

Self-Study Modules on Tuberculosis

3 Diagnosis of Tuberculosis Infection and Disease

**U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Centers for Disease Control and Prevention**

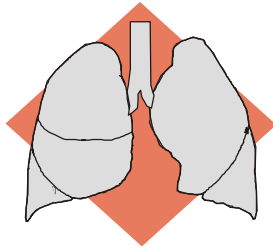
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Diagnosis of Tuberculosis Infection and Disease

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BACKGROUND

In this module, you will learn about the diagnosis of TB infection and disease. TB infection is diagnosed with the tuberculin skin test. The purpose of diagnosing TB infection is to identify (1) people with TB infection who may be given treatment to prevent them from developing TB disease and (2) people who may have TB disease and who need treatment to be cured. In most cases, TB disease is diagnosed with certain laboratory tests (bacteriologic examination); for patients who may have pulmonary TB disease, a chest x-ray is also useful for diagnosis. It is important to evaluate people who have symptoms of TB disease; if they are found to have TB disease, they need treatment to be cured and to avoid spreading TB to others. For this reason, the diagnosis of TB disease is crucial to controlling the spread of TB in homes and communities.

OBJECTIVES

After working through this module, you will be able to:

1. Explain the purpose of the tuberculin skin test.
2. Describe how the Mantoux tuberculin skin test is given.
3. Explain when the patient's arm is examined and how the induration is measured.
4. Explain why the Mantoux skin test is preferable to multiple-puncture tests.
5. Explain how the reaction to the Mantoux skin test is classified.
6. Describe the factors that can cause a false-positive reaction to the tuberculin skin test.
7. Explain how reactions to the tuberculin skin test are interpreted for BCG-vaccinated persons.
8. Describe the factors that can cause a false-negative reaction to the tuberculin skin test.
9. Discuss why and for whom anergy testing should be considered.



10. Describe the booster phenomenon.
11. Discuss why and when two-step tuberculin testing should be done.
12. List the four steps in diagnosing TB disease.
13. List the parts of the medical history that should lead a clinician to suspect TB.
14. Describe the symptoms of TB disease.
15. Explain the purposes of the chest x-ray in diagnosing TB disease.
16. List the four parts of a bacteriologic examination.
17. Outline the procedures for collecting sputum specimens.
18. Explain the purpose and significance of the acid-fast bacilli smear.
19. Explain the purpose and significance of the culture.
20. Explain the purpose and significance of drug susceptibility testing.



NEW TERMS

Look for the following new terms in this module and in the glossary.

acid-fast bacilli (AFB) – mycobacteria that stay stained even after they have been washed in an acid solution; may be detected under a microscope in a stained smear

anergy – the inability to react to a skin test because of a weakened immune system, often caused by HIV infection or severe illness (see **anergy testing**)

anergy testing – giving skin tests using two substances other than tuberculin; done to determine whether a person is anergic. People who do not react to any of the substances, including tuberculin, after 48 to 72 hours (that is, people who have less than 3 millimeters of induration to all of the skin tests), are considered anergic.

bacteriologic examination – tests done in a mycobacteriology laboratory to diagnose TB disease; includes examining a specimen under a microscope, culturing the specimen, and doing drug susceptibility testing

baseline skin test – the tuberculin skin test given to employees or residents in certain facilities when they start their job or enter the facility (see **TB screening program** and **two-step testing**)

BCG – bacille Calmette-Guérin (BCG), a vaccine for TB disease that is used in many countries but rarely used in the United States; may cause a false-positive reaction to the tuberculin skin test

boosted reaction – a positive reaction to a tuberculin skin test, due to a boosted immune response from a skin test given up to a year earlier; occurs in people who were infected a long time ago and whose ability to react to tuberculin had lessened. Two-step testing is used in TB screening programs to tell the difference between boosted reactions and reactions caused by recent infection (see **booster phenomenon** and **two-step testing**)

booster phenomenon – a phenomenon in which people (especially older adults) who are skin tested many years after becoming infected with *M. tuberculosis* may have a negative reaction to an initial skin test, followed by a positive reaction to a skin test given up to a year later; this happens because the first skin test boosts the immune response. Two-step testing is used in TB screening programs to tell the difference between boosted reactions and reactions caused by recent infection (see **two-step testing**)



bronchoscopy – a procedure used to obtain pulmonary secretions or lung tissue with an instrument called a bronchoscope; used only when patients cannot cough up sputum on their own and an induced specimen cannot be obtained

cavity – a hollow space within the lung, visible on a chest x-ray, that may contain many tubercle bacilli; often occurs in people with severe pulmonary TB disease

clinician – a physician, physician assistant, or nurse

colonies – groups of mycobacteria that have grown in a culture

culture – organisms grown on media (substances containing nutrients) so that they can be identified; a positive culture for *M. tuberculosis* contains tubercle bacilli, whereas a negative culture contains no detectable tubercle bacilli

drug susceptibility pattern – the list of drugs to which the strain of tubercle bacilli is susceptible and to which it is resistant

erythema – redness around the site of the injection when a Mantoux skin test is done; erythema is not considered when the reaction size is measured, because redness does not indicate that a person has TB infection

exposure to TB – time spent with someone who has infectious TB disease

false-negative reaction – a negative reaction to the tuberculin skin test in a person who has TB infection; may be caused by anergy, recent infection (within the past 10 weeks), or very young age (younger than 6 months old)

false-positive reaction – a positive reaction to the tuberculin skin test in a person who does not have TB infection; may be caused by infection with nontuberculous mycobacteria or by vaccination with BCG

gastric washing – a procedure done by inserting a tube through the patient's nose and passing it into the stomach; may be useful for obtaining sputum from children, who produce little or no sputum when they cough

induced sputum – sputum that is obtained by having the patient inhale a saline (salt water) mist, causing the patient to cough deeply; this procedure is used to help patients cough up sputum if they cannot do so on their own

induration – swelling that can be felt around the site of injection after a Mantoux skin test is done; the reaction size is the diameter of the swollen area (excluding any redness), measured across the forearm

infiltrate – a collection of fluid and cells in the tissues of the lung; visible on a chest x-ray in people with pulmonary TB disease



isolate – a group of organisms isolated, or separated, from a specimen; in an *M. tuberculosis* isolate, the organisms have been identified as *M. tuberculosis* (a positive culture for *M. tuberculosis*)

malaise – a feeling of general discomfort or illness

Mantoux tuberculin skin test – the preferred method of testing for TB infection; done by using a needle and syringe to inject 0.1 ml of 5 tuberculin units of liquid tuberculin between the layers of the skin (intradermally), usually on the forearm; the reaction to this test, usually a small swollen area (induration), is measured 48 to 72 hours after the injection and is classified as positive or negative depending on the size of the reaction and the patient's risk factors for TB

media – substances containing special nutrients for growing cultures of bacteria found in specimens

medical history – the part of a patient's life history that is important for diagnosing and treating TB infection or disease, including history of exposure, symptoms, diagnosis of TB infection or disease, and risk factors for TB disease

multiple-puncture test – tuberculin skin test done by puncturing the skin of the forearm with a set of short prongs or tines to inject tuberculin (for example, Tine test); although easy to give and convenient, these tests are not accurate and should not be used to determine whether a person has TB infection

mycobacteriology laboratory – a laboratory that deals specifically with *M. tuberculosis* and other mycobacteria

PPD skin test – a tuberculin skin test

purified protein derivative (PPD) – the type of tuberculin used in the Mantoux skin test

resistant – able to grow in the presence of a particular drug

skin test conversion – a change in a skin test reaction from negative to positive between screening intervals

smear – a specimen that has been smeared onto a glass slide, stained, washed in an acid solution, and then placed under the microscope for examination; used to detect acid-fast bacilli in a specimen

sputum – phlegm from deep in the lungs, collected in a sterile container for processing and examination



susceptible – able to be killed by a particular drug

symptoms of TB disease – conditions caused by TB disease. The symptoms of pulmonary TB disease include coughing, pain in the chest when breathing or coughing, and coughing up sputum or blood. The general symptoms of TB disease (pulmonary or extrapulmonary) include weight loss, fatigue, malaise, fever, and night sweats. The symptoms of extrapulmonary TB disease depend on the part of the body that is affected by the disease

TB screening program – a program in which employees and residents of a facility are periodically given tuberculin skin tests; done to identify people who have TB infection and possibly TB disease and to determine whether TB is being transmitted in the facility

tuberculin – protein from tubercle bacilli that have been killed by heating; used to determine whether a person has TB infection. Tuberculin is not a vaccine.

tuberculin unit – a standard strength of tuberculin used in the United States and Canada; a strength of 5 tuberculin units is used for the Mantoux tuberculin skin test

two-step testing – a strategy used in TB screening programs to distinguish a boosted reaction (caused by TB infection that occurred many years before the skin test) from a reaction caused by recent infection. If a person has a negative reaction to an initial skin test, a second test is given 1 to 3 weeks later; a positive reaction to the second test probably represents a boosted reaction, not recent infection. Two-step testing is used in many TB screening programs for skin testing employees when they start their job.



READING MATERIAL

Diagnosis of TB Infection: The Tuberculin Skin Test

.....
The tuberculin skin test is used to determine whether a person has TB infection.

.....
Tuberculin is not a vaccine.

The tuberculin skin test is used to determine whether a person has TB infection. In this test, a substance called tuberculin is injected into the skin. **Tuberculin** is protein derived from tubercle bacilli that have been killed by heating. In most people who have TB infection, the immune system will recognize the tuberculin because it is similar to the tubercle bacilli that caused infection. This will cause a reaction to the tuberculin. Tuberculin is used for diagnosing TB infection; **it is not a vaccine.**

Tuberculin testing is useful for

Examining a person who is not sick but who may have TB infection, such as a person who has been exposed to someone who has TB. In fact, the tuberculin skin test is the only way to diagnose TB infection before the infection has progressed to TB disease.

Screening groups of people for TB infection

Examining a person who has symptoms of TB disease

.....
The Mantoux tuberculin skin test is the preferred type of skin test.

Different types of tuberculin tests are available, such as the **Mantoux tuberculin skin test** and the multiple-puncture test. The Mantoux tuberculin skin test is the preferred type because it is the most accurate.



Mantoux Test

The Mantoux skin test is given by using a needle and syringe to inject 0.1 ml of 5 **tuberculin units** of liquid tuberculin between the layers of the skin (intradermally), usually on the forearm (Figure 3.1). A tuberculin unit is a standard strength of tuberculin.

The tuberculin used in the Mantoux skin test is also known as **purified protein derivative**, or **PPD**. For this reason, the tuberculin skin test is sometimes called a **PPD skin test**.

With the Mantoux skin test, the patient's arm is examined 48 to 72 hours after the tuberculin is injected. **Most people with TB infection have a positive reaction to the tuberculin.** The reaction is an area of **induration** (swelling that can be felt) around the site of the injection. The diameter of the indurated area is measured across the forearm (Figure 3.2); **erythema** (redness) around the indurated area is not measured, because the presence of erythema does not indicate that a person has TB infection (Figure 3.3).

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Most people with TB
infection have a positive
reaction to the tuberculin.
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.....
The reaction is an area of
induration, or swelling,
around the site of the
injection.
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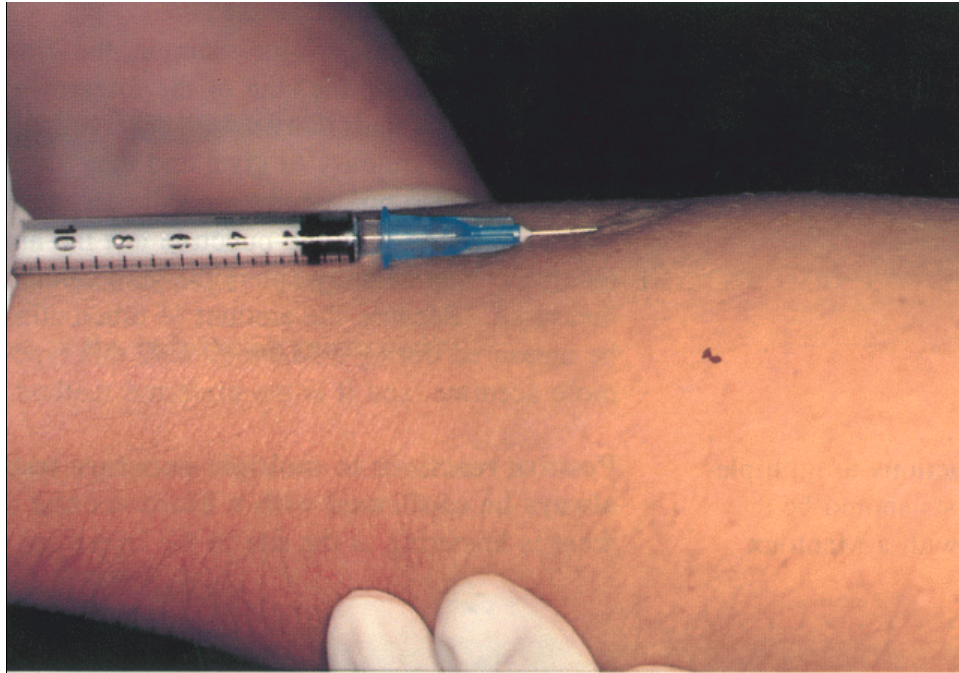


Figure 3.1 Giving the Mantoux tuberculin skin test.



Figure 3.2 Only the induration is being measured. This is **CORRECT**.



Figure 3.3 The erythema is being measured. This is **INCORRECT**.



.....
Multiple-puncture tests are easy to give and convenient, but they are not as accurate as the Mantoux skin test.
.....

.....
Positive reactions to multiple-puncture tests should be confirmed with a Mantoux test.
.....

Multiple-Puncture Test

Multiple-puncture tests (for example, the Tine test) are done by puncturing the skin of the forearm with a set of short prongs or tines coated with tuberculin. Multiple-puncture tests are easy to give, and they are convenient because they do not require a needle and syringe. However, in the multiple-puncture test the amount of tuberculin that actually enters the skin cannot be measured. Because the amount of tuberculin can always be measured during a Mantoux test, this type of test is more accurate, and it is the preferred method.

Positive reactions to multiple-puncture tests should always be confirmed with a Mantoux test (except when there is blistering at the site of the injection).

Study Questions 3.1-3.2

3.1. What is the tuberculin skin test used for?

3.2. How is the Mantoux tuberculin skin test given?

Answers on page 61.



Study Questions 3.3-3.5

3.3. With the Mantoux skin test, when is the patient's arm examined?

3.4. How is the induration measured?

3.5. Why is the Mantoux skin test preferable to multiple-puncture tests?

Answers on page 61.



.....
Whether a reaction to the Mantoux tuberculin skin test is classified as positive depends on the size of the induration and on the person's risk factors for TB.
.....

Classifying the Reaction

Whether a reaction to the Mantoux tuberculin skin test is classified as positive depends on the size of the induration and the person's risk factors for TB (Table 3.1).

An induration of **5 or more millimeters** is considered a positive reaction for the following people:

- # People with HIV infection
- # Close contacts of people with infectious TB
- # People with chest x-ray findings suggestive of previous TB disease
- # People who inject illicit drugs and whose HIV status is unknown

An induration of **10 or more millimeters** is considered a positive reaction for the following people:

- # People born in areas of the world where TB is common (foreign-born persons)
- # People who inject illicit drugs but who are known to be HIV negative
- # Low-income groups with poor access to health care
- # People who live in residential facilities (for example, nursing homes or correctional facilities)
- # People with medical conditions that appear to increase the risk for TB (not including HIV infection), such as diabetes
- # Children younger than 4 years old
- # People in other groups likely to be exposed to TB, as identified by local public health officials



An induration of **15 or more millimeters** is considered a positive reaction for people with no risk factors for TB. In most cases, people who have a very small reaction or no reaction probably do not have TB infection.

For **people who may be exposed to TB on the job** (such as health care workers and staff of nursing homes or correctional facilities), the classification of the skin test reaction as positive or negative depends on



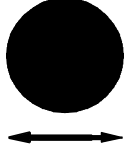
- # The size of the induration
- # The employee's individual risk factors for TB
- # The risk of exposure to TB in the person's job

Therefore, in facilities where the risk of exposure to TB is very low, 15 or more millimeters of induration may be considered a positive reaction for employees with no other risk factors for TB. In facilities where TB patients receive care, 10 or more millimeters of induration may be considered a positive reaction for employees with no other risk factors for TB.

Most people who have a positive skin test reaction will have a positive reaction if they are skin tested later in their lives, regardless of whether they receive treatment. This is because the tuberculin skin test detects the immune response to tuberculin, not the presence of tubercle bacilli in the body (see page 7).



Table 3.1
Classifying the Tuberculin Skin Test Reaction

 5 or more millimeters	 10 or more millimeters	 15 or more millimeters
<p>An induration of 5 or more millimeters is considered positive for</p> <ul style="list-style-type: none"># People with HIV infection# Close contacts# People who have had TB disease before# People who inject illicit drugs and whose HIV status is unknown	<p>An induration of 10 or more millimeters is considered positive for</p> <ul style="list-style-type: none"># Foreign-born persons# HIV-negative persons who inject illicit drugs# Low-income groups# People who live in residential facilities# People with certain medical conditions# Children younger than 4 years old# People in other groups as identified by local public health officials	<p>An induration of 15 or more millimeters is considered positive for</p> <ul style="list-style-type: none"># People with no risk factors for TB



Study Questions 3.6-3.7

3.6. What two factors are considered when classifying a skin test reaction as positive or negative? What additional factor is considered for people who may be exposed to TB on the job?

3.7. For which groups of people is 5 or more millimeters of induration considered a positive reaction? Name four.

Answers on page 62.



Study Questions 3.8-3.9

- 3.8. For which groups of people is 10 or more millimeters of induration considered a positive reaction? Name seven.**
- 3.9. For which group of people is 15 or more millimeters of induration considered a positive reaction?**

Answers on pages 62-63.

Case Study 3.1

**Which of the following patients have a positive tuberculin skin test reaction?
Circle the best answer(s).**

- a) Mr. West, 36 years old, HIV infected, 08 mm of induration**
- b) Ms. Hernandez, 26 years old, native of Mexico, 07 mm of induration**
- c) Ms. Jones, 56 years old, has diabetes, 12 mm of induration**
- d) Mr. Sung, 79 years old, resident of a nursing home, 11 mm of induration**
- e) Mr. Williams, 21 years old, no risk factors, 13 mm of induration**
- f) Ms. Marcos, 42 years old, chest x-ray findings suggestive of previous TB, 06 mm of induration**
- g) Ms. Rayle, 50 years old, husband has pulmonary TB, 09 mm of induration**

Answers on page 70.



.....
False-positive reactions can be caused by infection with nontuberculous mycobacteria or vaccination with BCG.
.....

False-Positive Reactions

The skin test is a valuable tool, but it is not perfect. Several factors can affect the skin test reaction. Two factors are **infection with nontuberculous mycobacteria** (mycobacteria other than *M. tuberculosis*) and **vaccination with BCG**. BCG (bacillus Calmette-Guérin) is a vaccine for TB disease that is used in many countries. However, it is rarely used in the United States because studies have shown that it is not completely effective. People who are infected with nontuberculous mycobacteria or who have been vaccinated with BCG may have a positive reaction to the tuberculin skin test even if they do not have TB infection. This is called a **false-positive reaction**.

There is NO RELIABLE WAY to distinguish a positive tuberculin reaction caused by vaccination with BCG from a reaction caused by true TB infection. However, the reaction is **more likely to be due to TB infection** if any of the following are true:

- # The reaction is large
- # The person was vaccinated a long time ago
- # The person comes from an area of the world where TB is common
- # The person has been exposed to someone with infectious TB disease
- # The person's family has a history of TB disease

.....
People who have a positive reaction should be further evaluated for TB disease, regardless of whether they were vaccinated with BCG.
.....

People who have a positive reaction should be further evaluated for TB disease, regardless of whether they were vaccinated with BCG.



Study Questions 3.10-3.11

3.10. Name two factors that can cause false-positive reactions to the tuberculin skin test.

3.11. Is there a reliable way to distinguish a positive tuberculin reaction caused by vaccination with BCG from a reaction caused by true TB infection?

Answers on page 63.



Case Study 3.2

A 30-year-old man who recently immigrated from India is given a tuberculin skin test and found to have 14 millimeters of induration. He reports that he was vaccinated with BCG as a child. He also says that his wife was treated for pulmonary TB disease last year.

Can you tell for sure whether this man has TB infection?

What factors make it more likely that this man's positive reaction is due to TB infection?

Answers on page 70.



False-negative reactions may be due to anergy, recent infection (within the past 10 weeks), or very young age.

False-Negative Reactions

Some people have a negative reaction to the tuberculin skin test even though they have TB infection. These are called **false-negative reactions**. False-negative reactions may be due to

- # Anergy
- # Recent TB infection (within the past 10 weeks)
- # Very young age (younger than 6 months old)

Anergy is the inability to react to skin tests because of a weakened immune system.

The most common cause of false-negative reactions is anergy. **Anergy** is the inability to react to skin tests because of a weakened immune system. Many conditions, such as HIV infection, cancer, or severe TB disease itself, can weaken the immune system and cause anergy. HIV infection is a main cause of anergy.

Because of their risk for anergy and their risk for TB, HIV-infected people may be tested for anergy if they have a negative reaction to the tuberculin skin test.

Because of their risk for anergy and their risk for TB, HIV-infected people may be tested for anergy if they have a negative reaction to the tuberculin skin test. **Anergy testing** is done by giving skin tests using two substances other than tuberculin. The recommended substances for anergy testing are mumps, *Candida* (a type of fungus), or tetanus extracts. Most healthy people will have a skin test reaction to one or more of these substances.

People who do not react to any of the substances used for anergy testing (including tuberculin) are considered anergic.

People who do not react to any of the substances, including tuberculin, after 48 to 72 hours (that is, people who have less than 3 millimeters of induration to all of the skin tests), are considered anergic. People who have a reaction (3 or more millimeters of induration) to any of the substances are NOT anergic. If a person being evaluated for anergy has a reaction of 5 or more millimeters of induration to tuberculin, he or she is considered to have TB infection, regardless of the reaction to the other substances.



.....
It takes 2 to 10 weeks after TB infection for the body's immune system to be able to react to tuberculin.
.....

Another cause of false-negative reactions is **recent TB infection** (infection within the past 10 weeks). It takes 2 to 10 weeks after TB infection for the body's immune system to be able to react to tuberculin. Therefore, after TB has been transmitted, it takes 2 to 10 weeks before TB infection can be detected by the tuberculin skin test. For this reason, close contacts of someone with infectious TB disease who have a negative reaction to the tuberculin skin test should be retested 10 weeks after the last time they were in contact with the person who has TB disease.

.....
Because their immune systems are not yet fully developed, children younger than 6 months old may have a false-negative reaction to the tuberculin skin test.
.....

A third cause of false-negative reactions is **very young age**. Because their immune systems are not yet fully developed, **children younger than 6 months old** may have a false-negative reaction to the tuberculin skin test.

A false-positive reaction or a false-negative reaction may occur when the tuberculin skin test is given incorrectly or the results are not measured properly. False-positive and false-negative reactions to the tuberculin skin test are summarized in Table 3.2.

.....
Any patient with symptoms of TB should be evaluated for TB disease, regardless of his or her skin test reaction.
.....

Any patient with symptoms of TB should be evaluated for TB disease, regardless of his or her skin test reaction. In fact, people with symptoms of TB should be evaluated for TB disease right away, at the same time that the tuberculin skin test is given. The symptoms of pulmonary TB disease include coughing, pain in the chest when breathing or coughing, and coughing up **sputum** (phlegm from deep in the lungs) or blood. The general symptoms of TB disease (pulmonary or extrapulmonary) include weight loss, fatigue, malaise, fever, and night sweats. The diagnosis of TB disease is discussed in more detail in the next section of this module.



Table 3.2
False-Positive and False-Negative Reactions
to the Tuberculin Skin Test

Type of Reaction	Possible Cause	People at Risk	Action to Take*
False-positive	Nontuberculous mycobacteria BCG vaccination	People infected with nontuberculous mycobacteria People vaccinated with BCG	Evaluate for TB disease if person has TB symptoms Assess likelihood of true TB infection (see five factors on page 17)
False-negative	Anergy Recent TB infection Very young age	HIV-infected people, other people with weakened immune systems People infected with <i>M. tuberculosis</i> within the past 10 weeks Children younger than 6 months old	May do anergy testing Retest 10 weeks after exposure to TB ended Retest when child is 6 months old and 10 weeks after exposure to TB ended

* Any patient with symptoms of TB should be evaluated for TB disease, regardless of his or her skin test reaction.



Study Questions 3.12-3.14

3.12. Name three factors that can cause false-negative reactions to the tuberculin skin test.

3.13. What is anergy?

3.14. How is anergy testing done?

Answers on page 63-64.



Study Questions 3.15-3.16

- 3.15. After TB has been transmitted, how long does it take before TB infection can be detected by the tuberculin skin test?**
- 3.16. What should be done if a patient has a negative skin test reaction but has symptoms of TB disease?**

Answers on page 64.

Case Study 3.3

Mr. Bell comes to the TB clinic for a tuberculin skin test. He believes that he has been exposed to TB, and he knows he is at high risk for TB because he is HIV infected. He is given a tuberculin skin test, and his reaction is read 48 hours later as 0 millimeters of induration.

What are three ways to interpret this result?

Answer on page 71.



.....
Certain facilities have TB screening programs, in which employees and residents are periodically given tuberculin skin tests.
.....

.....
In a TB screening program, employees or residents are skin tested when they start their job or enter the facility; repeat testing is done at regular intervals thereafter.
.....

.....
In order to detect TB transmission and identify people who have skin test conversions, accurate information must be obtained for every employee's skin tests.
.....

TB Screening Programs and Two-Step Testing

Many residential facilities, health care facilities, and other settings have **TB screening programs**. This means that employees and residents are periodically given tuberculin skin tests. The purposes of the screening program are to

- # Identify people who have TB infection and possibly TB disease, so that they can be given treatment as needed
- # Determine whether TB is being transmitted in the facility

In a TB screening program, employees or residents are skin tested when they start their job or enter the facility. This is called the **baseline skin test**. If they have a negative skin test reaction, they may be retested at regular intervals thereafter. (For most employees, repeat testing should be done at least once a year.)

Employees or residents whose skin test reaction converts from negative to positive between screening intervals have probably become infected with *M. tuberculosis*. These **skin test conversions** may indicate that TB is being transmitted in the facility. People with skin test conversions are at high risk of developing TB disease because they were infected with *M. tuberculosis* relatively recently (within the past 2 years). (See Module 1, Transmission and Pathogenesis of Tuberculosis.) In order to detect TB transmission and identify people who have skin test conversions, accurate information must be obtained for every employee's baseline skin test, as well as for additional skin tests.



.....
The booster phenomenon
can affect the accuracy of the
baseline skin test.
.....

.....
The booster phenomenon
happens when a skin test
boosts the ability of the
immune system to react to
tuberculin.
.....

One factor that can affect the accuracy of the baseline skin test is the **booster phenomenon**. The booster phenomenon happens because in some people who have TB infection, the ability to react to tuberculin lessens over time. When these people are skin tested many years after they became infected with *M. tuberculosis*, they may have a negative reaction. However, if they are tested again within a year of the first test, they may have a positive reaction. This is because the first skin test "jogged the memory" of the immune system, **boosting** its ability to react to tuberculin. It may appear that these people were infected between the first and second skin tests (recent TB infection). Actually, the second, positive reaction is a **boosted reaction** (due to TB infection that occurred a long time ago). The booster phenomenon occurs mainly among older adults. The booster phenomenon is illustrated in Figure 3.4.

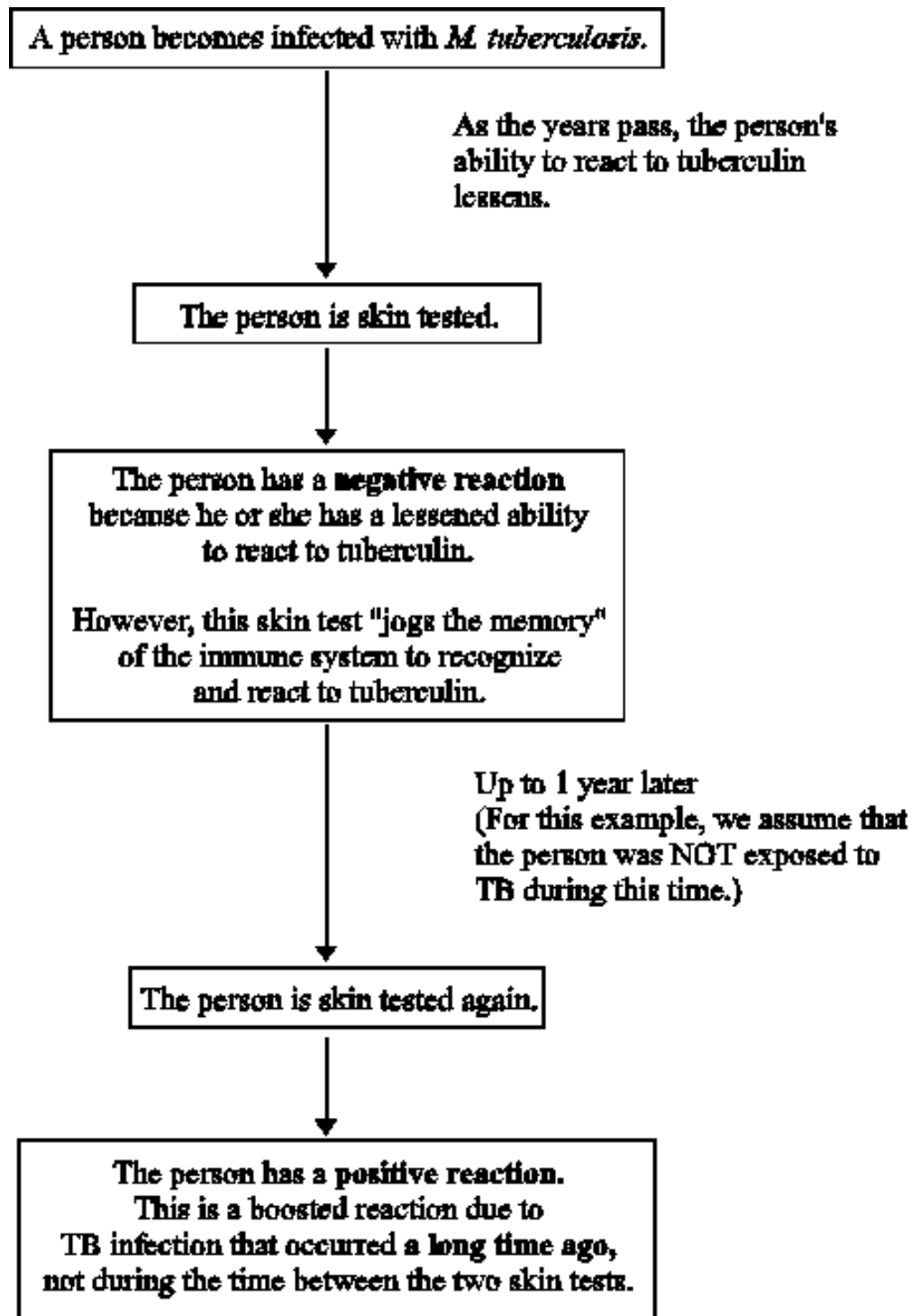


Figure 3.4 The booster phenomenon.



The booster phenomenon can present a problem in TB screening programs. This is because a negative reaction to the baseline skin test, followed by a positive reaction to a subsequent skin test that is given up to a year later, may be caused by either

Recent TB infection in a person who was NOT infected at the time of the baseline skin test, or

A boosted reaction in a person who WAS infected at the time of the baseline skin test

.....
Two-step testing is a strategy for telling the difference between boosted reactions and reactions caused by recent infection.

.....

To avoid misinterpretation, a strategy has been developed for telling the difference between boosted reactions and reactions caused by recent infection. This strategy, called **two-step testing**, means that if a person has a negative reaction to an initial skin test, he or she is given a second test 1 to 3 weeks later.

If the reaction to the second test is **positive**, it probably is a **boosted reaction** (due to TB infection that occurred a long time ago).

If the reaction to the second test is **negative**, the person is considered **uninfected**. In this person, a positive reaction to a skin test given later on will probably be due to recent infection.

.....
Two-step testing is used in many TB screening programs for skin testing employees when they start their job.

.....

Thus, because it provides accurate information about each employee's baseline skin test reaction, two-step testing is used in many TB screening programs for skin testing employees when they start their job. In particular, two-step testing is often used in hospitals and nursing homes. The procedure for two-step testing is shown in Figure 3.5.

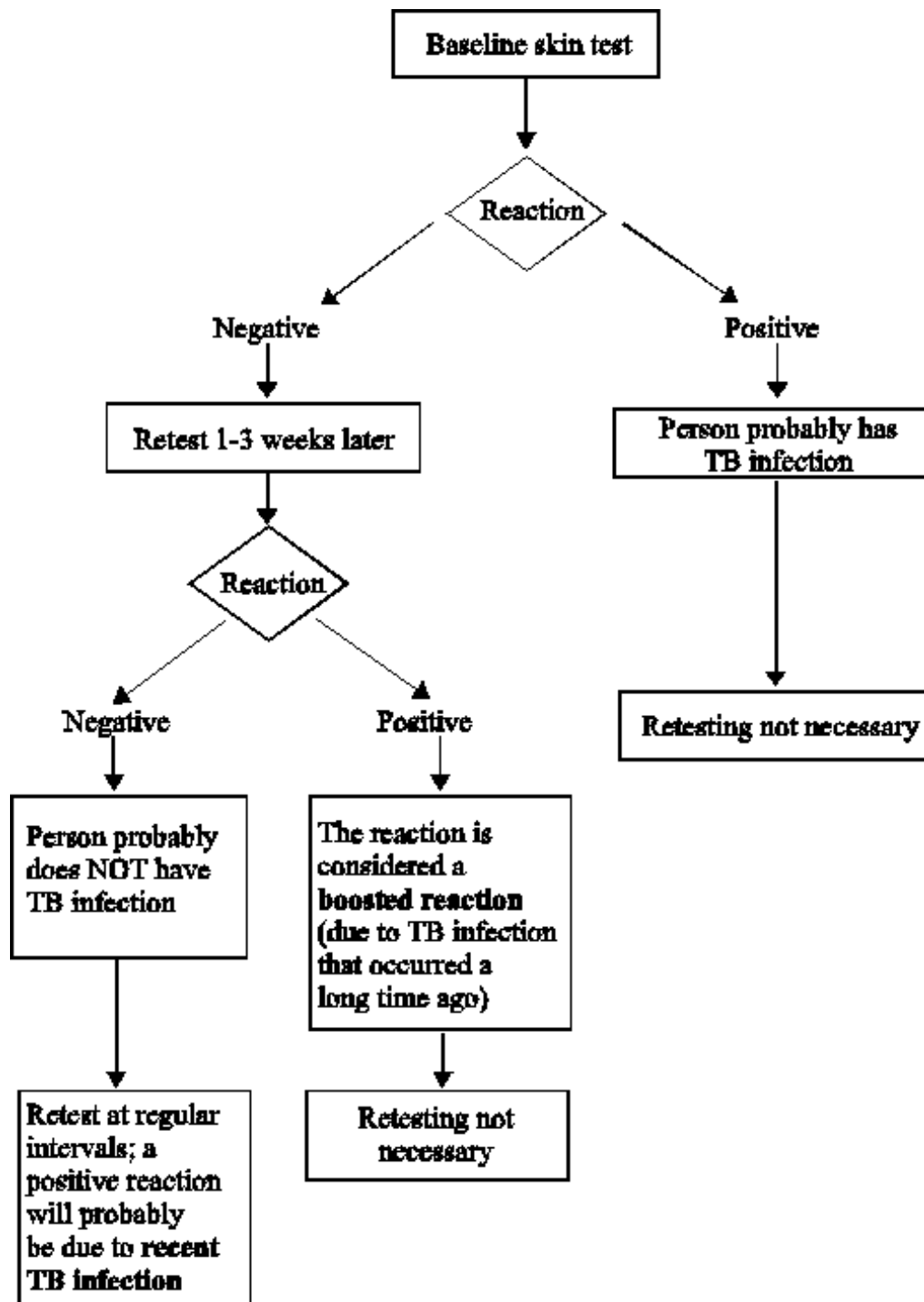


Figure 3.5 Two-step testing.



Study Questions 3.17-3.20

3.17. What is the booster phenomenon?

3.18. What is the purpose of two-step testing?

3.19. In what type of situation is two-step testing used?

3.20. How is two-step testing done?

Answers on page 65.



Case Study 3.4

Ms. Wilson is a 60-year-old nurse. When she started a job at the local hospital, she was given a tuberculin skin test, her first test in 25 years. Her reaction was read 48 hours later as 0 millimeters of induration. Six months later, she was retested as part of the TB screening program in the unit where she works. Her skin test reaction was read 48 hours later as 11 millimeters of induration.

What are two ways to interpret this result?

Answer on page 72.



Diagnosis of TB Disease

Before clinicians can diagnose TB disease in a patient, they must think of the possibility of TB when they see a patient with symptoms of TB or abnormal chest x-ray findings. Because TB is not as common as it was many years ago, many clinicians do not consider the possibility of TB when making diagnoses for patients who have symptoms of TB. When this happens, the diagnosis of TB may be delayed or even overlooked, and the patient will remain ill and possibly infectious.

.....
Anyone with symptoms of TB or a positive skin test reaction should be evaluated for TB disease.
.....

Anyone with **symptoms of TB** should be evaluated for TB disease. In addition, anyone found to have a **positive tuberculin skin test reaction** should be evaluated for TB disease.

Overview

There are four steps in diagnosing TB disease.

1. **The medical history.** A medical history is the part of a patient's life history that is important for diagnosing and treating the patient's medical condition. It includes social, family, medical, and occupational information about the patient. To obtain a medical history, the clinician should ask whether the patient has:
 - a. **Been exposed to a person who has infectious TB**
 - b. **Symptoms of TB disease**
 - c. **Had TB infection or TB disease before**
 - d. **Risk factors for developing TB disease**

Clinicians should suspect TB disease in patients with any of these factors.



1. **The tuberculin skin test.** Patients with symptoms of TB disease are often given a tuberculin skin test. However, they should always be evaluated for TB disease, regardless of their skin test results. Furthermore, clinicians should not wait for tuberculin skin test results when evaluating patients who have symptoms of TB disease. Instead, they should give the patient a tuberculin skin test at the same time as they start the other steps in the diagnosis of TB disease.

3. **The chest x-ray.** If the patient has TB disease in the lungs, the chest x-ray usually shows signs of TB disease.

4. **The bacteriologic examination.** This is the examination and the culture (growth) of clinical specimens (for example, sputum or urine) in the laboratory. The bacteriologic examination has four parts:
 - a. **Obtaining a specimen**
 - b. **Examining the specimen under a microscope**
 - c. **Culturing the specimen**
 - d. **Doing drug susceptibility testing on positive cultures**

The Medical History

a. Exposure to TB. One important part of the medical history is asking the patient about his or her **exposure** to TB. Patients should be asked whether they have spent time with someone who has infectious TB. Some people may have been exposed to TB in the distant past, when they were children. Others may have been exposed more recently.

.....
Some people may have been exposed to TB in the distant past, when they were children. Others may have been exposed more recently.
.....



Anyone who has been exposed to TB may have TB infection. Some people become infected with *M. tuberculosis* without knowing that they were exposed to it. The risk of being exposed to TB is higher for some occupations (for example, some health care workers) and in some residential facilities (for example, nursing homes or correctional facilities).

.....
People with TB disease may
or may not have symptoms.
.....

b. Symptoms of TB disease. Another important part of the medical history is checking for **symptoms** of TB disease. People with TB disease may or may not have symptoms. However, most patients with TB disease have one or more symptoms that led them to seek medical care. Occasionally, TB is discovered during a medical examination for an unrelated condition (for example, when a patient is given a chest x-ray before undergoing surgery). Usually, when patients do have symptoms, the symptoms have developed gradually, and they have been present for weeks or even months.

Pulmonary TB disease usually causes one or more of the following symptoms:

- # Coughing
- # Pain in the chest when breathing or coughing
- # Coughing up sputum (phlegm from deep in the lungs) or blood

The general symptoms of TB disease (pulmonary or extrapulmonary) include

- # Weight loss
- # Fatigue
- # Malaise
- # Fever
- # Night sweats



The symptoms of extrapulmonary TB disease depend on the part of the body that is affected by the disease. For example, TB of the spine may cause **pain in the back**; TB of the kidney may cause **blood in the urine**.

All of these symptoms may be caused by other diseases, but they should prompt the clinician to suspect TB disease.

.....
The clinician should ask the patient whether he or she has ever been diagnosed with or treated for TB infection or disease.
.....

c. Previous TB infection or TB disease. During the medical history, the clinician should ask the patient whether he or she has **ever been diagnosed with or treated for TB infection or disease**.

- # Patients known to have a positive skin test reaction probably have TB infection. If they were infected within the past 2 years, they are at high risk for TB disease.
- # Patients who have had TB disease before should be asked when they had the disease and how the disease was treated. If the regimen prescribed was inadequate or if the patient did not follow the recommended treatment, TB may recur, and it may be resistant to one or more of the drugs used.



.....
Some conditions appear to increase the risk that TB infection will progress to disease.
.....

d. Risk factors for developing TB disease. A fourth part of the medical history is checking for **risk factors** for developing TB disease. The following conditions appear to increase the risk that TB infection will progress to disease:

- # Infection with **HIV**, the virus that causes **AIDS**
- # Alcohol abuse and drug injection
- # Recent TB infection (within the past 2 years)
- # Chest x-ray findings suggestive of previous TB
- # Diabetes mellitus
- # Silicosis
- # Prolonged therapy with corticosteroids
- # Immunosuppressive therapy
- # Certain types of cancer (e.g., leukemia, Hodgkin's disease, or cancer of the head and neck)
- # Severe kidney disease
- # Certain intestinal conditions
- # Low body weight (10% or more below ideal)

Clinicians should determine whether patients have any of these conditions. In particular, HIV infection greatly increases the risk that TB infection will progress to TB disease.

A physical examination is an essential part of the evaluation of any patient. It cannot confirm or rule out TB disease, but it can provide valuable information about the patient's overall condition and other factors that may affect how TB disease is treated if it is diagnosed.



.....
Patients with symptoms of TB disease should always be evaluated for TB disease, regardless of their skin test results.
.....

The Tuberculin Skin Test

Patients with symptoms of TB disease are often given a tuberculin skin test to detect exposure to and infection with TB. However, as many as 20% of patients found to have TB disease have a negative tuberculin skin test reaction. For this reason, **patients with symptoms of TB disease should always be evaluated for TB disease, regardless of their skin test results.**

Furthermore, for patients with symptoms of TB disease, clinicians should not wait for tuberculin skin test results (48 to 72 hours) before starting other diagnostic tests.

A tuberculin skin test is not necessary for patients known to have had a previous positive tuberculin skin test reaction.



Study Questions 3.21-3.24

- 3.21. What are the four steps in diagnosing TB disease?**
- 3.22. What parts of a patient's medical history should lead a clinician to suspect TB?**
- 3.23. What are the common symptoms of pulmonary TB disease? What are the general symptoms of TB disease (pulmonary or extrapulmonary)?**
- 3.24. For patients with symptoms of TB disease, should clinicians wait for tuberculin skin test results before starting other diagnostic tests?**

Answers on pages 66-67.



.....
Chest x-rays are useful for
diagnosing TB disease
because about 85% of TB
patients have pulmonary TB.
.....

The Chest X-Ray

The chest x-ray is useful for diagnosing TB disease because about 85% of TB patients have pulmonary TB (TB disease in the lungs). Usually, when a person has TB disease in the lungs, the chest x-ray appears abnormal (Figure 3.6). It may show **infiltrates** (collections of fluid and cells in the tissues of the lung) or **cavities** (hollow spaces within the lung that may contain many tubercle bacilli).

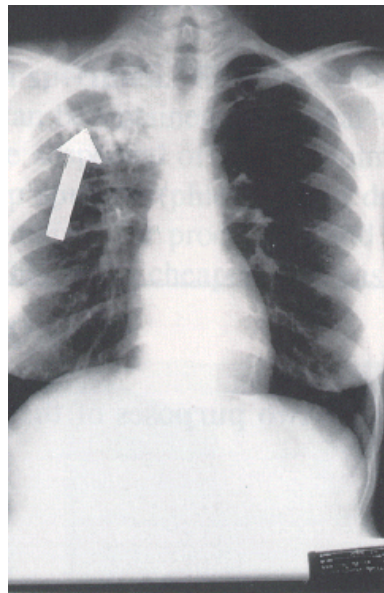


Figure 3.6 Abnormal chest x-ray. Arrow points to cavity in patient's right upper lobe. Left lobe is normal.

The purposes of the chest x-ray are to

- # Help rule out the possibility of pulmonary TB disease in a person who has a positive reaction to the tuberculin skin test
- # Check for lung abnormalities in people who have symptoms of TB disease



Diagnosis of Tuberculosis Infection and Disease

.....
The results of a chest x-ray cannot confirm that a person has TB disease.
.....

.....
In HIV-infected patients, pulmonary TB may have an unusual appearance on the chest x-ray.
.....

However, the results of a chest x-ray **cannot confirm that a person has TB disease**. A variety of illnesses may produce abnormalities whose appearance on a chest x-ray resembles TB. Although an abnormality on a chest x-ray may lead a clinician to suspect TB, **only a bacteriologic culture that is positive for *M. tuberculosis* proves that a patient has TB disease**. Moreover, a chest x-ray cannot detect TB infection.

In patients who are infected with HIV, pulmonary TB disease may have an unusual appearance on the chest x-ray. The chest x-ray may even appear entirely normal.

Study Questions 3.25-3.26

3.25. Name the two purposes of the chest x-ray.

3.26. Can the results of a chest x-ray confirm that a person has TB disease? Why or why not?

Answers on page 67.



The Bacteriologic Examination

The next step in diagnosing TB disease is the **bacteriologic examination**. This is done in a laboratory that specifically deals with *M. tuberculosis* and other mycobacteria (a **mycobacteriology laboratory**). There are four parts to a bacteriologic examination:

.....
A bacteriologic examination is done in a laboratory that specifically deals with *M. tuberculosis* and other mycobacteria.
.....

- a. Obtaining a specimen
- b. Examining the specimen under a microscope
- c. Culturing the specimen
- d. Doing drug susceptibility testing

.....
Patients suspected of having pulmonary TB disease may cough up sputum, which is collected in a sterile container for processing and examination.
.....

a. Obtaining a specimen. Specimens that will be sent to the laboratory can be obtained in several ways. Usually, patients who are suspected of having pulmonary TB disease simply cough up **sputum** (phlegm from deep in the lungs) into a sterile container for processing and examination (Figure 3.7). This is the cheapest and easiest procedure.



Figure 3.7 A TB patient has coughed up sputum and is spitting it into a sterile container. (The patient is sitting in a special sputum collection booth that prevents the spread of tubercle bacilli.)



.....
For an induced sputum sample, the patient inhales a saline mist, causing him or her to cough deeply.
.....

If a patient cannot cough up sputum on his or her own, other techniques can be used to obtain a specimen. An **induced sputum** sample can be obtained by having the patient inhale a saline (salt water) mist, which causes the patient to cough deeply. This procedure is easily done, and it should be used to help patients cough up sputum if they cannot do so on their own. Induced specimens are often clear and watery, so they should be labeled "induced specimen" so that they will not be confused with saliva. (Laboratories will not accept saliva as a specimen.)

.....
A bronchoscopy is done to obtain pulmonary secretions or lung tissue.
.....

Another procedure, **bronchoscopy**, can be used to obtain pulmonary secretions or lung tissue. In this procedure, an instrument called the bronchoscope is passed through the mouth directly into the diseased portion of the lung, and some sputum or lung tissue is removed. Bronchoscopy should be used only when patients cannot cough up sputum on their own and an induced specimen cannot be obtained.

.....
For gastric washing, a tube is inserted through the patient's nose and passed into the stomach to collect a sample of sputum that has been coughed into the throat and then swallowed.
.....

A fourth procedure, **gastric washing**, involves inserting a tube through the patient's nose and passing it into the stomach. The idea is to get a sample of sputum that has been coughed into the throat and then swallowed. Gastric washings are done in the morning because patients usually swallow sputum during the night. This procedure is usually used only when patients cannot cough up sputum on their own, an induced specimen cannot be obtained, and bronchoscopy cannot be done. However, gastric washings are often used for obtaining sputum from children. Most children produce little or no sputum when they cough.



.....
Health care workers should use precautions to control the spread of tubercle bacilli during sputum collection procedures.
.....

.....
In patients with extrapulmonary TB disease, specimens are obtained in various ways, depending on the part of the body that is affected.
.....

It is very important for health care workers to use precautions to control the spread of tubercle bacilli during these procedures and any other procedures that may cause persons who have pulmonary TB disease to cough. This is discussed further in Module 5, Infectiousness and Infection Control.

In patients who have **extrapulmonary TB disease**, **specimens other than sputum** are obtained. The specimen obtained from these patients depends on the part of the body that is affected. For example, urine samples are obtained from patients suspected of having TB disease of the kidney, and fluid samples are obtained from the area around the spine in patients suspected of having TB meningitis (TB disease in the membranes surrounding the brain).

The methods of obtaining a sputum specimen are summarized in Table 3.3.



Table 3.3
Methods of Obtaining a Sputum Specimen

Method	Description	Advantage	Disadvantage
Coughing up sputum	Patient coughs up sputum	Inexpensive Easy to do	Patient may not be able to cough up sputum on his or her own, or may spit up saliva instead of sputum
Inducing sputum	Patient inhales a saline mist, causing him or her to cough deeply	Easy to do	Specimens may be watery and may be confused with saliva (should be labeled "induced specimen") Requires special equipment
Bronchoscopy	Bronchoscope is passed through the mouth directly into the diseased portion of the lung, and some sputum or lung tissue is removed	Useful for obtaining sputum when coughing or inducing sputum does not work	More expensive Requires special equipment Must be done by a specialized physician in a hospital or clinic
Gastric washing	Tube is inserted through the patient's nose and passed into the stomach to get a sample of sputum that has been coughed into the throat and then swallowed	Useful for obtaining sputum in children, who usually produce little or no sputum when they cough	Must be done as soon as patient wakes up in the morning; patient may be required to stay in hospital



Case Study 3.5

Mr. Lee has a cough and other symptoms of TB disease, and he is evaluated with a chest x-ray. However, he is unable to cough up any sputum on his own for the bacteriologic examination.

What should be done?

Answer on page 72.



.....
Specimens are smeared onto a glass slide and stained so that they can be examined for acid-fast bacilli (AFB) under a microscope.
.....

b. Examining the specimen under a microscope. Before the specimen is examined under a microscope, it is smeared onto a glass slide and stained with a dye. This is called a **smear**. Then laboratory personnel use the microscope to look for **acid-fast bacilli** (AFB) on the smear (Figure 3.8). AFB are mycobacteria that stay stained even after they have been washed in an acid solution. Tubercle bacilli are one kind of AFB.

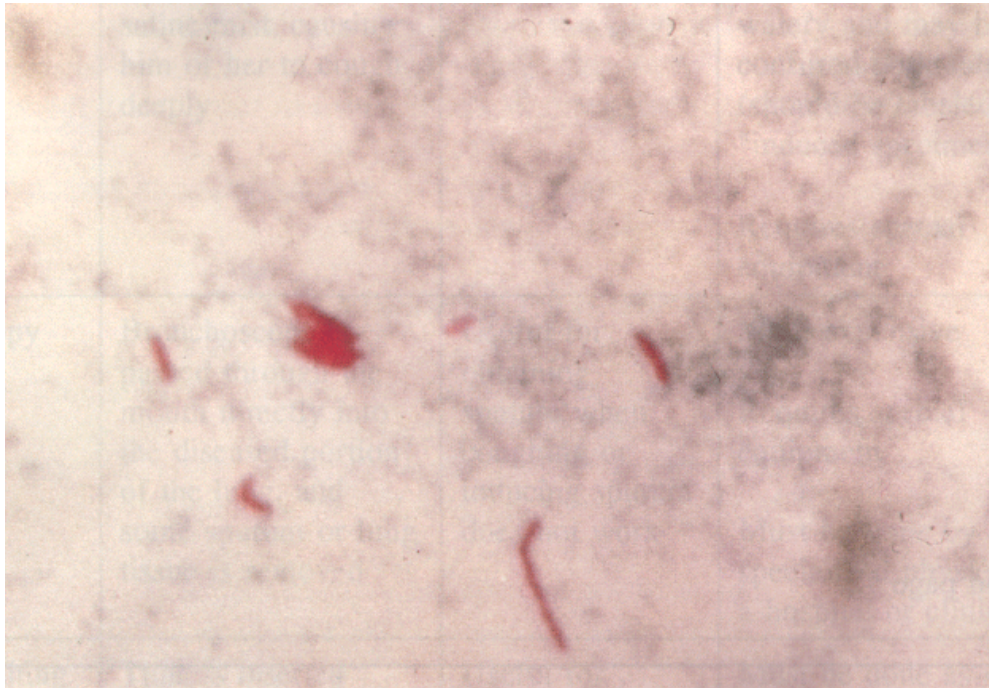


Figure 3.8 AFB smear. In this photograph, the AFB (shown in red) are tubercle bacilli.



.....
When AFB are seen in a smear they are counted and classified according to the number of AFB seen.
.....

When AFB are seen in a smear, they are counted. There is a system for reporting the number of AFB that are seen at a certain magnification. According to the number of AFB seen, the smears are classified as 4+, 3+, 2+, or 1+. In smears classified as 4+, 10 times as many AFB were seen as in smears classified as 3+; in 3+ smears, 10 times as many as in 2+ smears; and in 2+ smears, 10 times as many as in 1+ smears.

.....
A negative smear does not rule out the possibility of TB because there can be AFB in the smear that were not seen.
.....

Smears that are classified as 4+ and 3+ are considered strongly positive; 2+ and 1+ smears are considered moderately positive. If very few AFB are seen, the smear is classified by the actual number of AFB seen (no plus sign). For example, if only 4 AFB were seen in the entire smear, the smear is classified as "4 AFB seen." Smears classified in this way are considered weakly positive. Finally, if no AFB are seen, the smear is called negative. But a negative smear **does not rule out** the possibility of TB because there can be AFB in the smear that were not seen.

It takes only a few hours to prepare and examine a smear. Therefore, the results of the smear examination should be available to the clinician within 1 day.

.....
The results of the smear examination can be used to help determine the infectiousness of the patient.
.....

The results of the smear examination can be used to help determine the infectiousness (contagiousness) of the patient. Patients who have many tubercle bacilli in their sputum have a positive smear. Patients who have positive smears are considered infectious because they can cough many tubercle bacilli into the air. (This is discussed in more detail in Module 5, Infectiousness and Infection Control.) However, because AFB are not always tubercle bacilli, patients who have positive smears do not necessarily have TB. Furthermore, as mentioned previously, patients who have negative smears may have TB.

The classification of smears is summarized in Table 3.4.



Table 3.4
Smear Classifications and Results

Classification of Smear	Smear Result	Infectiousness of Patient
4+	Strongly positive	Probably very infectious
3+	Strongly positive	Probably very infectious
2+	Moderately positive	Probably infectious
1+	Moderately positive	Probably infectious
Actual number of AFB seen (no plus sign)	Weakly positive	Probably infectious
No AFB seen	Negative	May not be infectious*

* The criteria for determining whether a patient may be considered noninfectious are discussed in Module 5, Infectiousness and Infection Control.

Study Questions 3.27-3.29

3.27. What are the four ways to collect sputum specimens? Indicate which procedure is the cheapest and easiest to perform.

3.28. What do laboratory personnel look for in a smear?

3.29. What does a positive smear indicate about a patient's infectiousness?

Answers on pages 67-68.



Case Study 3.6

Ms. Thompson gave three sputum specimens, which were sent to the laboratory for smear examination and culture. The smear results were reported as 4+, 3+, and 4+.

What do these results tell you about Ms. Thompson's diagnosis and her infectiousness?

Answer on page 73.

Case Study 3.7

Mr. Sagoo has symptoms of TB disease and a cavity on his chest x-ray, but all of his sputum smears are negative for acid-fast bacilli.

Does this rule out the diagnosis of pulmonary TB disease?

Why or why not?

Answers on page 73.



.....
All specimens should be cultured, regardless of whether the smear is positive or negative.
.....

.....
Culturing the specimen is necessary to determine whether the specimen contains *M. tuberculosis* and to confirm a diagnosis of TB disease.
.....

c. Culturing the specimen. Culturing the specimen means growing the mycobacteria on **media**, substances that contain nutrients, in the laboratory (Figure 3.9). When the mycobacteria have formed **colonies** (groups), they can be identified. All specimens should be cultured, regardless of whether the smear is positive or negative.

Culturing the specimen is necessary to determine whether the specimen contains *M. tuberculosis* and to confirm a diagnosis of TB disease. (However, in some cases, patients are diagnosed with TB disease on the basis of their signs and symptoms, even if their specimen does not contain *M. tuberculosis*.)



Figure 3.9 Colonies of *M. tuberculosis* growing on media.



.....
The first procedure in culturing the specimen is to detect the growth of the mycobacteria. This can take from 4 days to 8 weeks.
.....

The first procedure in culturing the specimen is to detect the growth of the mycobacteria. Mycobacteria grow very slowly. When solid media are used to culture the specimen, it can take as long as 2 to 8 weeks for the growth of the mycobacteria to be detected. However, rapid culturing methods that involve liquid media can decrease this time to 4 to 8 days.

.....
The second procedure is to identify the organism that has grown.
.....

The second procedure is to identify the organism that has grown. All types of mycobacteria will grow in solid or liquid media. For this reason, laboratory tests must be done to determine whether the organism is *M. tuberculosis* or one of the nontuberculous mycobacteria. Traditional tests require an additional 3 to 6 weeks from the time the cultures have grown. However, other tests have been developed to shorten the time it takes to identify the type of mycobacteria present in clinical specimens.

.....
When *M. tuberculosis* is identified in a patient's culture, the patient is said to have a positive culture for *M. tuberculosis*.
.....

When *M. tuberculosis* is identified in a patient's culture, the patient is said to have a **positive culture** for *M. tuberculosis*. A positive culture for *M. tuberculosis*, also called an *M. tuberculosis* **isolate**, confirms the diagnosis of TB disease.

.....
A positive culture for *M. tuberculosis* confirms the diagnosis of TB disease.
.....

When *M. tuberculosis* is NOT identified in a patient's culture, the patient is said to have a **negative culture** for *M. tuberculosis*. A negative culture does not necessarily rule out the diagnosis of TB disease; as mentioned earlier, some patients with negative cultures are diagnosed with TB disease on the basis of their signs and symptoms.

The differences between sputum smears and cultures are summarized in Table 3.5.



Table 3.5
Differences Between Sputum Smears and Cultures

Feature	Smears (see Figure 3.8)	Cultures (see Figure 3.9)
Equipment needed	Microscope, glass slides, special dyes	Incubators, safety cabinet, culture plates or tubes, culture media, biochemicals for tests
Time needed to make report	1 day	2 to 8 weeks
Basis of procedure	Looking for AFB on slide under microscope	Growth of tubercle bacilli or other mycobacteria on culture media in incubator
Significance of a negative report	Patient is less likely to be infectious Does not rule out TB disease (culture may be positive)	No live tubercle bacilli found in the specimen Does not rule out TB disease (live tubercle bacilli may be in other specimens and/or in the patient)
Significance of a positive report	Patient is more likely to be infectious (if AFB are tubercle bacilli) AFB could be nontuberculous mycobacteria	Confirms diagnosis of TB disease



Criteria for Reporting TB Cases

All 50 states, the District of Columbia, New York City, U.S. dependencies and possessions, and independent nations in free association with the U.S.* report TB cases to the federal Centers for Disease Control and Prevention (CDC) based on certain criteria. Each reported TB case is checked to make sure that it meets the criteria. All cases that meet the criteria, called **verified TB cases**, are counted each year.

Cases that meet **one** of these three sets of criteria are counted as verified TB cases:

1. The patient has a positive culture for *M. tuberculosis*
or
2. The patient has a positive smear for AFB, but a culture has not been done or cannot be done
or
3. The patient has a positive tuberculin skin test reaction, has other signs and symptoms of TB disease, is being treated with two or more TB drugs, and has been given a complete diagnostic evaluation

In addition, cases that do not meet any of these sets of criteria (for example, a patient who is anergic and has a negative culture for *M. tuberculosis* but who has signs and symptoms of TB disease) may be counted as a verified TB case if a health care provider has reported the case and decided to treat the patient for TB disease.

*The dependencies, possessions, and independent nations include Puerto Rico, the U.S. Virgin Islands, Guam, American Samoa, the Republic of the Marshall Islands, the Commonwealth of the Northern Mariana Islands, and the Federated States of Micronesia.



.....
Drug susceptibility tests determine which drugs will kill the tubercle bacilli that are causing disease in a particular patient.
.....

.....
The results of drug susceptibility tests can help clinicians choose the appropriate drugs for each patient.
.....

.....
Drug susceptibility tests should be done when a patient is first found to have a positive culture for *M. tuberculosis*.
.....

.....
Drug susceptibility tests should be repeated if a patient has a positive culture for *M. tuberculosis* after 2 months of treatment or if a patient does not seem to be getting better.
.....

d. Doing drug susceptibility testing. Drug susceptibility tests, the final part of the bacteriologic examination, are done to determine which drugs will kill the tubercle bacilli that are causing disease in a particular patient. Tubercle bacilli that are killed by a particular drug are said to be **susceptible** to that drug, whereas those that can grow even in the presence of a particular drug are said to be **resistant** to that drug. The **drug susceptibility pattern** of a strain of tubercle bacilli is the list of drugs to which the strain is susceptible and to which it is resistant.

The results of drug susceptibility tests can help clinicians choose the appropriate drugs for each patient. This is very important. Patients with TB disease who are treated with drugs to which their strain of TB is resistant may not be cured. In fact, their strain of TB may become resistant to additional drugs.

Drug susceptibility tests should be done when a patient is first found to have a positive culture for *M. tuberculosis* (that is, the first isolate of *M. tuberculosis*). In addition, drug susceptibility tests should be repeated if a patient has a positive culture for *M. tuberculosis* after 2 months of treatment or if a patient does not seem to be getting better. That way, the clinician can find out whether the patient's strain of TB has become resistant to certain drugs; if necessary, the clinician may change the drugs used for treating the patient.



In the laboratory, drug susceptibility testing can be done using solid media. Organisms that grow in media containing a specific drug are considered resistant to that drug (Figure 3.10). This technique is slow, taking as long as 8 to 12 weeks. Rapid methods for drug susceptibility testing can shorten this time to 3 weeks.

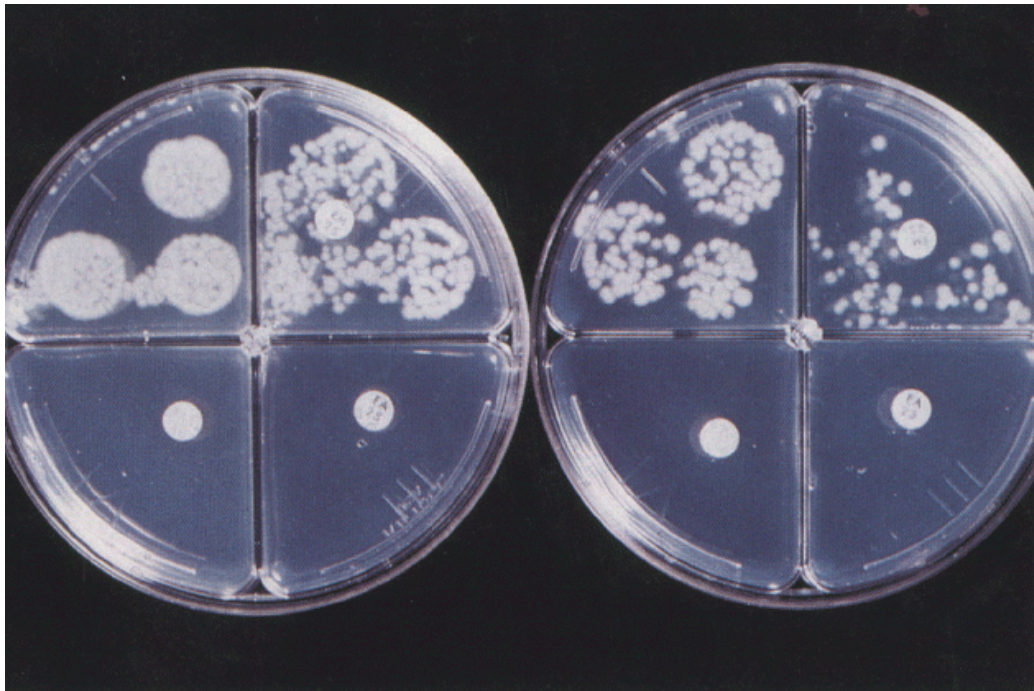


Figure 3.10 Drug susceptibility testing on solid media. Organisms are resistant to the drug in the upper right compartment and susceptible to the drugs in the lower compartments. Upper left contains no drugs.



Study Questions 3.30-3.33

- 3.30. Why is it necessary to culture a specimen?**
- 3.31. What does a positive culture for *M. tuberculosis* mean? How is this important for the TB diagnosis?**
- 3.32. Why are drug susceptibility tests done?**
- 3.33. How often should drug susceptibility tests be done?**

Answers on pages 68-69.



Case Study 3.8

In the public health clinic, you see a patient, Ms. Sanchez, who complains of weight loss, fever, and a cough of 4 weeks' duration. When questioned, she reports that she has been treated for TB disease in the past and that she occasionally injects heroin.

What parts of Ms. Sanchez's medical history lead you to suspect TB disease?

What diagnostic tests should be done?

Answers on page 74.



SUMMARY

The tuberculin skin test is used to determine whether a person has TB infection. The Mantoux tuberculin skin test is the preferred type of skin test because it is the most accurate. This test is done by using a needle and syringe to inject tuberculin between the layers of the skin, usually on the forearm. After 48 to 72 hours, the patient's arm is examined for a reaction (an induration). The diameter of the indurated area (the swelling, not the redness) is measured across the forearm. Most people with TB infection have a positive reaction to the tuberculin.

Whether a reaction to the Mantoux tuberculin skin test is classified as positive depends on the size of the induration, the person's risk factors for TB, and for people who may be exposed to TB on the job, the risk of exposure to TB in the person's job.

Several factors can affect how the skin test reaction is interpreted. Some factors, such as infection with nontuberculous mycobacteria (mycobacteria other than *M. tuberculosis*) and vaccination with BCG, can cause false-positive reactions. Other factors, such as anergy, recent infection, and very young age can cause false-negative reactions. HIV-infected people may be tested for anergy if they have a negative reaction to the tuberculin skin test. Also, close contacts of someone with infectious TB disease who have a negative reaction to the tuberculin skin test should be retested 10 weeks after the last time they were in contact with the person who has TB.

In many TB screening programs, two-step testing is used for skin testing employees when they start their job. Two-step testing is a strategy for telling the difference between boosted reactions and reactions caused by recent infection.

There are four steps in diagnosing TB disease. The first is the medical history. This means asking the patient whether he or she has been exposed to a person with TB, has symptoms of TB disease, has had TB infection or TB disease before, or has risk factors for developing TB disease. The symptoms of pulmonary TB disease include coughing, pain in the chest when breathing or coughing, and coughing up sputum or blood. The general symptoms of TB disease (pulmonary or extrapulmonary) include weight loss, fatigue, malaise, fever, and night sweats. The symptoms of extrapulmonary TB disease depend on the part of the body that is affected by the disease.



Second, patients with symptoms of TB disease may be given a tuberculin skin test. However, they should always be evaluated for TB disease, regardless of their skin test results. Furthermore, clinicians should not wait for tuberculin skin test results when evaluating patients who have symptoms of TB disease.

The third step is the chest x-ray. One purpose of the chest x-ray is to help rule out the possibility of pulmonary TB disease in a person who has a positive reaction to the tuberculin skin test. Another purpose is to check for lung abnormalities in people who have symptoms of TB disease. However, the results of a chest x-ray cannot confirm that a person has TB disease.

The fourth step is to do a bacteriologic examination. First, a specimen is obtained from the patient. A sputum specimen is obtained from patients suspected of having pulmonary TB disease; other specimens are obtained from patients suspected of having extrapulmonary TB disease. Either way, this specimen is smeared onto a slide, stained, and examined under a microscope for the presence of acid-fast bacilli. When acid-fast bacilli are seen in a smear, they are counted, and the smear is classified according to this number. Patients with positive smears are considered infectious.

Next, the specimen is cultured, or grown, so that laboratory personnel can determine whether it contains *M. tuberculosis*. Special tests are used to identify the mycobacteria once they have grown enough to be detected. A positive culture for *M. tuberculosis* confirms the diagnosis of TB disease.

After the specimen has been cultured, it is tested for drug susceptibility. The results of drug susceptibility tests can help clinicians choose the appropriate drugs for each patient.



Additional Reading

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ANSWERS TO STUDY QUESTIONS

3.1. What is the tuberculin skin test used for? (page 7)

The tuberculin skin test is used to determine whether a person has TB infection.

3.2. How is the Mantoux tuberculin skin test given? (page 8)

The Mantoux skin test is given by using a needle and syringe to inject 0.1 ml of 5 tuberculin units of liquid tuberculin between the layers of the skin (intradermally), usually on the forearm.

3.3. With the Mantoux skin test, when is the patient's arm examined? (page 8)

The patient's arm is examined 48 to 72 hours after the tuberculin is injected.

3.4. How is the induration measured? (page 8)

The diameter of the indurated area is measured across the forearm; erythema (redness) around the indurated area is not measured, because the presence of erythema does not indicate that a person has TB infection.

3.5. Why is the Mantoux skin test preferable to multiple-puncture tests? (page 10)

The Mantoux skin test is preferable to multiple-puncture tests because it is more accurate. In multiple-puncture tests, the amount of tuberculin that actually enters the skin cannot be measured. In the Mantoux test, however, the amount of tuberculin can always be measured. Therefore, the Mantoux test is more accurate, and it is the preferred method.



3.6. What two factors are considered when classifying a skin test reaction as positive or negative? What additional factor is considered for people who may be exposed to TB on the job? (pages 12-13)

Whether a reaction to the Mantoux tuberculin skin test is classified as positive depends on the size of the induration and the person's risk factors for TB.

For people who may be exposed to TB on the job, an additional factor is considered: the risk of exposure to TB in the person's job.

3.7. For which groups of people is 5 or more millimeters of induration considered a positive reaction? Name four. (page 12)

An induration of 5 or more millimeters is considered a positive reaction for

- # People with HIV infection
- # Close contacts of people with infectious TB
- # People with chest x-ray findings suggestive of previous TB disease
- # People who inject illicit drugs and whose HIV status is unknown

3.8. For which groups of people is 10 or more millimeters of induration considered a positive reaction? Name seven. (page 12)

An induration of 10 or more millimeters is considered a positive reaction for

- # People born in areas of the world where TB is common (foreign-born persons)
- # People who inject illicit drugs but who are known to be HIV negative
- # Low-income groups with poor access to health care
- # People who live in residential facilities (for example, nursing homes or correctional facilities)
- # People with medical conditions that appear to increase the risk for TB (not including HIV infection), such as diabetes
- # Children younger than 4 years old
- # People in other groups likely to be exposed to TB, as identified by local public health officials



3.9. For which group of people is 15 or more millimeters of induration considered a positive reaction? (page 13)

An induration of 15 or more millimeters is considered a positive reaction for people with no risk factors for TB.

3.10. Name two factors that can cause false-positive reactions to the tuberculin skin test. (page 17)

Two factors that can cause false-positive reactions are infection with nontuberculous mycobacteria (mycobacteria other than *M. tuberculosis*) and vaccination with BCG.

3.11. Is there a reliable way to distinguish a positive tuberculin reaction caused by vaccination with BCG from a reaction caused by true TB infection? (page 17)

No, there is no reliable way to distinguish a positive tuberculin reaction caused by vaccination with BCG from a reaction caused by true TB infection. However, the reaction is more likely to be due to TB infection if any of the following are true:

- # The reaction is large
- # The person was vaccinated a long time ago
- # The person comes from an area of the world where TB is common
- # The person has been exposed to someone with infectious TB disease
- # The person's family has a history of TB disease

3.12. Name three factors that can cause false-negative reactions to the tuberculin skin test. (page 20)

False-negative reactions may be due to

- # Anergy
- # Recent TB infection (within the past 10 weeks)
- # Very young age (younger than 6 months old)



3.13. What is anergy? (page 20)

Anergy is the inability to react to skin tests because of a weakened immune system. Many conditions, such as HIV infection, cancer, or severe TB disease itself, can weaken the immune system and cause anergy. HIV infection is a main cause of anergy.

3.14. How is anergy testing done? (page 20)

Anergy testing is done by giving skin tests using two substances other than tuberculin. The recommended substances for anergy testing are mumps, *Candida* (a type of fungus), or tetanus extracts. Most healthy people will have a skin test reaction to one or more of these substances.

People who do not react to any of the substances, including tuberculin, after 48 to 72 hours (that is, people who have less than 3 millimeters of induration to all of the skin tests), are considered anergic. People who have a reaction (3 or more millimeters of induration) to any of the substances are NOT anergic. If a person being evaluated for anergy has a reaction of 5 or more millimeters of induration to tuberculin, he or she is considered to have TB infection, regardless of the reaction to the other substances.

3.15. After TB has been transmitted, how long does it take before TB infection can be detected by the tuberculin skin test? (page 21)

After TB has been transmitted, it takes 2 to 10 weeks before TB infection can be detected by the tuberculin skin test.

3.16. What should be done if a patient has a negative skin test reaction but has symptoms of TB disease? (page 21)

Any patient with symptoms of TB disease should be evaluated for TB disease, regardless of his or her skin test reaction. In fact, people with symptoms of TB disease should be evaluated for TB disease right away, at the same time that the tuberculin skin test is given.



3.17. What is the booster phenomenon? (page 26)

The booster phenomenon is a phenomenon in which people (especially older adults) who are skin tested many years after becoming infected with *M. tuberculosis* may have a negative reaction to an initial skin test, followed by a positive reaction to a skin test given up to a year later. This happens because in some people who have TB infection, the ability to react to tuberculin lessens over time. The first skin test "jogs the memory" of the immune system, boosting its ability to react to tuberculin.

3.18. What is the purpose of two-step testing? (page 28)

The purpose of two-step testing is to tell the difference between boosted reactions and reactions caused by recent infection. Because it provides accurate information about each employee's baseline skin test reaction, two-step testing is used in many TB screening programs for skin testing employees when they start their job.

3.19. In what type of situation is two-step testing used? (page 28)

Two-step testing is used in many TB screening programs for skin testing employees when they start their job.

3.20. How is two-step testing done? (page 28)

If a person has a negative reaction to an initial skin test, he or she is given a second test 1 to 3 weeks later.

- # If the reaction to the second test is positive, it is considered a boosted reaction (due to TB infection that occurred a long time ago).
- # If the reaction to the second test is negative, the person is considered uninfected. In this person, a positive reaction to a skin test given later on will probably be due to recent TB infection.



3.21. What are the four steps in diagnosing TB disease? (pages 32-33)

The four steps in diagnosing TB disease are

1. The medical history
2. The tuberculin skin test
3. The chest x-ray
4. The bacteriologic examination

3.22. What parts of a patient's medical history should lead a clinician to suspect TB? (pages 32, 33-36)

Clinicians should suspect TB disease in patients who have

- a. Been exposed to a person who has infectious TB,
- b. Symptoms of TB disease,
- c. Had TB infection or TB disease before, or
- d. Risk factors for developing TB disease.

3.23. What are the common symptoms of pulmonary TB disease? What are the general symptoms of TB disease (pulmonary or extrapulmonary)? (pages 34-35)

Pulmonary TB disease usually causes one or more of the following symptoms:

- # Coughing
- # Pain in the chest when breathing or coughing
- # Coughing up sputum or blood

The general symptoms of TB disease (pulmonary or extrapulmonary) include

- # Weight loss
- # Fatigue
- # Malaise
- # Fever
- # Night sweats

The symptoms of extrapulmonary TB disease depend on the part of the body that is affected



by the disease. For example, TB of the spine may cause pain in the back; TB of the kidney may cause blood in the urine.

3.24. For patients with symptoms of TB disease, should clinicians wait for tuberculin skin test results before starting other diagnostic tests? (page 37)

No. For patients with symptoms of TB disease, clinicians should not wait for tuberculin skin test results before starting other diagnostic tests.

3.25. Name the two purposes of the chest x-ray. (page 39)

The purposes of the chest x-ray are to

- # Help rule out the possibility of pulmonary TB disease in a person who has a positive reaction to the tuberculin skin test
- # Check for lung abnormalities in people who have symptoms of TB disease

3.26. Can the results of a chest x-ray confirm that a person has TB disease? Why or why not? (page 40)

No, the results of a chest x-ray cannot confirm that a person has TB disease. This is because a variety of illnesses may produce abnormalities whose appearance on a chest x-ray resembles TB. Although an abnormality on a chest x-ray may lead a clinician to suspect TB, only a bacteriologic culture that is positive for *M. tuberculosis* proves that a patient has TB disease.

3.27. What are the four ways to collect sputum specimens? Indicate which procedure is the cheapest and easiest to perform. (pages 41-42)

- # Usually, patients who are suspected of having pulmonary TB disease simply cough up sputum and the sputum is collected in a sterile container for processing and examination. This is the cheapest and easiest procedure. If a patient cannot cough up sputum on his or her own, other techniques can be used to obtain a specimen.
- # An induced sputum sample can be obtained by having the patient inhale a saline (salt water) mist, which causes the patient to cough deeply.



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- # Bronchoscopy can be used to obtain pulmonary secretions or lung tissue. In this procedure, an instrument called the bronchoscope is passed through the mouth directly into the diseased portion of the lung, and some sputum or lung tissue is removed.
- # Gastric washing involves inserting a tube through the patient's nose and passing it into the stomach. The idea is to get a sample of sputum that has been coughed into the throat and then swallowed.

3.28. What do laboratory personnel look for in a smear? (page 46)

Laboratory personnel use the microscope to look for acid-fast bacilli (AFB) on the smear. AFB are mycobacteria that stay stained even after they have been washed in an acid solution. Tubercle bacilli are one kind of AFB.

3.29. What does a positive smear indicate about a patient's infectiousness? (page 47)

The results of the smear examination can be used to help determine the infectiousness (contagiousness) of the patient. Patients who have many tubercle bacilli in their sputum have a positive smear. Patients who have positive smears are considered infectious because they can cough many tubercle bacilli into the air.

3.30. Why is it necessary to culture a specimen? (page 50)

Culturing the specimen is necessary to determine whether the specimen contains *M. tuberculosis* and to confirm a diagnosis of TB disease. (However, in some cases, patients are diagnosed with TB disease on the basis of their signs and symptoms, even if their specimen does not contain *M. tuberculosis*.)

3.31. What does a positive culture for *M. tuberculosis* mean? How is this important for the TB diagnosis? (page 51)

A positive culture for *M. tuberculosis* means that *M. tuberculosis* has been identified in a patient's culture. A positive culture for *M. tuberculosis* confirms the diagnosis of TB disease.



3.32. Why are drug susceptibility tests done? (page 54)

Drug susceptibility tests are done to determine which drugs will kill the tubercle bacilli that are causing disease in a particular patient. The results of drug susceptibility tests can help clinicians choose the appropriate drugs for each patient.

3.33. How often should drug susceptibility tests be done? (page 54)

Drug susceptibility tests should be done when a patient is first found to have a positive culture for *M. tuberculosis*. In addition, drug susceptibility tests should be repeated if a patient has a positive culture for *M. tuberculosis* after 2 months of treatment or if a patient does not seem to be getting better.



ANSWERS TO CASE STUDIES

3.1. Which of the following patients have a positive tuberculin skin test reaction?

- * a) Mr. West, 36 years old, HIV infected, 08 mm of induration
- b) Ms. Hernandez, 26 years old, native of Mexico, 07 mm of induration
- * c) Ms. Jones, 56 years old, has diabetes, 12 mm of induration
- * d) Mr. Sung, 79 years old, resident of a nursing home, 11 mm of induration
- e) Mr. Williams, 21 years old, no risk factors, 13 mm of induration
- * f) Ms. Marcos, 42 years old, chest x-ray findings suggestive of previous TB, 06 mm of induration
- * g) Ms. Rayle, 50 years old, husband has pulmonary TB, 09 mm of induration

(a), (c), (d), (f), (g)

3.2. A 30-year-old man who recently immigrated from India is given a tuberculin skin test and found to have 14 millimeters of induration. He reports that he was vaccinated with BCG as a child. He also says that his wife was treated for pulmonary TB disease last year.

Can you tell for sure whether this man has TB infection?

No. This man does have a positive reaction to the tuberculin skin test (10 or more millimeters is considered a positive reaction for a foreign-born person). However, this may be a false-positive reaction because he has been vaccinated with BCG.

What factors make it more likely that this man's positive reaction is due to TB infection?

First, this man has a fairly large reaction (14 mm). Second, he was vaccinated a long time ago, when he was a child. Third, this man is from an area of the world where TB is common, so he was probably exposed to TB in his native country. Therefore, he is at increased risk for TB infection. Fourth, his wife has had pulmonary TB, which further increases the probability that he has been exposed to TB.

Because he has a positive skin test reaction, this man should be further evaluated for TB disease.



3.3. Mr. Bell comes to the TB clinic for a tuberculin skin test. He believes that he has been exposed to TB, and he knows he is at high risk for TB because he is HIV infected. He is given a tuberculin skin test, and his reaction is read 48 hours later as 0 millimeters of induration.

What are three ways to interpret this result?

There are three possible reasons why Mr. Bell had no reaction to the tuberculin skin test.

Q First, he may not have TB infection.

Q Second, he may be anergic. People who are HIV infected are more likely to be anergic than persons who are not HIV infected. If Mr. Bell is anergic, he would be unable to react to tuberculin even if he did have TB infection. To determine whether he is anergic, a clinician can test him with two substances other than tuberculin.

Q Third, it may be less than 10 weeks since he was exposed to TB. After TB has been transmitted, it takes 2 to 10 weeks before TB infection can be detected by the tuberculin skin test. Mr. Bell should be retested 10 weeks after he was last exposed to TB.



3.4. Ms. Wilson is a 60-year-old nurse. When she started a job at the local hospital, she was given a tuberculin skin test, her first test in 25 years. Her reaction was read 48 hours later as 0 millimeters of induration. Six months later, she was retested as part of the TB screening program in the unit where she works. Her skin test reaction was read 48 hours later as 11 millimeters of induration.

What are two ways to interpret this result?

There are two possible explanations for this result.

Q One explanation is that Ms. Wilson may have been exposed to and infected with *M. tuberculosis* sometime in the 6 months between her first and second skin tests.

Q The other explanation is the booster phenomenon. If Ms. Wilson was infected with *M. tuberculosis* many years ago, her ability to react to tuberculin may have decreased. This would explain why she did not react to the first tuberculin skin test. Then the first tuberculin test may have boosted the ability of her immune system to react to tuberculin. This would explain why she had a positive reaction to the second test, which was given within a year of the first test. If this scenario is true, Ms. Wilson's positive reaction would not mean that she was recently infected with *M. tuberculosis*.

This problem in interpreting Ms. Wilson's reaction would have been avoided if she had been tested with a two-step procedure when she first joined the hospital. In any event, because she has a positive reaction, Ms. Wilson should be evaluated for TB disease.

3.5. Mr. Lee has a cough and other symptoms of TB disease, and he is evaluated with a chest x-ray. However, he is unable to cough up any sputum on his own for the bacteriologic examination.

What should be done?

If a patient cannot cough up a sputum specimen, other techniques can be used to obtain sputum. First, clinicians can try to obtain an induced sputum sample. If they cannot obtain an induced sputum sample, a bronchoscopy or gastric washing may be done.

3.6. Ms. Thompson gave three sputum specimens, which were sent to the laboratory for



smear examination and culture. The smear results were reported as 4+ , 3+ , and 4+ .

What do these results tell you about Ms. Thompson's diagnosis and her infectiousness?

These results show that Ms. Thompson's sputum specimens contain many acid-fast bacilli. Because the smears are positive, clinicians should suspect that Ms. Thompson has TB disease. They should also consider her infectious. However, it is possible that these acid-fast bacilli are mycobacteria other than tubercle bacilli. Therefore, the diagnosis of TB disease cannot be proven until the culture results are available.

3.7. Mr. Sagoo has symptoms of TB disease and a cavity on his chest x-ray, but all of his sputum smears are negative for acid-fast bacilli.

Does this rule out the diagnosis of pulmonary TB disease?

No.

Why or why not?

M. tuberculosis may grow in the cultures even though there were no acid-fast bacilli on the smear. Mr. Sagoo's symptoms and his abnormal chest x-ray suggest that he does have pulmonary TB disease.



3.8. In the public health clinic, you see a patient, Ms. Sanchez, who complains of weight loss, fever, and a cough of 4 weeks' duration. When questioned, she reports that she has been treated for TB disease in the past and that she occasionally injects heroin.

What parts of Ms. Sanchez's medical history lead you to suspect TB disease?

Ms. Sanchez has symptoms of TB disease (weight loss, fever, and a persistent cough). Also, in the past she has been treated for TB disease. We don't know whether she completed therapy, but until we can prove otherwise, we should assume that she has TB disease again. Her history of injecting illicit drugs (heroin) is another risk factor for TB.

What diagnostic tests should be done?

People who have TB symptoms should be evaluated for TB disease. Because she has symptoms of pulmonary TB disease (coughing), Ms. Sanchez should be given a chest x-ray. In addition, a sputum specimen should be collected for smear and culture, and drug susceptibility testing should be done if the culture is positive for *M. tuberculosis*. A tuberculin skin test may be helpful for the diagnosis of TB, but it is not necessary.