Hemorrhagic Rhinitis
An Immunologic Disease Due to Hexahydrophthalic Anhydride

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This is a descriptive study of six men who had been occupationally exposed to heated epoxy resin containing hexahydrophthalic anhydride (HHPA) who presented with rhinitis, nasal mucosal erosions, and significant epistaxis; three also had asthma. When they were removed from exposure to HHPA, the rhinitis symptoms, nasal erosions, and epistaxis resolved spontaneously. All six had high titers of IgG and IgE against HHP-HSA as determined by an enzyme-linked immunosorbent assay (ELISA). Other asymptomatic workers with similar HHPA exposure had very low or negative titers of IgG and IgE against HHP-HSA. We conclude that these results are very suggestive of an immunologic mechanism being responsible for the rhinitis, nasal mucosal erosions, and epistaxis that occurred in the six described HHPA workers.

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ELISA = enzyme-linked immunosorbent assay; HHP-HSA = hexahydrophthalyl-human serum albumin; HSA = human serum albumin; LRSS = late respiratory systemic syndrome; NIOSH = National Institute of Occupational Safety and Health; PBS = phosphate-buffered saline solution; PDA = pulmonary disease anemia syndrome; TMA = trimellitic anhydride

Acid anhydrides are low molecular weight, reactive chemicals that can haptenize autologous proteins to produce a variety of immunologic respiratory diseases in sensitized individuals. Trimellitic anhydride (TMA) is a model chemical that can cause IgE mediated rhinitis and/or asthma and two delayed pulmonary syndromes, each associated with a high level of total specific antibody: late respiratory systemic syndrome (LRSS) and pulmonary disease anemia syndrome (PDA). Hexahydrophthalic anhydride (HHPA) has been described to cause IgE-mediated respiratory sensitization. However, to our knowledge, neither LRSS nor PDA due to HHPA has been described. Rhinitis and epistaxis but not nasal erosions or concomitant immunologic sensitization have been reported due to TMA. We report six adult men who presented with rhinitis, nasal mucosal erosions, and epistaxis who were occupationally exposed to heated epoxy resin containing HHPA. Serologic studies with hexahydrophthalyl-human serum albumin (HHP-HSA) were supportive of an immunologic mechanism.

METHODS
Clinical Evaluation of HHPA Workers
A surveillance study of approximately 50 workers in a plant manufacturing insulators for electrical equipment was conducted using an occupational respiratory questionnaire (collaboratively developed by the National Institute of Occupational Safety and Health and the Allergy Division of the University of Cincinnati).
Table 1—Summary of Workers With Rhinitis, Erosion(s)

Epistaxis Due to HHPA Fumes

<table>
<thead>
<tr>
<th>Worker/ Age, yr/ Sex</th>
<th>Race</th>
<th>Diagnoses</th>
<th>Exposure Category</th>
<th>Titer IgG-a—HHP-HSA</th>
<th>Titer IgE-a—HHP-HSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/25/M Black</td>
<td></td>
<td>Rhinitis, erosions, epistaxis</td>
<td>5</td>
<td>10⁴</td>
<td>10⁴</td>
</tr>
<tr>
<td>2/23/M White</td>
<td></td>
<td>Rhinitis, erosions, epistaxis</td>
<td>5</td>
<td>10⁴</td>
<td>10⁴</td>
</tr>
<tr>
<td>3/36/M Black</td>
<td></td>
<td>Asthma, rhinitis, erosions, epistaxis</td>
<td>6</td>
<td>&gt;10⁴</td>
<td>&gt;50</td>
</tr>
<tr>
<td>4/29/M Black</td>
<td></td>
<td>Rhinitis, erosions, epistaxis</td>
<td>3</td>
<td>&gt;10⁴</td>
<td>&gt;50</td>
</tr>
<tr>
<td>5/28/M White</td>
<td></td>
<td>Asthma, rhinitis, erosions, epistaxis</td>
<td>5</td>
<td>10⁴</td>
<td>10⁴</td>
</tr>
<tr>
<td>6/37/M Hispanic</td>
<td></td>
<td>Asthma, rhinitis, erosions, epistaxis</td>
<td>5</td>
<td>10⁴</td>
<td>10⁴</td>
</tr>
</tbody>
</table>

of the substrate, p-nitrophenyl phosphate (Sigma Phosphatase 104) at a concentration of 1 mg/ml in 10 percent diethanolamine buffer, at a pH of 9.8. Development was allowed to proceed until the positive control sample reached a predetermined optical density. The optical density at 405 nm was read using an automated ELISA reader (Bio-Tek Model EL-312, Bio-Tek Instruments, Inc. Winooski, VT). The individuals performing the serologic assays had no knowledge of the clinical information of the subjects.

RESULTS

Clinical Evaluation

Demographic information is listed in Table 1. All were men ranging in age from 23 to 37 years. Each of the six workers had rhinitis, nasal mucosal erosions, and epistaxis as determined by questionnaire, interview, and examination (Table 1). With removal from exposure, erosions and epistaxis resolved. Three workers also had symptoms, interval pulmonary function tests, and physical findings consistent with asthma. Results of annual baseline pulmonary function tests and chest radiographs were normal in all individuals.

Exposure Category

Worker exposure category is also listed in Table 1. One worker had an intermediate exposure category of 3 while the others had the highest categories of 5 or 6.

Immunologic Evaluation

The titers of IgG and IgE against HHP-HSA are listed in Table 1. All had specific IgG antibody titers of at least 1,000 while all had specific IgE titers of greater than 50. Each of the workers was also skin test positive to prick test with 5 mg/ml or intradermal with 1 μg/ml HHP-HSA.

DISCUSSION

Although rhinitis and asthma have been described due to HHPA and other anhydrides, nasal mucosal erosions and concomitant immunologic sensitization have not. This syndrome is similar in some respects to PDA syndrome which has been described to be immunologically mediated. Sera from patients with PDA due to TMA have been demonstrated to contain antibody that is capable of hemolyzing RBCs that have been haptenized with TMA. The antibody in those patients was also capable of causing direct agglutination of haptenized RBCs and of causing indirect agglutination using antihuman IgG, IgA, or IgM. The hemolytic assay results may well have biologic significance in that they demonstrate the existence of complement-fixing antibodies capable of destroying TMA-haptenized cells. This is likely an in vitro model of occurrences in the airways of individuals with PDA.

We hypothesize that HHPA haptenizes proteins and cell surfaces in the respiratory tract, in this case, the nasal mucosa. IgE against HHP-HSA would be immunopathogenic in causing allergic rhinitis symptoms. Perhaps IgG directed against HHP-HSA would cause cellular damage in the nasal mucosa just as IgG directed against TM-HSA can cause in vitro hemolysis and, presumptively, pulmonary hemorrhage. The difference in location (nasal vs pulmonary) may well be due to particle size, but this has not been studied. Further immunologic characterization of antibodies in these HHPA workers would be required to definitively prove their cytolytic capability.

We considered the possibility that the erosions and epistaxis were simply due to high levels of irritant exposure. However, the industrial hygiene data did not suggest levels to be high enough to be capable of tissue destruction. Moreover, other employees with similar exposure to HHPA but without antibody or only low levels of antibody did not have similar problems.

In summary, our evaluation of workers exposed to HHPA leads us to conclude that specific immunologic sensitization is likely to cause not only asthma and rhinitis but nasal erosions and epistaxis as well.

REFERENCES

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5 Sepulveda R, Longbottom JL, Pepys J. Enzyme linked immunosorbent assay (ELISA) for IgG and IgE antibodies to protein and polysaccharide antigens of *Aspergillus fumigatus*. Clin Allergy 1979; 9:359-71

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