pulmonary vascular lesions in the absence of antigenic challenge, due probably to histocompatibility differences. Mitogenic stimulation, on the other hand, with Con A should efficiently stimulate most T-cells present, thereby amplifying cell-mediated reactions, in contrast to specific antigen which stimulates only the small percentage of T-cells recognizing that antigen.

Animals sensitized, then challenged with BSA developed only minimal injury, despite the presence of both circulating precipitins and cutaneous Arthus reactivity to intradermal antigen challenge. Moreover, our ability to demonstrate antigen, immunoglobulin and C3 in venules at Arthus skin test sites, but not in pulmonary vascular lesions, argues against any significant immune-complex damage in the lung. Conversely, inhalation of Con A resulted in injury resembling that seen in the Hamman-Rich syndrome, and suggests that plant lectins and other mitogenic substances which occur naturally may, when inhaled, provoke similar interstitial injury in man. The present demonstration of Con A-induced injury in unsensitized recipients further suggests that T-cells within the lung can be stimulated by inhaled materials, and that such T-cell stimulation, if sufficient in degree, may play an important role in naturally-occurring environmental lung disease. Conceivably, complex antigen mixtures might prove as pathogenic as mitogens, by virtue of their ability to stimulate larger numbers of T-cells in toto.

Injury produced following combined challenge to BSA-sensitized animals clearly differs both in extent and pattern from that expected had changes induced by Con A alone been simply superimposed upon that seen in BSA-sensitized, BSA challenged animals. The observed association of granulomatous interstitial inflammation, vasculitis and necrosis, together with granulomatous airway injury seen in intubated animals, bears a close resemblance to the changes in Wegener's granulomatosis. The presence of immunoglobulin aggregates, demonstrated within diseased alveoli by immunofluorescence, suggests that Con A-induced injury is enhancing the effectiveness of humoral mechanisms, perhaps by facilitating contact between circulating antibody and intra-alveolar antigen. Similarly, demonstrations of T-cells at the sites of injury argues for concomitant cell-mediated reactions.

This study indicates that cellular mechanisms may be particularly important in initiating immunologic inhalation injury, but that humoral mechanisms may serve to severely augment such cell-mediated injury. In addition, an association between inhalation injury and the clinical entities of Wegener's granulomatosis and Hamman-Rich syndrome is suggested.

REFERENCES

Humidifier Lung: Hypersensitivity Pneumonitis Related to Thermotolerant Bacterial Aerosols*

Peter F. Kohler, M.D.; Gary Gross, M.D.; John Salvoaggio, M.D.; and June Hawkins, M.D.

Antigens from thermophilic Actinomyces species growing in air conditioners and humidifiers have been implicated in causing hypersensitivity pneumonitis. A similar role for thermotolerant bacteria has not been documented despite the fact that these organisms are uniformly present in contaminated humidifiers and air conditioners, exceeding Actinomyces colonies by approximately 15-fold, and often are recovered when cultures are negative for thermophilic Actinomyces. In fact, to prevent overgrowth by thermophilic bacteria, inhibitors are frequently included in media used for culturing Actinomyces.

Limited information is available on the taxonomy of these bacterial species. They are classified as thermotolerant because growth is enhanced at 56°C compared to 37°C. The rod-shaped bacilli, resembling B serus, are both gram-negative and positive.

Our interest in the pathogenic potential of thermotolerant bacterial aerosols arose when they were cultured from the home humidifiers of two housewives with hypersensitivity pneumonitis.

CASE REPORTS

CASE 1

The patient, a 31-year-old white housewife with atopic rhinitis and asthma, developed increasing cough, dyspnea, chills, fever and intense myalgia in late September, 1972. Chest x-ray film demonstrated bilateral basal infiltrates; she was hospitalized for ten days and received antibiotics for presumptive bacterial pneumonia. Within six hours of returning home, symptoms recurred and she was readmitted for another ten days. Once again following discharge, fever, cough, dyspnea and myalgias developed after six hours in her home and she was referred to the University of Colorado Medical Center. On admission, her temperature was 39.2°C, bilateral crackling rales were present at the lung bases, chest x-ray film showed basal infiltrates, WBC was 24,900/mm³ with 90 percent neutrophils, and Po2 was 52

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home after staying elsewhere for several weeks. Her
inated peptone broth and agar cultures at the
midifier in their forced-air heating system two years previous-
tolerant bacteria and
increased from
mm
He
1
mm Hg (normal in Denver 65 to 75). Within 24 hours, the
Po2 had spontaneously increased to 65 mm Hg and she was afebrile.

Environmental history revealed that she had lived in the
home for eight years and that her husband, a heating
conditioning repairman, had installed an inline hu-
midifier in their forced-air heating system two years previously.
The patient claimed that the humidifier was emptied and cleaned regularly. On inspection of the humidifier, however,
gross contamination of the fluid was obvious and thermo-
tation of 0.2 mg/ml by the Folin-Lowry technique. The sera of
both patients' husbands, three of their children who lived at
were turned off. In October, chills, fever, myalgias, cough and
dyspnea again developed and resolved within days after
prednisone treatment was started.

In November, the humidifier fluid was cultured in peptone
agar and broth and abundant bacterial growth occurred at
50°C. The humidifier was removed and the patient returned to
her home after staying elsewhere for several weeks. Her FVC
increased from 2.0 to 2.8 L (83 percent of predicted) without
any other therapy over a three month period.

T vulgaris was initially considered to be the most likely
causal factor in her recurrent pneumonitis, but a possible role
for the thermophilic bacteria was first evaluated. By bron-
chial challenge, approximately 1 mg of lyophilized and
sonicated bacteria dissolved in saline solution was delivered
via a Maxi-Mist aerosolizer. Within two hours, chills, fever,
cough, dyspnea and basilar rales developed with a fall in
FVC to 1.5 at 7 hours (Fig 2). Prednisone, 40 mg daily for 4
days was given with prompt clearing of symptoms. Since the
bronchial challenge, there has been no recurrence of symp-
toms, but a mild reduction in FVC, 2.83 L or 83 percent of
predicted, persists. A similar challenge in a 50-year-old
farmer with hypersensitivity pneumonitis caused by field dust
was negative indicating an immunologically specific response
by the patient to the thermotolerant bacteria.

CASE 2

The patient, a 50-year-old white housewife with atopic
rhinitis, had lived in the same home, heated by forced
air, since 1965. In 1970, an inline humidifier was installed
with the water reservoir being emptied and cleaned regularly
every one to two months.

Pulmonary symptoms first occurred in October, 1972 when
chills, fever, cough, dyspnea occurred on two separate occas-
ions and antibiotics were prescribed. In December a similar
symptom complex complex recurrent and she was hospitalized with
"pneumonia" after a chest x-ray film showed bilateral infiltrates. Prednisone was given, initially 35 mg/day decreasing
5 mg each day, and the chest x-ray film showed normal
findings. Between February and April, 1973, two identical recurrences associated with abnormal chest x-ray examina-
tions resolved within days after prednisone was given. From
May to September, 1973 the forced air heating and humidifi-
er were turned off. In October, chills, fever, myalgias, cough
and dyspnea again developed and resolved within days after
prednisone treatment was started.

In November, the humidifier fluid was cultured in peptone
agar and broth and abundant bacterial growth occurred at
50°C. The filtered humidifier fluid had a protein concentra-
tion of 0.2 mg/ml by the Folin-Lowry technique. The sera of
patient 1 and 2 had precipitating antibody by Ouchterlony
analysis to antigens in the filtered humidifier fluid. Sera from
both patients' husbands, three of their children who lived at
home, 12 blood bank donors, and five patients with broncho-
pulmonary aspergillosis were negative when tested in parallel.
Neither patient had serum precipitins to aspergillus or
thermophilic Actinomycetes antigens.

DISCUSSION

Since removal of the humidifier in November, 1974, patient 1 has been asymptomatic with normal pulmonary
function and chest x-ray picture. Aerosol challenge with
1:10 and undiluted filtered humidifier fluid in March,
1975, however, did not evoke any change in pulmonary
function.

Strong evidence for thermotolerant bacterial aerosols
being the etiology of the hypersensitivity pneumonitis in
patient 1 was provided by the positive aerosol challenge. In
patient 2, although the negative challenge speaks against this etiology, the positive serum precipitating
antibody and clinical improvement after the humidifier
was removed suggest that thermotolerant bacterial aerosols may have caused her recurrent pneumonitis.

These studies do not define whether the recurrent
pneumonitis in these housewives was related to humoral
or cell-mediated immunity. They do emphasize that
contamination of home humidifiers by thermotolerant
bacteria should be considered in the workup of patients with suspected hypersensitivity pneumonitis. It is emphasized that a majority of humidifier fluids will be positive for thermotolerant bacteria when cultured. For example, in our survey of humidifiers from Denver physicians’ homes, 7/9 were culture-positive for thermotolerant bacteria, but not Actinomycetes. Under appropriate conditions of host exposure and with an exaggerated immunologic response(s), type as yet determined, these bacterial aerosols can produce hypersensitivity pneumonitis.

REFERENCES


Desquamative Interstitial Pneumonia following Chronic Nitrofurantoin Therapy*


Thirteen cases of pulmonary fibrosis attributed to chronic nitrofurantoin use have been described previously.† Three additional patients who developed diffuse interstitial lung disease during chronic (two to five years) nitrofurantoin therapy have been studied. Clinical findings included exertional dyspnea and basilar rales. Chest roentgenograms demonstrated interstitial infiltrates, more prominent in the bases (Fig 1). Pulmonary function studies were characterized by a restrictive defect and moderate impairment of gas transfer (Table 1).

Lung biopsies examined by light microscopy in two patients were characterized by large numbers of intra-alveolar mononuclear cells and other pathologic changes consistent with desquamative interstitial pneumonia (DIP), in contrast to the nonspecific fibrosing interstitial pneumonitis previously reported by others (Fig 2). The appearance of one biopsy studied by electron microscopy was similar to that described for DIP. Hyperplastic cells lining alveolar septa had microvilli and contained lamellar inclusions typical of granular (type II) pneumocytes; intra-alveolar cells had the morphologic features of macrophages (Fig 3), including long pseudopodia, numerous electron-dense cytoplasmic granules, and only rarely a lamellar inclusion.

Immuno-fluorescence studies on one biopsy showed deposits of IgE and C3 component of complement within interstitial cells. By in vitro studies, nitrofurantoin failed to induce lymphoblast transformation or release of

Table 1—Selected Pulmonary Function Before and After Treatment of Nitrofurantoin Lung Disease*

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Patient No. 1 Before</th>
<th>Patient No. 1 After</th>
<th>Patient No. 2 Before</th>
<th>Patient No. 2 After</th>
<th>Patient No. 3 Before</th>
<th>Patient No. 3 After</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forced Vital Capacity, liter</td>
<td>1.70 (67%)</td>
<td>2.00 (79%)</td>
<td>3.00 (65%)</td>
<td>4.55 (99%)</td>
<td>2.36 (59%)</td>
<td>4.16 (106%)</td>
</tr>
<tr>
<td>Total Lung Capacity, liter</td>
<td>3.67 (100%)</td>
<td>3.50 (96%)</td>
<td>4.79 (80%)</td>
<td>6.15 (103%)</td>
<td>4.58 (79%)</td>
<td>6.30 (108%)</td>
</tr>
<tr>
<td>DLCO,† ml/min/mm Hg</td>
<td>12 (70%)</td>
<td>11.4 (67%)</td>
<td>16.5 (65%)</td>
<td>18.2 (72%)</td>
<td>11.3 (61%)</td>
<td>18.2 (98%)</td>
</tr>
<tr>
<td>PaO₂, mm Hg</td>
<td>76</td>
<td>82</td>
<td>66</td>
<td>83</td>
<td>80</td>
<td>70†</td>
</tr>
<tr>
<td>PaCO₂, mm Hg</td>
<td>34</td>
<td>41</td>
<td>36</td>
<td>34</td>
<td>38</td>
<td>44‡</td>
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<td>pH, units</td>
<td>7.43</td>
<td>7.34</td>
<td>7.44</td>
<td>7.52</td>
<td>7.38</td>
<td>7.52</td>
</tr>
</tbody>
</table>

*Patient No. 1 treated by discontinuing nitrofurantoin. Patients No. 2 and No. 3 treated by discontinuing nitrofurantoin and beginning corticosteroids
†Single breath diffusion
‡Exercise blood gas values
Parentheses = percent predicted value

FIGURE 1. Diffuse bilateral interstitial changes seen at both bases, slightly more prominent on the left in case 1 at time of diagnosis.