigated, as derived from the prechallenge readings, were FEV1, (measured in liters), FEF25% (measured in liters per second), FEF50% (measured in liters per second), FEF75%, (measured in liters per second), FVC (measured in liters), and the ratios of FEV1/FVC, FEF25%/FVC, FEF50%/FVC and FEF75%/FVC.

Bronchial Challenge with Distilled Water

The challenge method used a single-step protocol adapted from that previously described by Götz et al. and in all cases was supervised by a physician trained in respiratory medicine. During the 10-min challenge, the child was positioned seated with a nose clip and instructed to breathe normally and regularly. Immediately after the challenge spirometry was repeated. When resting bronchoconstriction, defined as a ratio of FEV1/FVC of less than 0.7, was detected, the challenge was not performed.

A Habel M608 ultrasonic nebulizer (Habel Medizintechnik, Vienna, Austria) was used. At an airflow of 12 L/min particle sizes varied between 0.5 and 18 μm. The nebulizer was designed to produce particles with a median diameter of 8 μm. For each challenge, the nebulizer cylinder was filled with 150 ml of distilled water maintained at a temperature of 4°C. Volume output was determined twice a day for each of the two nebulizers in use and averaged 16.9 (SD: 3.7) ml/min. A 20-cm expiratory tube was connected to the nebulizer and a pediatric mouthpiece with a three-way valve permitted expired air to be exhaled into the atmosphere.

Data Analysis

Within-subject variability of FEV1 was estimated as the percentage change between the first and the second prechallenge readings. By examining random change in FEV1, between repeated measures, we estimated the false-positive rates to be expected for thresholds of bronchial responsiveness (Table 1). Bronchial responsiveness following distilled water challenge was calculated as the percentage reduction from the second prechallenge FEV1.

First, the response to distilled water was investigated as a continuous variable and the shape of the distribution examined. Second, the significance of a positive response to distilled water, defined as a decrease in FEV1 ≥10 percent, was investigated. Influence of conditions of measurement (such as area of residence and nebulizer output) and effects of sex, age, height, and prechallenge lung function were analyzed by logistic regression using Egret. The same statistical methods were employed to relate a positive response to UNDW with presence of respiratory disease, symptoms, and risk factors. The sensitivity and specificity of the distilled water challenge test in detecting asthmatic subjects was calculated.

RESULTS

Overall, bronchial response to distilled water was significantly (p = 0.001) associated with a previous diagnosis of asthma and asthmatic children demonstrated a ninefold greater probability of a positive response than did nonasthmatic subjects. Other respiratory symptoms such as cough and cough during the night observed for the preceding year also were found to be associated in univariate analysis but appeared to be only partly independent in multivariate analysis.

Of 490 children measured, 24 (5 percent) were unable to perform spirometry satisfactorily, two demonstrated resting bronchoconstriction, and eight were unwilling to complete the distilled water challenge. Analysis of the questionnaires of these 34 children

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Table 1—Comparative Magnitude of Random Variability in FEV1 and Response to Distilled Water Challenge with Expected False-Positive Rates

<table>
<thead>
<tr>
<th>Probability of Decrease in FEV1 Due to Random Variability*</th>
<th>Random Decrease in FEV1 Probability of Decrease in FEV1 following Distilled Water Challenge*</th>
<th>Nonasthmatic Sample Subjects</th>
<th>Nonasthmatic Subjects</th>
<th>Expected False-Positive Rates† for Distilled Water Challenge, %†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease in FEV1, Sample Random</td>
<td>(n = 446)</td>
<td>(n = 435)</td>
<td>Sample Random</td>
<td>(n = 446)</td>
</tr>
<tr>
<td>5-9%</td>
<td>0.186 (83)</td>
<td>0.051 (23)</td>
<td>0.046 (20)</td>
<td>28</td>
</tr>
<tr>
<td>10-14%</td>
<td>0.085 (38)</td>
<td>0.018 (8)</td>
<td>0.016 (7)</td>
<td>21</td>
</tr>
<tr>
<td>15-19%</td>
<td>0.036 (16)</td>
<td>0.004 (2)</td>
<td>0.005 (2)</td>
<td>12</td>
</tr>
<tr>
<td>≥20%</td>
<td>0.011 (5)</td>
<td>0.002 (1)</td>
<td>0.002 (1)</td>
<td>20</td>
</tr>
</tbody>
</table>

*Values in parentheses are numbers of subjects.
†Expected false-positive rates for distilled water challenge resulting from random variability in spirometry were calculated as follows: probability of decrease due to random variability/probability of decrease following challenge.
revealed one asthmatic subject among them; however, these subjects did not have an excess of respiratory symptoms when compared with the children tested. The mean age of the remaining sample subjects (n = 446) was 9.0 (SD: 0.9) years; 48.6 percent of this group were boys and 51.4 percent girls.

Distribution of Spirometry and Bronchial Response to Distilled Water Challenge

The distribution of random DFEV₁% shows that in eight out of 446 children (1.8 percent) the FEV₁ dropped by 10 percent or more for the second prechallenge measurement (Fig 1). When the same threshold was applied to the distribution of DFEV₁% induced by distilled water 38 out of 446 children (8.5 percent) demonstrated a corresponding postchallenge drop (Fig 2). Consequently for children found to be responsive to UNDW at a 10 percent threshold, there will be about 21 percent (eight out of 38) false-positives (Table 1) due to random variability in spirometry. Variance of random DFEV₁% by respiratory disease and symptoms indicated that for asthmatic children random variability was seven times greater than that observed for nonasthmatic subjects. However, random DFEV₁% as observed for a population excluding known asthmatic subjects did not substantially alter the corresponding false-positive rates (Table 1) for UNDW DFEV₁%.

The shape of the distilled water response distribution was found to be unimodal. Values were distributed continuously and skewness toward greater responsiveness was observed. Mean distilled water-induced decrease of FEV₁ was 2.0 percent, with 90 percent of the values falling between an increase of 5.8 percent and a decrease of 12.7 percent (Fig 2). Thirty-eight (8.5 percent) of the children demonstrated a decrease ≥10 percent and 83 (18.6 percent) children had a decrease ≥5 percent.
Table 2—Bronchial Response to Distilled Water* and Its Relationship to Respiratory Disease and Symptoms in 446 Children Aged 7 to 10 Years

<table>
<thead>
<tr>
<th>Variable</th>
<th>Prevalence, %†</th>
<th>OR‡</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physician's diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>2.5 (11)</td>
<td>9.1</td>
<td>2.4-34.9</td>
<td>0.001</td>
</tr>
<tr>
<td>Wheezy bronchitis</td>
<td>11.4 (51)</td>
<td>1.2</td>
<td>0.44-3.3</td>
<td>0.71</td>
</tr>
<tr>
<td>Respiratory symptoms apart from colds</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>7.8 (35)</td>
<td>3.0</td>
<td>1.11-8.0</td>
<td>0.03</td>
</tr>
<tr>
<td>Cough during night</td>
<td>6.9 (31)</td>
<td>3.4</td>
<td>1.11-10.8</td>
<td>0.03</td>
</tr>
<tr>
<td>Cough when playing</td>
<td>4.0 (18)</td>
<td>2.5</td>
<td>0.67-9.1</td>
<td>0.17</td>
</tr>
<tr>
<td>Breathlessness during night</td>
<td>3.6 (16)</td>
<td>3.3</td>
<td>0.86-13.0</td>
<td>0.08</td>
</tr>
<tr>
<td>Breathlessness when playing</td>
<td>3.4 (15)</td>
<td>2.0</td>
<td>0.42-9.5</td>
<td>0.38</td>
</tr>
<tr>
<td>Wheeze</td>
<td>2.5 (11)</td>
<td>3.3</td>
<td>0.64-16.8</td>
<td>0.15</td>
</tr>
<tr>
<td>Breathlessness with wheeze</td>
<td>3.8 (17)</td>
<td>2.9</td>
<td>0.78-11.4</td>
<td>0.10</td>
</tr>
<tr>
<td>Any respiratory symptom</td>
<td>15.6 (70)</td>
<td>3.8</td>
<td>1.70-8.3</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Positive response was defined as a postchallenge drop in FEV, ≥10 percent.
†Values in parentheses are numbers of subjects.
‡All OR estimates are adjusted for conditions of measurement (site of measurement and nebulizer output).

**Conditions of Measurement**

Nebulizer output (odds ratio [OR] 1.05; p = 0.41) was found not to be significant for a positive response to UNDW. Odds ratios relating site-specific probability of response compared with site 1 were 1.1 (p = 0.78) for site 2; 0.59 (p = 0.31) for site 3, and 0.78 (p = 0.62) for site 4, respectively. Although conditions of measurement did not predict bronchial response, they were demonstrated to confound the association between response to distilled water challenge and respiratory disease. Hence all subsequent regression models were adjusted for site and nebulizer output.

**Effect of Sex, Age, Height, and Baseline Lung Function**

Bronchial response did not vary significantly between boys (9.6 percent responders) and girls (9.0 percent responders) (p = 0.86). The OR of 0.69 (95 percent confidence interval [CI] 0.47 to 0.98; p = 0.04) for age indicated an about 30 percent smaller frequency of response for each year increase in age. Height was found nonsignificant (OR 0.97; p = 0.22). Of lung function parameters investigated, only FEF75% was of significance (p = 0.04). Each unit increase in FEF75% predicted an approximately 40 percent smaller probability of response (OR 0.62; 95% CI 0.39 to 0.98). However when age and FEF75% were kept in the same model effect estimates became nonsignificant (for age, OR 0.76 [p = 0.17]; for FEF75%, OR 0.70 [p = 0.15]).

**Respiratory Disease and Symptoms**

A previous diagnosis of asthma was the best predictor of bronchial response to distilled water (OR 9.1; 95 percent CI 2.4 to 34.9; p = 0.001), but wheezy bronchitis showed no association (OR 1.2; 95 percent CI 0.44 to 3.3; p = 0.71).

Respiratory symptoms significantly associated with a positive challenge test were presence of cough (OR 3.0; 95 percent CI 1.1 to 8.0; p = 0.03) and presence of cough during the night (OR 3.4; 95 percent CI 1.1 to 10.8; p = 0.03). Presence of wheeze (OR 3.3; 95 percent CI 0.64 to 16.8; p = 0.15), as was observed for other symptoms, did not reach statistical significance (Table 2). Response to UNDW was, however, about four times more likely for those reporting any respiratory symptom than for those reporting no symptoms at all (OR 3.8; 95 percent CI 1.7 to 8.4; p = 0.001).

**Skin-Prick Test and Other Risks**

A single-effect estimate was fitted over all three strata of skin test positivity and the OR for each step increase was 4.8 (95 percent CI 1.65 to 13.8; p = 0.004). Of other risk factors investigated, neither maternal smoking (OR 0.48; 95 percent CI 0.20 to 1.1; p = 0.09) nor recent upper respiratory tract illness (OR 1.8; 95 percent CI 0.66 to 5.1; p = 0.24) was related to a positive distilled water challenge test.

**Significant Predictors in Relation to a Previous Diagnosis of Asthma**

Effect estimates for significant predictors of a positive distilled water challenge test like presence of any respiratory symptom (OR 3.0; 95 percent CI 1.2 to 7.2; p = 0.012) and atopy (OR 3.2; 95 percent CI 0.99

Table 3—Predictors of Bronchial Response to Distilled Water* Apart from a Physician's Diagnosis of Asthma

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR†</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atopy</td>
<td>3.2</td>
<td>0.99-10.1</td>
<td>0.05</td>
</tr>
<tr>
<td>Any respiratory symptom</td>
<td>3.0</td>
<td>1.2-7.2</td>
<td>0.012</td>
</tr>
<tr>
<td>Cough</td>
<td>2.7</td>
<td>0.95-7.4</td>
<td>0.06</td>
</tr>
<tr>
<td>Cough during night</td>
<td>2.5</td>
<td>0.7-8.8</td>
<td>0.15</td>
</tr>
</tbody>
</table>

*Positive response was defined as a postchallenge drop in FEV, ≥10 percent.
†All OR estimates are adjusted for a physician's diagnosis of asthma and conditions of measurement.

CHEST / 102 / 3 / SEPTEMBER, 1992 767
to 10.1; p = 0.05) attenuated when asthma was fitted simultaneously (Table 3). These multivariate analyses indicate that variables significant for a positive distilled water challenge test probably all relate to the same asthmatic trait.

**Sensitivity and Specificity of UNDW Response to Detect Asthma**

Four of 11 asthmatic subjects tested were responsive to the distilled water challenge (for a fall in FEV₁ ≥ 10 percent) with a maximum decrease of 25 percent in one child. However, 34 (7.8 percent) of 435 nonasthmatic subjects also were classified as responsive. With a 10 percent cutoff point, the sensitivity of the challenge to detect asthmatic subjects was 36 percent and the specificity 92 percent. The corresponding predictive values for a positive and negative test result were 10.5 and 98 percent, respectively.

**Discussion**

We assessed bronchial responsiveness in 446 primary schoolchildren aged 7 to 10 years by means of a single-step distilled water challenge test. Although the use of distilled water in measuring bronchial responsiveness has been extensively evaluated in laboratory studies, it has, to our knowledge, not yet been evaluated for epidemiologic purposes. The challenge was well tolerated by all children and no challenge had to be terminated because of side effects like cough. Although not directly monitored, it was our impression that cough occurred in about 5 percent of children and when present lasted for a few seconds at the beginning of a test. This observation also would be consistent with two different pathways postulated for the cough and bronchoconstrictive response to distilled water.

Hopp et al recently reported that a reaction to UNDW was highly specific for asthma, as other authors have noted. Hopp and his colleagues studied 40 asthmatic and 26 control subjects; 66 percent of the asthmatic subjects showed a positive response, while only two of the control subjects reacted to the challenge. These investigators concluded that a positive test could be used to support a diagnosis of asthma. However, the prevalence of asthma in their sample was 60 percent, thus leading to a very low frequency of false-positive results. In population-based samples, the prevalence of asthma generally is much lower (in our sample 2.5 percent). A very high specificity is necessary to achieve a high positive predictive value, which would be needed to verify asthma by a positive distilled water challenge. The positive predictive value was only 10.5 percent in our sample, thus making it impossible to draw any clinical conclusions from a positive screening test.

In our population sample, response to distilled water challenge was distributed continuously and unimodally, as has been observed with other provocation techniques. A division into normal and increased responsiveness in populations seems arbitrary. Although asthmatic subjects tended to be on the right-hand tail of the UNDW DFEV₁% distribution, 7.8 percent of subjects denying asthma also were responsive. Baseline lung function, respiratory infections, history of allergy, and respiratory symptoms are known to affect the level of responsiveness when pharmacologic provocation techniques are used. Measuring bronchial response by nonpharmacologic methods, eg, exercise testing or cold air inhalation, has proven to be less sensitive in connecting reactivity to variables associated with respiratory illness. Weiss et al studied airway responsiveness in a population sample of adults and children by means of eucapnic hyperpnea. Using a 9 percent cutoff point for DFEV₁%, they reported that only a physician's diagnosis of asthma was a predictor of responsiveness. Nineteen percent of subjects denying asthma were found to be responsive, compared with 7.8 percent in our sample.

**Table 4—Distilled Water Challenge and Sensitivity to Asthma for Different Studies**

<table>
<thead>
<tr>
<th>Clinical Studies</th>
<th>Sample Size/ Age Range, y</th>
<th>Amount Inhaled, ml</th>
<th>Decrease in FEV₁ to Define Response, %</th>
<th>Sensitivity to Asthma, %</th>
<th>Type of Nebulizer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Galdes-Sebaldt et al</td>
<td>21/7-16</td>
<td>...</td>
<td>10</td>
<td>71</td>
<td>DeVilbiss model 65</td>
</tr>
<tr>
<td>Lemire et al</td>
<td>11/20-43</td>
<td>44</td>
<td>20</td>
<td>91</td>
<td>DeVilbiss ultra neb 100</td>
</tr>
<tr>
<td>Bascom and Bleecker</td>
<td>15/25-40</td>
<td>38</td>
<td>20</td>
<td>53</td>
<td>DeVilbiss model 65</td>
</tr>
<tr>
<td>Anderson et al</td>
<td>55/11-56</td>
<td>33</td>
<td>20</td>
<td>100</td>
<td>Mist O2 Gen EN 143a</td>
</tr>
<tr>
<td>Black et al</td>
<td>12/20-41</td>
<td>33</td>
<td>20</td>
<td>75</td>
<td>Mist O2 Gen EN 143 a</td>
</tr>
<tr>
<td>Hopp et al</td>
<td>66/21-37</td>
<td>82</td>
<td>10</td>
<td>76</td>
<td>DeVilbiss model 646</td>
</tr>
<tr>
<td>Epidemiologic study, present report</td>
<td>446/7-10</td>
<td>20</td>
<td>10</td>
<td>36</td>
<td>Habel m608</td>
</tr>
</tbody>
</table>

Distilled Water Challenge in Children (Frischer et al)
also found a significant positive correlation between responsiveness and younger age. The same tendency also was present in our sample (p = 0.04).

The low sensitivity of the UNDW challenge in detecting asthma in our sample can be explained, in part, by the protocol. The average nebulized fluid load resulted in approximately 20 ml inhaled. Galdez-Sebaldt et al. found a sensitivity of 71 percent using increasing amounts of water. Lemire et al. found ten of 11 asthmatic subjects responsive to an inhalation of approximately 50 ml. Of the asthmatic subjects whom Hopp et al. studied, 66 percent had a drop in FEV1 of at least 20 percent below baseline after inhalation of more than 80 ml. Bascom and Bleecker, on the other hand, found a sensitivity of 53 percent when an average amount of only 38 ml was inhaled (Table 4).

Another explanation for the low sensitivity of the distilled water challenge in our sample could be prechallenge use of antiasthmatic medication and severity of asthmatic disease. Contrary to clinical studies, where treatment often is withheld prior to challenge, such an effort was thought unethical for our population-based setting. Of four asthmatic subjects found reactive to the challenge (DFEV1, % ≥ 10) only one reported daily use of antiasthmatic drugs, while for nonresponsive asthmatic subjects this was the case for four out of seven. In clinical studies, asthmatic subjects were better defined, and all used a stepwise inhalation protocol. However, there were large differences in the amount of water needed to elicit bronchoconstriction. In a study by Anderson et al., a total of 33 ml of distilled water was delivered, but 51 percent of asthmatic subjects responded after inhalation of only 2 ml. On the other hand, as reported by Bascom and Bleecker, even a tenfold increase in the amount of water nebulized could not cause bronchoconstriction in some asthmatic subjects. Taken together these studies indicate that distilled water is a potent airway stimulus for asthmatic subjects. However, the circumstances causing variation in response as suggested by large between-study differences need further clarification before a commonly accepted protocol can be established.

There is good correlation between response to UNDW and that to exercise testing (r = 0.66; p < 0.01) [response to exercise was expressed as the percent fall in FEV1, following exercise and response to UNDW was the volume nebulizer output producing a 20 percent fall in FEV1]. However, response to methacholine or hyperosmolar aerosols is usually not found to correlate well with distilled water challenge. When cold air and UNDW challenges have been performed on the same subjects, some good and some poor agreement have been reported. The UNDW challenge is thought to alter osmolarity of bronchial mucosa, thus leading to mediator release by inflammatory airway cells. In a recent paper describing responsiveness to UNDW in heart-lung transplant recipients, a close correlation was found between histologic signs of rejection and a positive challenge; however, transplant rejection and methacholine-induced bronchial responsiveness were not associated. In subjects responsive to distilled water, perivascular infiltrates of bronchial mucosa were documented, and Higgenbottom et al. speculated that specific airway inflammation might be responsible for the observed correlation.

In population-based studies, asthma prevalence can be expected to be between 3 and 5 percent. Under such circumstances, a highly specific test (to lower the rate of false-positive results) is of relatively greater importance in ruling out disease than a very sensitive one, since there will be very few false-negative results (because of the low number of asthmatic subjects), even with a low sensitivity. However, assuming a prevalence of 20 percent, as is encountered in pediatric outpatients, the negative predictive value for the distilled water challenge test would still be 84 percent.

For a prevalence of asthma as observed for our sample (2.5 percent), a negative test result is consistent with an extremely low likelihood (= 2 percent) of undiagnosed asthma. In contrast, because of the low predictive value of a positive test in the population setting, UNDW challenge does not usefully identify asthmatic subjects alone. This finding may well support the contention that asthma is likely to be underdiagnosed in a population and that subclinical or latent respiratory airway reactivity is not infrequent. Given its hypothesized cell-mediated mechanism, the assessment of response to distilled water provides a new tool to investigate asthmatic airway inflammation. The relationship previously observed for selected clinical populations between asthmatic disease and distilled water response was corroborated for a large representative population sample of children.

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REFERENCES
1 Allegra L, Bianco S. Non-specific broncho-reactivity obtained with an ultrasonic aerosol of distilled water. Eur J Respir Dis 1990, 61 (suppl 106):41-9
3 Anderson SD, Schoeffel R, Finney M. Evaluation of ultrasonically nebulized solutions for provocation testing in patients with...
4 Sheppard D, Rizk NW, Bouhey HA, Bethel RA. Mechanism of cough and bronchoconstriction induced by distilled water. Am Rev Respir Dis 1983; 86:10-4
5 Fabbri LM, Mapp CE, Hendrick DJ. Comparison of ultrasonically nebulized distilled water and hyperventilation with cold air in asthma. Ann Allergy 1984; 53:172-7
11 Lemire TS, Hopp RJ, Bewtra AK, Nair NM, Townley RC. Comparison of ultrasonically nebulized distilled water and cold air hyperventilation challenges in asthmatic patients. Chest 1989; 95:85-102
13 Black JL, Smith CM, Anderson B. Cromolyn sodium inhibits the increased responsiveness to methacholine that follows ultrasonically nebulized water challenge in patients with asthma. J Allergy Clin Immunol 1987; 90:39-44
16 Hopp RJ, Christy J, Bewtra AK, Nair NM, Townley RG. Incorporation and analysis of ultrasonically nebulized distilled water challenges in an epidemiologic study of asthma and bronchial reactivity. Ann Allergy 1988; 60:129-33
19 Florey CV, Leeder SR. Methods for cohort studies of chronic airflow limitation. WHO Reg Publ Eur Ser 1982; 12:134-60