The Tuberculin Test

Section on Diseases of the Chest

The tuberculin test is a major diagnostic tool. A positive reaction to the tuberculin test indicates the presence of tuberculous infection, but the degree of activity, if any, or the severity of the disease process cannot be thus determined. There are also other limitations of the test as noted later in this discussion.

A routine tuberculin test should be performed sometime during the first year of life and annually or biennially thereafter. It is, of course, always indicated when there has been known contact with a tuberculous adult. In the latter instance, if the tuberculin reaction is negative, the test should be repeated eight to ten weeks after the removal of the contact. If the child remains in contact with a tuberculous adult, the tuberculin test should be repeated at three-month intervals.

Tuberculin solution, utilized in skin testing, is available in two forms, purified protein derivative (PPD) and old tuberculin (OT) solution. PPD is the tuberculin solution now recommended because it is a more specific product. It is the protein of the tubercle bacillus obtained from filtrates of heat-killed cultures of tubercle bacilli that have been grown on a synthetic medium and then precipitated either by trichloracetic acid or neutral ammonium sulfate. The latter precipitant is used in the United States. The World Health Organization has designated one large batch of PPD (No. 49608, manufactured by Dr. Florence Seibert in 1939) as the international standard tuberculin (PPD-S).1 PPD is available commercially; it was formerly dispensed in tablet form and dissolved in a measured amount of diluent before use. Because tuberculoprotein, when diluted in a buffered diluent, is adsorbed in varying amounts by glass and plastics, it is now required that a small amount of polysorbate (e.g., Tween 80 at 5 ppm) be added by the manufacturer to the diluent to reduce adsorption.2 In order to minimize reduction in potency by adsorption, tuberculin should never be transferred from one container to another and skin tests should be given as soon as practicable after the syringe has been filled.

OT solution, which has been known since the time of Koch, has some variation of potency in different batches. When kept in a refrigerator, OT is satisfactory for skin testing for at least two weeks and probably for a one-month period.3

The most accurate and reliable method of tuberculin testing is the Mantoux (intracutaneous) test. A measured amount of tuberculin solution (PPD or OT) of known concentration is injected intracutaneously. For this test, a syringe so graduated that fractional parts of a milliliter may be measured and a short-bevel 26- or 27-gauge needle should be used. Tuberculin is thermostable, and traces of it remain on syringes and glassware after ordinary cleansing methods. A syringe for tuberculin testing should, therefore, not be utilized for other skin tests. A separate needle is used for each patient. If the needle and the syringe are not of the disposable variety, they should be sterilized by autoclaving. If this is not possible,
they should be boiled for 30 minutes.

Exactly 0.1 ml of the testing material is injected into the skin on the volar surface of the forearm. Unless a definite wheal follows injection, the test is not satisfactory and a false-negative reaction may be obtained. This is particularly true if the material is injected subcutaneously or there is leakage at the site.

The test is read 48 to 72 hours later, and the area of induration should be measured at its greatest transverse diameter. An induration less than 5 mm in diameter constitutes a negative reaction. If the area of induration measures between 5 and 9 mm in diameter, the reaction must be considered doubtful, and the test should be repeated with the same dosage of tuberculin. The second test may be negative, but if it shows the same degree of reaction, an attempt should be made to arrange for simultaneous testing with tuberculin solution (PPD, 5 TU) and the antigens of the unclassified mycobacteria, when such antigens are available. Since the greatest amount of research and experience has been with PPD Battey (PPD-B), prepared from a Group III strain, and since high cross-reactivity (low specificity) is exhibited by these antigens, PPD-B is recommended at present as the companion for PPD-tuberculin for comparative skin testing. Such tests often result in a small tuberculin reaction (5 to 9 mm in diameter of induration) and a much larger reaction to the antigen of the unclassified mycobacteria (15 to 20 mm in diameter of induration), thereby suggesting that the reaction to tuberculin is a heterologous one.

If the tuberculin test, utilizing either OT (10 TU) or PPD (5 TU), produces an area of induration measuring 10 mm or more, the result is considered positive.

A Mantoux test may produce a severe local reaction. There may be much erythema and induration or even vesiculation or ulceration at the site of the injection in persons with a high degree of sensitivity to tuberculin, sometimes requiring the local use of hydrocortisone ointment. There may be associated lymphangitis or regional lymphadenopathy. Phlyctenular conjunctivitis is an uncommon complication, and a constitutional reaction with fever is rare.

As noted above, the dose of tuberculin suggested for routine skin testing and for mass immunization programs is 5 TU. This test presumably detects almost all of the persons infected with tuberculosis. Nonspecific reactions may occur when the amount of tuberculin is increased beyond 10 TU.

The other tuberculin tests (Heaf, tuberculin tine, and Mono-Vacc) do not have the advantage of quantitative tuberculin testing afforded by the Mantoux test.

The Heaf test, devised in England and now utilized to some extent in this country, requires special apparatus for its use. The so-called Heaf gun makes six simultaneous skin punctures 1 mm deep through a layer of concentrated PPD (100,000 TU/ml). The test is read three to seven days later, and the presence of four or more papules constitutes a positive reaction. However, unless vesiculation occurs, a positive reaction should in all instances be corroborated by a Mantoux test. The apparatus for this test is now available with disposable needle cartridges, and these may be resterilized and used again if so desired.

The tuberculin tine test (Rosenthal) is one of the most practical tuberculin screening tests now in use. The sterilized disposable unit consists of four tines which have been predipped in an OT concentrate (four times the standard strength of OT solution). The production of one or more papules measuring 2 mm or more in diameter constitutes a doubtful reaction. In a strongly positive reaction a rosette consisting of four confluent areas of induration may result. Fusion of at least two papules is necessary for the result to be considered positive. Mild reactions must be corroborated by a Mantoux test. The test is inexpensive, sterile, disposable, and simple to apply.

The Mono-Vacc test is the newest of the tuberculin skin tests. It utilizes a device consisting of a nine-point plastic scarifier mounted on the outer side of a ring which fits on the thumb. A plastic tube containing OT solution is sealed around the points. The tube is removed just before application, and the tuberculin solution is squeezed onto the points. The material is then applied by pressing the points into the skin of the forearm. An area of induration measuring 2 mm in diameter constitutes a doubtful reaction and must be corroborated by a Mantoux test. An area of induration measuring 5 mm in diameter is considered positive, but corroborated by a Mantoux test is advisable. If vesiculation occurs the reaction is positive.

False-positive tuberculin reactions may occur. As noted above, it has been suggested (Edwards et al.) that the Mantoux reaction measuring between 5 and 9 mm in diameter of induration is suspect and they have pointed out that in certain sections of the United States the number of such reactions is abnormally large. The suggestion has been
made that many of these nonspecific reactions may be the result of infection with the so-called unclassified (atypical) mycobacteria. The incidence of these mycobacteria appears to be much greater in some areas of the country than in others.

Other causes of a false-positive tuberculin reaction are not of great frequency. Hypersensitivity to the phenol, glycerin, or bouillon in OT solution may be productive of redness and induration within the first 24 to 48 hours after application of the test. If the reading is done 48 to 72 hours after the test has been performed, the local response produced by such hypersensitivity has practically always disappeared.

BCG vaccination, utilizing the vaccine manufactured in the United States, is usually productive of a tuberculin reaction measuring 5 to 9 mm in diameter of induration. If a patient who has received BCG vaccine shows a reaction to PPD (5 TU) measuring 15 mm or more in diameter of induration, the likelihood of superinfection with virulent tubercle bacilli must be considered.

There are a certain number of false-negative tuberculin reactions; the most important of these occurs after infection takes place and before allergy sets in, as manifested by a positive tuberculin reaction. It is important to remember that an infant or child who is known to have been exposed to a tuberculous adult must not be adjudged free of infection, as far as that particular contact is concerned, until he has a negative tuberculin reaction at least ten weeks after contact with the tuberculous person has ceased.

False-negative reaction may occur in those with overwhelming tuberculous disease, such as an infant moribund with tuberculous meningitis. This does occur, but is not nearly so frequent as was generally believed.

Certain cases of malnutrition, dehydration, and inanition may show a false-negative tuberculin reaction.

During the course of measles the tuberculin reaction will be partially or completely depressed, but hypersensitivity again becomes manifest ten days to six weeks later. Tuberculous children vaccinated against measles may have a depressed tuberculin reaction for the same period of time, and those with severe rubella may have a depressed reaction for one to three weeks. Suppression of the tuberculin reaction is also said to occur with varicella, influenza, infectious mononucleosis, primary atypical pneumonia, sarcoidosis, and following the injection of live and killed viral vaccine. Adrenocorticosteroid therapy also may be the cause of a false-negative tuberculin reaction.

False-negative reactions relating to the tuberculin itself may occur. In addition to improper dilutions, bacterial contamination, and exposure to heat or light, there may be adsorption of tuberculoprotein to container walls. It has been demonstrated that about 25% of tuberculin in solution is lost 20 minutes after the syringe was filled, and 80% at 24 hours. Much of this adsorption is eliminated by the required addition of a surface active agent such as Tween 80.

Faulty administration and improper reading of the reaction may also give false-negative results.

In the presence of phlyctenular conjunctivitis or erythema nodosum, or if there is a history of intimate exposure to infectious tuberculosis, a lower strength of PPD or OT solution or the use of the tine or Mono-Vacc test is indicated. Failure to observe this precaution may lead to worsening of the disease process, and may be especially harmful to the diseased eye.

Edward M. Sewell, M.D.
Donna O'Hare, M.D.
Edwin L. Kendig, Jr., M.D., Chairman

REFERENCES
The Tuberculin Test: Section on Diseases of the Chest
Edward M. Sewell, Donna O'Hare and Edwin L. Kendig, Jr.

Pediatrics 1974;54;650

Updated Information & Services
including high resolution figures, can be found at:
http://pediatrics.aappublications.org/content/54/5/650

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
https://shop.aap.org/licensing-permissions/

Reprints
Information about ordering reprints can be found online:
http://classic.pediatrics.aappublications.org/content/reprints
The Tuberculin Test: Section on Diseases of the Chest
Edward M. Sewell, Donna O'Hare and Edwin L. Kendig, Jr.
Pediatrics 1974;54;650

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pediatrics.aappublications.org/content/54/5/650