Tuberculosis has reemerged as a growing public health problem in the United States, particularly for homeless people. Skin testing with purified protein derivative (tuberculin) (PPD) is the standard method used to screen for infection with tuberculosis. Among the homeless population, however, multiple lifestyle risk factors, such as alcohol and drug use, poor nutrition, and poor health, can result in deficient cellular immunity, possibly leading to false-negative PPD skin test results.

Homeless persons who have a history of intravenous (IV) drug use are also at a greater risk of acquiring the human immunodeficiency virus (HIV). Those who are infected with HIV can become anergic as a result of impaired cellular immunity, particularly those persons with a CD4 count of less than 200/μL. Anergy is defined as a lack of delayed type hypersensitivity (DTH) response to intradermal skin testing. Anergy testing is recommended for those who are HIV positive to minimize the possibility of a false-negative PPD test result. Many persons, however, can be infected with HIV, yet they have not been tested or they are unwilling to report the results of their HIV test.

Several researchers who have examined the prevalence of anergy and the effectiveness of tuberculin skin testing in incarcerated and drug-addicted persons have found that some have decreased levels of DTH response, especially those with low T-cell counts. The issue of anergy in the homeless, however, has not been well investigated. As health care providers working in a clinic for homeless persons, we were concerned about anergy interfering with the sensitivity of tuberculosis screening.

In studies of healthy volunteers the rate of cutaneous anergy has been reported to be 5 to 7 percent by classical skin testing. The purpose of our study was to determine whether anergy occurred at higher rates among homeless persons, rendering PPD skin testing an ineffective screening test for tuberculosis in this population. A high rate of anergy coupled with a high frequency of...
Table 1. Demographic Data for Anergy Among Study Participants (n = 100) by Race.

<table>
<thead>
<tr>
<th>Demographic Characteristics</th>
<th>White (n = 27)</th>
<th>Black (n = 62)</th>
<th>Hispanic (n = 11)</th>
<th>Total (n = 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>23 (85)</td>
<td>51 (82)</td>
<td>8 (73)</td>
<td>82 (82)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>36.6 ± 10.2</td>
<td>39.3 ± 8.8</td>
<td>34.3 ± 5.6</td>
<td>38.0 ± 9.0</td>
</tr>
<tr>
<td>Male</td>
<td>36.0 ± 10.4</td>
<td>39.6 ± 8.6</td>
<td>33.1 ± 5.9</td>
<td>38.0 ± 9.1</td>
</tr>
<tr>
<td>Female</td>
<td>40.0 ± 9.7</td>
<td>38.1 ± 10.2</td>
<td>37.3 ± 4.0</td>
<td>38.4 ± 8.9</td>
</tr>
<tr>
<td>Months in shelter</td>
<td>21.0 ± 21.4</td>
<td>19.2 ± 24.0</td>
<td>11.1 ± 18.5</td>
<td>18.8 ± 22.8</td>
</tr>
<tr>
<td>Male</td>
<td>21.2 ± 21.9</td>
<td>19.9 ± 25.5</td>
<td>11.8 ± 21.0</td>
<td>19.4 ± 24.0</td>
</tr>
<tr>
<td>Female</td>
<td>20.3 ± 20.9</td>
<td>16.4 ± 16.1</td>
<td>9.3 ± 12.7</td>
<td>16.1 ± 16.1</td>
</tr>
<tr>
<td>HIV status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>3 (11)</td>
<td>6 (10)</td>
<td>1 (9)</td>
<td>10 (10)</td>
</tr>
<tr>
<td>Negative</td>
<td>15 (56)</td>
<td>33 (53)</td>
<td>6 (55)</td>
<td>54 (54)</td>
</tr>
<tr>
<td>Unknown</td>
<td>9 (33)</td>
<td>23 (37)</td>
<td>4 (36)</td>
<td>36 (36)</td>
</tr>
</tbody>
</table>

HIV - human immunodeficiency virus.

Tuberculosis infection would pose an important public health risk.

Methods

This study was conducted at a nurse-managed health clinic located in an inner-city homeless shelter in Yonkers, NY. A more detailed description of the clinic has been previously published. A consecutive convenience sample of 105 underserved men and women who volunteered to participate were enlisted using posted advertisements, word of mouth, and recruitment of clinic patients into the study. The participants were either currently homeless, living in a shelter, or formerly homeless and using the soup kitchen located at the shelter. Any person with a history of a positive PPD test or tuberculosis disease was excluded from the study. Many of the study volunteers had been screened for tuberculosis (by PPD testing only) in recent months at a county-wide intake unit, reducing the number of study participants who had positive responses to the PPD test (with intact DTH) in our group.

Approval of the study protocol was received from the Institutional Review Board of St. Joseph's Medical Center (the affiliated hospital) before initiation of the study. Informed consent was obtained from those who agreed to be in the study and who were eligible to participate. A questionnaire was read to each participant to elicit demographic data regarding age, sex, race, and self-reported HIV status, alcohol use, intravenous drug use, and number of months homeless.

Anergy testing was performed using three antigens, candidin, mumps, and trichophytin, administered intradermally on the left arm using the Mantoux method. The PPD was administered on the right arm using the same method. These antigens were selected based on the recommendations and availability of the antigens at our institution.

Of the 105 persons who were tested, 100 (95 percent) returned to have their skin tests read 48 hours later by either one of the study investigators (JF, SK) or by other trained nursing staff. To maximize the number of persons returning for skin-test readings, each person was given a return appointment.

Based on CDC recommendations, a positive DTH response was defined as induration of 2 mm or greater for any of the three antigens or the PPD. According to CDC guidelines for tuberculosis screening, however, a person is considered PPD positive if the induration measured 5 mm or greater. A person was considered anergic if none of the antigens, including the PPD, produced a response greater than 2 mm.

A power calculation before beginning the study determined that a sample size of 100 would give 80 percent power to detect an increase in anergy prevalence from the expected rate of 5 percent to 15 percent, using a two-sided chi-square test with a type 1 error rate of 5 percent.
statistical analysis of the results was not applicable because of the small size of the subgroups.

Results
Demographic data of the 100 study participants can be found in Table 1. The study population was 62 percent black, 27 percent white, and 11 percent Hispanic; 82 percent was male, and the mean age was 38 years. There were no significant demographic differences between men and women. Overall, 10 percent said they were HIV positive, 54 percent said they were negative, and 36 percent did not know. There was no difference in HIV status among the racial groups.

Of the 100 persons who returned for a follow-up reading, 5 (5 percent) were found to be PPD positive, and 5 (5 percent) were found to be anergic. All of the latter were HIV positive by self-report.

Of the 95 participants with intact cellular immunity, positive responses were 93 (98 percent) to the mumps antigen, 11 (12 percent) to candidin, 6 (6 percent) to PPD, and 4 (4 percent) to trichophytin (Table 2). Of the four antigens, mumps produced a reaction in most subjects. The mean induration for the four tests was 1.0 mm for PPD, 1.42 mm for candidin, 15.62 mm for mumps, and 0.2 mm for trichophytin. (If the nonresponders were eliminated from the analysis, the mean induration was 16.00 mm for PPD, 12.91 mm for candidin, 16.80 mm for mumps, and 4.25 mm for trichophytin). One nonresponder to mumps responded only to candidin, and 1 participant responded only to trichophytin.

Twenty-six percent of participants reported using intravenous drugs, and 48 percent reported alcohol use. Those who used intravenous drugs were much more likely than those who did not to be HIV positive, 27 versus 4 percent (risk ratio = 6.6). One (4 percent) of 26 participants who used intravenous drugs had an unknown HIV status compared with 47 percent of those who did not use drugs. Six percent of those who used alcohol reported a positive HIV test, whereas 14 percent of those who denied using alcohol reported positive HIV tests. The mean and range of induration for the mumps antigen by drug and alcohol use and HIV status are displayed in Table 3.

There were strong associations between intravenous drug use and anergy and between HIV status and anergy. Stratified by drug use, HIV status continued to have a strong relation with anergy as measured by millimeters of induration from the mumps challenge (Table 4). Those who did not report drug use and whose HIV status was unknown had the same level of reactivity as those who were HIV negative by report. There was no association between alcohol use and anergy.

All anergic and PPD-positive participants had chest radiographs to rule out tuberculosis, and all were found to be negative, except for 1 PPD-positive person who was lost to follow-up. All PPD-positive participants were advised to undergo HIV testing.

Discussion
The results of this study suggest that there is not an increased occurrence of anergy among homeless persons except for those who are known to be HIV infected. The group of homeless participants in this study had strong responses to intradermal skin testing, particularly to mumps antigen. We expected the results to show an increase in anergy of at least 10 percent above published norms\(^7,8\) (which was felt to be clinically relevant);
in fact, however, we discovered a low rate of 5 percent in those available for follow-up. Although mumps antigen alone was highly sensitive in detecting DTH, the addition of candidin and trichophytin antigens increased the sensitivity a minimal amount.

A false-negative skin test result for DTH has many possible causes, such as inactive antigen, an antigen to which the person tested was never exposed, an improper intradermal injection technique, or an inexperienced evaluator missing induration. A false-positive test probably does not exist; if induration occurs, DTH is intact.

A possible sampling problem in this study relates to the earlier screening of potential participants undertaken at the county intake clinic. Hypothetically this screening could have decreased the pool of study participants who had intact DTH by eliminating those persons with recent positive PPD tests and thus increased the rate of anergy in our study population. Our observed rate of 5 percent, however, is actually lower than the published rates of anergy in the general population.

The high reactivity rate of mumps antigen in the study (98 percent) might reflect widespread immunization or infection with mumps. Perhaps viral antigens stimulate a greater DTH response. The absence of mumps as a test antigen in several previous studies could explain their lower rates of positive DTH results. The Multitest (by Mérieux), a popular screening device for DTH, does not include mumps antigen and uses a multipuncture technique (tine) rather than an intradermal technique. The CDC recommends that the Multitest not be used for research on anergy.4

The incentive of $5, given upon completion of the test, contributed greatly to the high return rate of participants. The convenient location of the clinic was also a factor in the high completion rate.

In this study setting, the best screening test to determine whether anergy testing is necessary proved to be a careful history for HIV infection, which succeeded in including all the patients with absent DTH. Self-report of HIV positivity was highly predictive (50 percent) of anergy. At this time, the investigators do not recommend routine testing for anergy in the adult non-HIV infected homeless population in Yonkers, NY. Anergy does not appear to be common in the HIV-negative homeless population in our population, and the PPD test remains a reliable tool for screening for tuberculosis in the absence of a history of HIV positivity. Studies among other homeless groups in other communities would help to confirm these results.

Colleen Clark provided statistical analysis, Debbie Kelly contributed conceptual work and assisted with data collection, Tatjana Dance assisted with data collection, Kenneth Sax created the database, and Jennifer Cesana did the literature review.

References


5. Graham NM, Nelson KE, Solomon L, Bonds M,

