The Loss of Tuberculin Sensitivity in Certain Patients with Active Pulmonary Tuberculosis*


Through a careful determination of the tuberculin sensitivity of patients over a long period of time, a few tuberculous patients have been identified who were no longer able to react to tuberculin. Distinctive clinical and roentgenographic changes and, in some instances, the histopathologic changes associated with this deterioration in sensitivity status are detailed.

The tuberculin test, widely used as a diagnostic aid in detecting cases of tuberculosis, is not infallible. In rare instances patients with active tuberculosis may be tuberculin-negative.1,2 As stated in one well-known textbook,4 "Patients critically ill with tuberculosis or other diseases, and especially patients with tuberculous effusion of the pleura, pericardium, meninges, or peritoneum may fail to react to tuberculin...". With today’s effective chemotherapy a case of pulmonary tuberculosis in which the patient is unable to react to tuberculin is most unusual, but the fact that such cases do occur must be recognized. Data gathered at the William H. Maybury Sanatorium over the past three decades make it possible to recognize certain clinical and pathologic characteristics of far-advanced tuberculosis which are associated with the loss of tuberculin sensitivity.

**MATERIAL AND METHODS

Dilutions made from a 2 liter batch of Old Tuberculin obtained in 19391 have been used during the past 30 years for all routine tuberculin tests at Maybury Sanatorium. Available data4 indicate that the potency of the tuberculin has remained constant. Newly admitted patients at Maybury were given a Mantoux test using 0.1 ml of dilutions of 1:10,000, 1:1,000, 1:100 and 1:10 O.T. serially at 48-hour intervals until a reaction was obtained or until all dilutions had been used. An area of induration 5 mm or more in diameter was considered a positive reaction.

Maybury Sanatorium was maintained by the City of Detroit strictly as a tuberculosis facility. Patients were sent there because of a definite diagnosis of tuberculosis or because of an abnormal chest roentgenogram suspected of being caused by tuberculosis. During the 22-year period from January 1, 1947 to January 1, 1969, the sanatorium had 9,974 newly admitted patients whose tuberculin sensitivity was studied.

RESULTS

In tabulating the results each patient was assigned to one of five different sensitivity levels, or groups, depending upon the dilution of tuberculin to which he reacted. The final "O" group was reserved for those who failed to react to 1:10 O.T. The proportion of patients found in the various sensitivity groups has been published elsewhere.1,4 In the present series bacteriologic evidence of tuberculosis infection was found in 55 of the "O" group—0.55 percent of the 9,974 new admissions. These patients were considered to be tuberculin-nonreactive (anergic).

In addition to the above 55 newly admitted patients, the record of patients readmitted to Maybury Sanatorium includes the names of six patients who, during the time they were away from the sanatorium, became tuberculin-nonreactive. These six are listed in Table 1. Roentgenograms from cases 1 and 2 are shown in Figures 1 and 2.

Prior to 1949 streptomycin was either in short supply or completely unavailable at Maybury San-
LOSS OF TUBERCULIN SENSITIVITY

Table 1—Patients Who Became Nonreactive to Tuberculin

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Race</th>
<th>Sex, Age</th>
<th>First Tuberculin Sensitivity</th>
<th>Last Tuberculin Sensitivity</th>
<th>Acid-fast Bacilli in Sputum</th>
<th>Date of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>W</td>
<td>F 28</td>
<td>8/18/41, 1,000</td>
<td>6/20/44, 0</td>
<td>++++</td>
<td>7/21/44</td>
</tr>
<tr>
<td>2</td>
<td>W</td>
<td>M 25</td>
<td>10/24/42, 10,000</td>
<td>2/10/47, 0</td>
<td>++++</td>
<td>3/18/47</td>
</tr>
<tr>
<td>3</td>
<td>W</td>
<td>M 47</td>
<td>9/28/43, 10,000</td>
<td>8/22/47, 0</td>
<td>++++</td>
<td>9/2/47</td>
</tr>
<tr>
<td>4</td>
<td>W</td>
<td>F 39</td>
<td>2/2/41, 1,000</td>
<td>4/24/48, 0</td>
<td>++++</td>
<td>5/1/48</td>
</tr>
<tr>
<td>5</td>
<td>W</td>
<td>M 50</td>
<td>1/13/48, 1,000</td>
<td>7/14/50, 0</td>
<td>++++</td>
<td>9/6/50</td>
</tr>
<tr>
<td>6</td>
<td>W</td>
<td>M 45</td>
<td>3/23/65, 10,000</td>
<td>10/15/65, 0</td>
<td>++++</td>
<td>10/24/65</td>
</tr>
</tbody>
</table>

The loss of tuberculin sensitivity in the sanatorium. For that reason none of the first four patients in Table 1 was given the drug. Patient No. 5 received a 42 gm course of streptomycin when he was hospitalized at Maybury in 1948, and left the sanatorium against medical advice. This probably left him with a population of streptomycin-resistant mycobacteria and made his treatment with the antibiotic in 1950 relatively ineffective. Patient No. 6 had received streptomycin, isoniazid and PAS before coming to Maybury. Treatment with the same three drugs in October, 1965, was ineffective.

From Figures 1 and 2 it is evident that, accompanying the loss of tuberculin sensitivity, there has been a marked extension of disease in both lungs of the patient. A similar extension of disease was shown by the “before and after” roentgenograms of the four other patients listed in Table 1. The new disease is usually described by the roentgenologist as “areas of exudative infiltration,” implying that the “spread” has occurred within the past several weeks. In those cases which have come to autopsy the sections of lung taken through the areas of new disease do indeed show an acute exudative reaction. There is no tissue necrosis. (Only in hypersensitive tissues does the tubercle bacillus and its products cause tissue destruction.) Moreover there is no sign of tuberculous granuloma formation at the periphery of these new lesions. In other words tubercle bacilli, in the lungs of the anergic tuberculous patient, stimulate a pyogenic and nonnecrotizing pulmonary response similar to what one might expect in acute pneumococcal pneumonia.

**Characteristic Findings in Tuberculin-nonreactive Patients**

Aside from the primary characteristic of failing to react to 10 mg of OT, the nonreactive tuberculous patients have the following findings in common:

1. Smears of the sputum show great numbers of acid-fast bacilli* which, on culture, are found to be *M. tuberculosis*.

2. The chest roentgenogram shows cavitation and gives evidence of an extensive recent spread of disease.

3. The patients are always critically ill. In the days before streptomycin was available all of them died within a few weeks.

4. All of the patients are markedly emaciated.

*The marked proliferation of tubercle bacilli in the lungs of these patients is suggestive of that found in the lungs of desensitized tuberculous guinea pigs.*

![Figure 1. Case 1, A (left) woman, age 28; roentgenogram of September 18, 1941. A therapeutic pneumothorax is seen on the left. B (right) roentgenogram of May 30, 1944. The patient left against medical advice soon after the roentgenogram shown in 1A was taken and failed to continue her pneumotherapy. When admitted again the left lung had reexpanded. It contained multiple cavities.](image1)

![Figure 2. Case 2, A (left) man, age 25; roentgenogram of October 24, 1942. B (right) roentgenogram of February 20, 1947. There are bilateral cavities.](image2)
having lost from 30 to 50 pounds during the six or eight months preceding admission.

5. All of them have high white cell counts, some above 20,000, with 90 percent or more of polymorphonuclear leukocytes.

Newly Admitted Nonreactive Patients

The group of 55 newly admitted patients who were nonreactive to tuberculin included cases of tuberculous meningitis, miliary tuberculosis, tuberculous peritonitis, tuberculous pleurisy with effusion, and one patient (with tubercle bacilli in his sputum) who failed to react to tuberculin after receiving deep radiation therapy for carcinoma of the esophagus. However, the majority, 31 patients, presented clinical findings similar to those of the patients listed in Table 1. Detailed information regarding six of them is given in Table 2. The roentgenograms of three patients are shown in Figures 3 to 5. Definitive evidence regarding tuberculin hypersensitivity prior to their Maybury admission is lacking in these six patients, but cavitation such as shown in Figures 3 to 5 for patients 7, 8 and 9 would be difficult to explain on any basis other than previous tuberculin hypersensitivity in the patient. The roentgenograms of patients 10, 11 and 12 likewise showed pulmonary cavitation.

Chemotherapy was not available for patients 7, 8, 9 and 10, who died after the indicated number of days in the sanatorium. Patient 11, a teen-age girl, improved under streptomycin therapy to a point where she could have a lobectomy and be discharged from the sanatorium. Patient 12, after four months of chemotherapy, was transferred to another institution for custodial care. Both patients regained their hypersensitivity to tuberculin, patient 11 reaching the 10,000 level; patient 12 the 1,000 level. In the sense that they were near death when admitted to the sanatorium, the term moribund might have been applied to all of the Table 2 patients. As shown by the experience with patients 11 and 12, however, and the experience of other workers the nearly fatal process occurring in the anergic tuberculous patient can usually be reversed by chemotherapy.

Discussion

The term tuberculin-nonreactive is a broad characterization which applies equally to the individual who fails to react to tuberculin because he has never been exposed to the tubercle bacillus, and to the 12 patients listed in Tables 1 and 2. In this respect tuberculin anergy is a more specific term since it implies abnormal hyposensitivity to tuberculin. The 1 mg dose of OT (0.1 ml of the 1:100 dilution) is comparable in potency to the second strength dose (0.005 mg) of PPD, the patients in the present study were nonreactive to

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**Table 2—Patients Who Were Tuberculin-Nonreactive When First Admitted to the Sanatorium**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Race</th>
<th>Sex, Age</th>
<th>White Blood Cells</th>
<th>Polymorphs (%)</th>
<th>Acid-fast Bacilli in Sputum</th>
<th>Time in Sanatorium</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>W</td>
<td>M 64</td>
<td>16,400</td>
<td>93</td>
<td>++++</td>
<td>8 days</td>
</tr>
<tr>
<td>8</td>
<td>W</td>
<td>M 54</td>
<td>14,100</td>
<td>90</td>
<td>++++</td>
<td>16 days</td>
</tr>
<tr>
<td>9</td>
<td>N</td>
<td>F 40</td>
<td>22,400</td>
<td>92</td>
<td>++++</td>
<td>10 days</td>
</tr>
<tr>
<td>10</td>
<td>N</td>
<td>F 19</td>
<td>11,800</td>
<td>84</td>
<td>++++</td>
<td>18 days</td>
</tr>
<tr>
<td>11</td>
<td>N</td>
<td>F 16</td>
<td>10,100</td>
<td>82</td>
<td>++++</td>
<td>18 months</td>
</tr>
<tr>
<td>12</td>
<td>W</td>
<td>M 58</td>
<td>20,800</td>
<td>85</td>
<td>++++</td>
<td>4 months</td>
</tr>
</tbody>
</table>

*Figure 3. Case 7, man, age 64; roentgenogram of January 16, 1948, showing a far-advanced tuberculous process involving areas throughout both lungs. There are bilateral cavities.*
LOSS OF TUBERCULIN SENSITIVITY

The explanation for this extreme anergy to tuberculin is not clear, but it seems evident that different factors may be involved in different cases. For example, Mackaness\textsuperscript{10} has emphasized the fact that the tubercle bacillus is a facultative intracellular parasite and as such gives rise in cells of the reticuloendothelial system to immune processes similar to those initiated in Listerellosis, one of these being delayed-type hypersensitivity. The virus diseases, also, are characterized by intracellular parasitism and it has long been known\textsuperscript{11} that an acute virus infection, such as measles, in the tuberculous patient may cause a marked lowering of the tuberculin sensitivity level. Presumably this is due to viral parasitism of the cells responsible for producing hypersensitivity. Similarly in an acute exacerbation of tuberculosis these cells may be overwhelmed by the intracellular phase of the tubercle bacillus.

Bauer\textsuperscript{12} showed many years ago that the tuberculous patient can be desensitized by injecting gradually increasing subcutaneous or intramuscular doses of tuberculin. Tuttle and associates\textsuperscript{13} noted that a depression of tuberculin sensitivity occurred following thoracoplasty in certain types of acute exudative tuberculosis. This was ascribed to the absorption of tuberculin-like material into the bloodstream and was termed “autotuberculinization.” Also, in the patient with far advanced pulmonary tuberculosis with cavitation the repeated bronchogenic dissemination of tuberculoprotein might result in sufficient absorption of the material to bring about a desensitization similar to that which occurs when large doses of tuberculin are injected intramuscularly. Since this tuberculoprotein has come from bacillary growth in the patient’s own cavities the term “autodesensitization”\textsuperscript{*} has been applied to the process.\textsuperscript{2,4}

The possibility of encountering a tuberculin-nonreactive patient with far advanced pulmonary tuberculosis has lessened greatly over the years. In the single year, 1947, following World War II, 11 such patients were included among 648 new admissions to Maybury; during the past two years the 702 new patients included only two of the anergic type, each with far advanced disease. Nevertheless, the fact that these two occurred in this period of chemotherapy indicates that the problem still exists and that the possibility of pulmonary tuberculosis, even in the tuberculin-nonreactive patient, must always be kept in mind.

\textsuperscript{*}The usage would be similar to “autointoxication”—poisoning due to some toxin generated within the patient’s body.
REFERENCES


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NOTHING'S NEW UNDER THE SUN

Bologna is one of the oldest universities in Europe; according to some, the oldest. The charter (1158) granted the Bolognese students two very important privileges: freedom of travel and freedom from the jurisdiction of civil courts. From the beginning, Bologna was a university of students. This student university was as distinct from anything that preceded it, as from any modern institution that developed from it. The students elected their masters as well as their rector, the importance of whom was such that he took precedence over a Cardinal visiting the city. One feature of the inauguration of a new rector was a scramble at the end of the ceremony, when his robe was torn from his back by the assembled students and the pieces later sold back to him. The professors were held to strict accountability in the performance of their duties and could not be absent a single day without leave. They were also required to take an oath of obedience to the representatives of the students. Those professors who refused had no means of collecting their lecture fees, and their lectures might be boycotted and all social intercourse with the offending professor forbidden.

Major, R.H.: A History of Medicine, C. C Thomas, Springfield, 1954