False Positive Tuberculosis Skin Test Results

John C. Grabau, PhD, MPH
George T. DiFerdinando, Jr., MD, MPH
Lloyd F. Novick, MD, MPH

Dr. Grabau is the Assistant Director of the Bureau of Tuberculosis Control, New York State Department of Health. Dr. DiFerdinando is the Director, Bureau of Tuberculosis Control, and Assistant Professor, Department of Epidemiology, School of Public Health, State University of New York at Albany. Dr. Novick is Professor, Department of Epidemiology, School of Public Health, State University of New York at Albany.

Tearsheet requests to John C. Grabau, PhD, MPH, Bureau of Tuberculosis Control, New York State Department of Health, ESP, Corning Tower, Room 840, Albany, New York 12237-0627; tel. 518-474-4845; fax 518-473-6164.

SYNOPSIS

THE RE-EMERGENCE OF tuberculosis as a significant public health threat has led to greatly renewed activity in tuberculin skin testing to identify infected persons. However, even use of the preferred skin test technique (intradermal injection of purified protein derivative via the Mantoux method) can lead to either false positive or false negative results. Interpretation of a Mantoux test can be influenced by cross reactions with other mycobacteria, intertester variation, host-response variation, and product related problems.

At least 25 apparent false positive purified protein derivative skin test reactions in New York State in 1992 appeared to be associated with lots of the derivative produced by one manufacturer. These unexpected skin test results led to examination of a product with an altered appearance that may have caused the unanticipated responses. After announcement of these false positive results to the press, the company removed the product from the market. Food and Drug Administration analysis later revealed particulate matter in vials of the suspected lots of purified protein derivative.

Tuberculosis (TB), a disease once thought to be ready for elimination, has re-emerged as a major public health threat in New York State and the nation (*1–3*). In New York State, the number of new cases of tuberculosis reached its lowest point in 1978 with 2,060 cases (11.5 per 100,000). After a decade-long increase in both New York City and the remainder of the State, the State's rate had increased to 25.2 per 100,000 by 1992, two and one-half times the national rate. Although New York State has 7.1 percent of the nation's population, the 4,574 new cases of active TB reported in 1992 represented 17.1 percent of the nationally reported cases (*2*).

The increase of TB in New York brought pressures to expand greatly tuberculin skin testing (TST) programs throughout the State. The increase in incident cases, the broad prevalence of single- and multiple-drug resistant strains (*4–6*), and the rapid development of disease in those persons coinfected with human immunodeficiency virus (HIV) (*7*) all encouraged increased TST screening to avoid disease through prevention. The documented and well-publicized incidents of institutional spread of TB (*8–10*) and the higher risk of

infection among the new wave of refugees and immigrants coming to New York in the 1980s further increased the demand for broad-scale TST use.

The preferred method of testing for TB infection is injection of purified protein derivative (PPD) via the Mantoux test (*11*). Although the Mantoux test is currently the best procedure through which TB infection can be assessed, the test is not without problems. Mantoux test results may be influenced by (*a*) cross reaction with mycobacterial infections other than *M. tuberculosis*; (*b*) inter-tester variation, which includes both planting and interpreting the results; (*c*) host response variations such as antigen overload, boosting, age, and so forth; and (*d*) product related problems including variations among manufacturers and between lots (*12–18*).

We report several clusters of false positive TST results apparently associated with one brand of PPD solution, which occurred during a brief period in 1992 in State areas outside of New York City. After assessment of the product by the manufacturer and the Food and Drug Administration, the PPD solution was withdrawn from the United States market.

Methods

The Bureau of Tuberculosis Control, New York State Department of Health, routinely conducts case surveillance, provides technical assistance, and maintains oversight of county health department TB Control Programs throughout the State. State-employed staff members in six regional offices facilitate communication and collaboration with local health departments. Health care professionals are encouraged to report any unusual reactions to TST to the local health unit and the State. At the State level, reports of product problems are logged and reviewed continuously to identify any patterns.

In 1992, the State Bureau of Tuberculosis Control was consulted by a number of different health care providers about outcomes of TB skin test screening programs that produced unanticipated results. After identification of possible false positive reactions, skin test materials collected from the sites were forwarded to the manufacturer and to the Food and Drug Administration for analysis. These three tuberculin skin test products are discussed subsequently: Product A (Aplisol, Parke Davis), Product S (Sclavo, Sclavo), and Product T (Tubersol, Connaught).

Results

Cluster 1. Ten members of a volunteer rescue squad were tested by the New York State Department of Correctional Services because of their frequent contact with inmates with possible TB during transport of prisoners between various correctional and health facilities. Four rescue squad members were read as tuberculin skin test (TST) positive (10 millimeters or more) when tested with either product A or product S. Two people had prior multipuncture tests recorded as 0 millimeters, the third person had no record of a previous test. Investigation by State Department of Health staff members of potential sources of exposure revealed no clearly documented exposure. Because of the number of convertors without a clear documented exposure, State TB program officials recommended a county retest with product T. On retesting, of the four people with recent TSTs 10 millimeters of more, two produced 0 millimeter results using product T; the other two reactive persons refused retesting.

Cluster 2. Results of the routine annual employee screening program at an inpatient facility yielded unexpectedly high numbers of staff members with newly positive (5 millimeters or more) TST results. Three separate testing series reported over a two-month period found 23 employees with apparently newly positive TSTs; at least 14 of the 23 were documented to have been tested with product S, while the remaining nine were tested with either product A or S. Retesting of 20 of the employees with product T showed only three with significant reactions of 5 millimeters or more.

Cluster 3. At a county-run neighborhood health center, 11 of 60 health center employees (18.3 percent) undergoing routine annual testing were identified as skin test converters while using product S. Three employees had reactions 13 millimeters or larger using product S; retesting with product T showed 0 millimeters induration for each. Both the State and county TB program officials recommended retesting of the remaining eight reported converters. After a counter recommendation from the union representing the workers, none of the eight accepted retesting.

Cluster 4. In a State long-term care facility, five employees had unusual TST reactions with 3–7 millimeter subcutaneous nodules inconsistent with the T-cell intradermal infil-

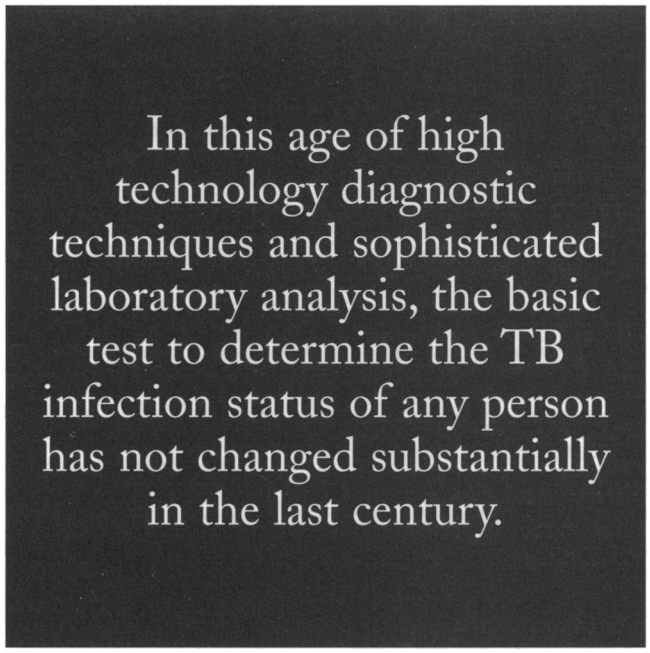
Reported clusters of unanticipated positive purified protein derivative results, New York State, 1992

Site	Date	Number reported positives	Number retested	Number retested positive
Rescue squad	February	4	2	0
Psychiatric hospital	April	6	6	0
	April	8	7	1
	May	9	7	2
Health center	July	11	3	0
Long-term care	July	5	5	0
Prison	August	11	[1]11	0

[1]One inmate had a recent live vaccine immunization and should be discounted, and a second inmate had significant TB disease that could impair the DTH response.

tration produced by a typical Mantoux response. The nodules occurred up to 10 days after planting the TST. One person also experienced a flared six-inch area at 24 hours without pain or itching which subsided within 48 hours. Each person had at least two prior negative PPD tests prior to the reported series. Subsequent retesting using product T one to four weeks later yielded no significant reactions.

Cluster 5. The last event observed in this series was among 11 Department of Correctional Services prisoners with prior histories of negative TST reactions and tested on the same day using one lot of product S. Each prisoner had large positive indurations when tested on intake to the prison system. When retested with product T, all 11 inmates had 0 millimeter reactions.



State Department of Health response. Review of these incidents suggested the possibility of a statewide problem of high rates of false positivity associated with product S. The State Department of Health collected information on lot numbers of the PPD materials used; all of the apparent false-positive results using product S were associated with three specific lots. Samples of implicated lots were obtained and sent to the Food and Drug Administration for testing. The Centers for Disease Control and Prevention was notified of the potential problem and queried about any other reports; there were no other recent product related problems reported.

Representatives of the manufacturer of product S were invited to State Department of Health offices to review the data and evaluate the results. The Department then issued a press release recommending that all institutions and individual practitioners in the State stop using implicated lots of product S until further notice.

For persons who had positive results on a TST using product S, the State Department of Health recommended:

1. Those who tested positive in the past year with one of the lots should be retested.
2. Those who tested positive from an unknown lot from product S should be retested.
3. Those who tested positive from a product S lot that has not been implicated should consult their physician. and
4. Persons on preventive therapy as a result of a positive test from product S should be considered for retesting.

In addition to the press release, the State Department of Health sent letters to physicians throughout the State with these four recommendations, offering consultation on issues surrounding testing and the various products available for use.

Company response. After an inspection of the production site and specific evaluation of implicated batches, the company reported observing visible particles in one of the implicated batches, which were hypothesized to be undissolved antigen. The company indicated that further testing would take place immediately and that all products manufactured by the company would be withdrawn from the United States.

The manufacturer issued a letter that was sent to wholesale purchasers of their products, stating, "A comprehensive review of production facilities and processes is now in progress and should be completed by the end of 1992. On the basis of the review, we have concluded that a number of manufacturing changes, introduced to improve product quality, were not fully reported to the FDA in years past. Because we wish to insure that all the responsibilities of a manufacturer in the United States are fully met, we have decided to cease distribution of all...vaccines and tests until our review is complete and all regulatory responsibilities are fulfilled. There are no safety or efficacy concerns regarding...products,..."

Food and Drug Administration inspection. The Food and Drug Administration (FDA) reported three vials examined contained particulates. Most were small and milk colored, and some were filaments up to 3 millimeters in length. The liquid was transparent, the volume was consistent, and the crimp seals were intact. Testing did not reveal any problems with the potency of samples taken from the implicated lots.

Discussion

A number of independent TST programs conducted in mid-1992 at various locations throughout New York State identified unanticipated skin test converters detected at routine TB skin testing programs. Staff members observing the unexpected results at some institutions immediately contacted the State Department of Health for consultation, while at the others, retesting with another PPD product was

conducted prior to notifying the State of apparent false positive results. Four of the five clusters described had classical TST responses; cluster 4 (with nodular reactions) is included because of its unusual features. Each of these clusters occurred independently. The circumstances surrounding the testing and the demography of those tested were somewhat different. Thus while the results may not be "additive," the cumulative evidence justified evaluation and action.

The strength of the argument for false positives is somewhat compromised, given that much of the analysis is on numerator data. Retesting was limited to those testing unexpectedly positive with product S, and not retesting the apparent negatives. As a result, computation of rates of false negatives or false positives is not possible. Calculations of "false" rates is also precluded by the absence of testing with an error free PPD standard solution. Nevertheless, the clustering of unanticipated positive TSTs (that is, no known exposure) in several different locations, occurring over short periods of time with a small number of production lots, strongly suggested problems with the testing solution. Although the product was withdrawn from the market, the company's decision to withdraw was attributed to missed notification of the FDA about changes in the manufacturing process and not to any safety or efficacy concerns.

The importance of accurately recording the manufacturer and lot number of PPD testing products became evident during this investigation. In a limited number of cases, the product used for the test was not recorded; some locations had PPD testing materials onsite from two different manufacturers, but the documenting information was not written in the patient chart. This experience led the State Department of Health to recommend patient charts include the manufacturer and lot number for all TSTs.

Given the rise in TB incidence within the State and the nation, the prevalence of HIV infection, the emergence of multiple drug-resistant TB, and the absence of an absolute test for TB infection, clinicians must consider TB when evaluating a patient with compatible symptoms, independent of the TST result.

The epidemiology of TB surrounding any individual patient must be carefully considered. Is there an explanation for a positive skin test? Has there been a recent exposure, does the person live or work in an environment at risk for TB infection? Conversely, is it reasonable that a person testing TST negative might in fact be positive?

Although the PPD test using the Mantoux method is the best option currently available to assess TB infection status, it is less than perfect. The test should be used as a tool to help the clinician gauge the likelihood of infection, but it is not diagnostic. A careful review of TB epidemiology for each person can greatly enhance the clinician's ability to interpret accurately the meaning of a PPD response and treat or not treat the patient appropriately.

In this age of high technology diagnostic techniques and sophisticated laboratory analysis, the basic test to determine the TB infection status of any person has not changed substantially in the last century. Careful consideration of circumstances surrounding any person's health status and likelihood of exposure to TB, in conjunction with results from a properly administered and interpreted TST, are the clinician's key assets in determining the probability of TB infection for anyone. The decision to treat, either preventively or curatively, is based on the clinician's evaluation of all information available.

The authors wish to thank all the physicians and nurses throughout the State who alertly recognized the possibility of product problems and reported those suspicions to the New York State Department of Health. We also thank staff members of the Bureau of Tuberculosis Control who assisted in conducting this investigation and preparing the manuscript.

References

1. Estimates of future global tuberculosis morbidity and mortality. MMWR Morbid Mortal Wkly Rep 42: 961–964, Dec. 17,1993.
2. Expanded tuberculosis surveillance and tuberculosis morbidity—United States, 1993. MMWR Morbid Mortal Wkly Rep 43: 361–366, May 27, 1994.
3. TB/HIV the connection; what health care workers should know. Centers for Disease Control and Prevention, Atlanta, Ga, September 1993.
4. Multidrug-resistant tuberculosis in a hospital - Jersey City, New Jersey 1990–1992. MMWR Morbid Mortal Wkly Rep 43: 417–419, June 10,1994.
5. Block, A. B., et al.: Nationwide survey of drug resistant tuberculosis in the United States. JAMA 271: 665–671, Mar. 2, 1994.
6. Frieden, T. P., et. al.: The emergence of drug-resistant tuberculosis in New York City. N Engl J Med 328: 521–526, Feb. 25, 1993.
7. Ellner, J. J., et. al.: Tuberculosis symposium: emerging problems and promise. J Infect Dis 168; 537–551, September 1993.
8. Nosocomial transmission of multidrug-resistant tuberculosis among HIV-infected persons - Florida and New York, 1988–1991. MMWR Morbid Mortal Wkly Rep 40: 585–591, Aug. 30, 1991.
9. Valway, S. E., et al.: Multidrug-resistant tuberculosis in the New York State prison system, 1990–1991. J Infect Dis 170: 151–156, July 1994.
10. Tuberculosis outbreak among persons in a residential facility for HIV-infected persons. MMWR Morbid Mortal Wkly Rep 40: 649–652, Sept. 27, 1991.
11. Schlossberg, D.: Tuberculosis. Ed. 2. Springer-Verlang, New York, 1987.
12. Chaparas, S., et al.: Tuberculin test, variability with the Mantoux procedure. Am Rev Resp Disease 132; 175–177, July 1985.
13. Huebner, R., Schein, M., and Bass, J.: The tuberculin skin test. Clin Infect Dis 17: 968–975, December 1993.
14. Lifson, A., et al.: Discrepancies in tuberculin skin testing results with two commercial products in a population of intravenous drug users. J Infect Dis 168: 1048–1051, October 1993.
15. Lanphear, O., Linnemann, C., and Cannon, C.; A high false-positive rate of tuberculosis associated with aplisol: an investigation among health care workers. J Infect Dis 169: 703–704, March 1994.
16. Mellor, J.: False-positive results of mantoux tests. Can Med Assoc J 132:1403, June 15, 1985.
17. Shands, J. W., et al.: Tuberculin testing in a tertiary hospital: product variability. Infection control and hospital epidemiology 15: 758–760, December 1994.
18. Cieslak, J. J., et al.: A pseudoepidemic of tuberculin skin test conversion caused by a particular lot of purified protein derivative of tuberculin test solution. Ped Infect Dis J 14: 392–393, May 1995.