Lec.5\ Dr. Widad Abd AL Jabbar

B. Isoniazid

Isoniazid, along with rifampin, is one of the two most important TB drugs.

Mechanism of action

Isoniazid is a prodrug activated by a mycobacterial catalase–peroxidase (KatG). Isoniazid targets the enzymes acyl carrier protein reductase (InhA) and β-ketoacyl-ACP synthase (KasA), which are essential for the synthesis of mycolic acid. Inhibiting mycolic acid leads to a disruption in the bacterial cell wall.

Antibacterial spectrum

Isoniazid is specific for the treatment of M. tuberculosis, although M. kansasii may be susceptible at higher drug concentrations. Most NTM are resistant to INH. The drug is particularly effective against rapidly growing bacilli and is also active against intracellular organisms.

Resistance

Resistance follows chromosomal mutations, including 1) mutation or deletion of KatG (producing mutants incapable of prodrug activation), 2) varying mutations of the acyl carrier proteins, or 3) overexpression of the target enzyme InhA. Cross-resistance may occur between isoniazid and ethionamide.

Pharmacokinetics

Isoniazid is readily absorbed after oral administration. Absorption is impaired if isoniazid is taken with food, particularly high-fat meals. The drug diffuses into all body fluids, cells, and caseous material (necrotic tissue resembling cheese that is produced in tuberculous lesions). Drug concentrations in the cerebrospinal fluid (CSF) are similar to those in the serum. Isoniazid undergoes N-acetylation and hydrolysis, resulting in inactive products. Isoniazid acetylation is genetically regulated, with fast acetylators exhibiting a 90-minute serum half-life, as compared with 3 to 4 hours for slow acetylators (Figure 32.4). Excretion is through glomerular filtration and secretion, predominantly as metabolites (Figure 32.5). Slow acetylators excrete more of the parent compound.

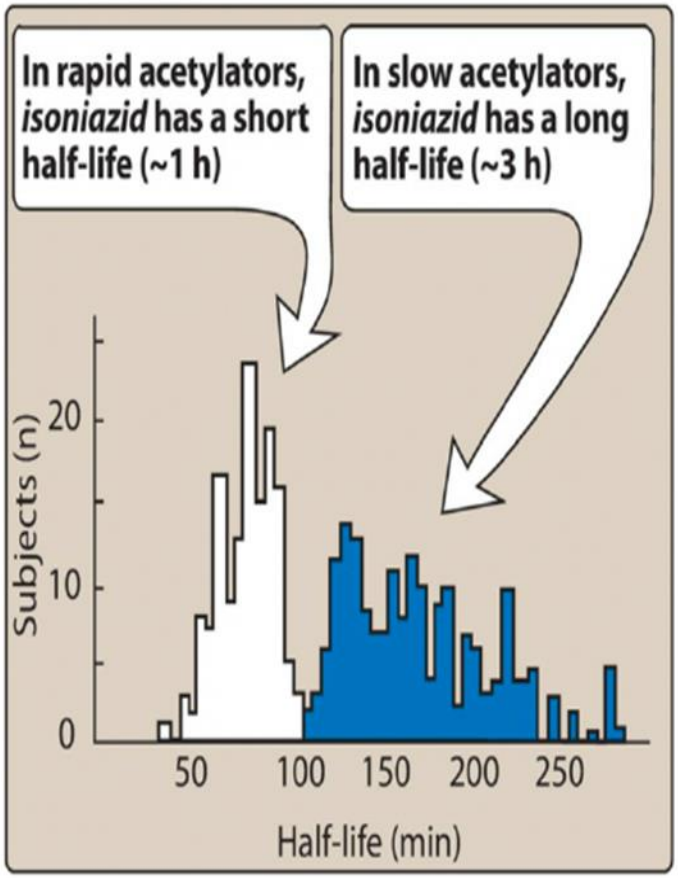

Figure 32.4 Bimodal distribution of *isoniazid* half-lives caused by rapid and acetylation of the drug.

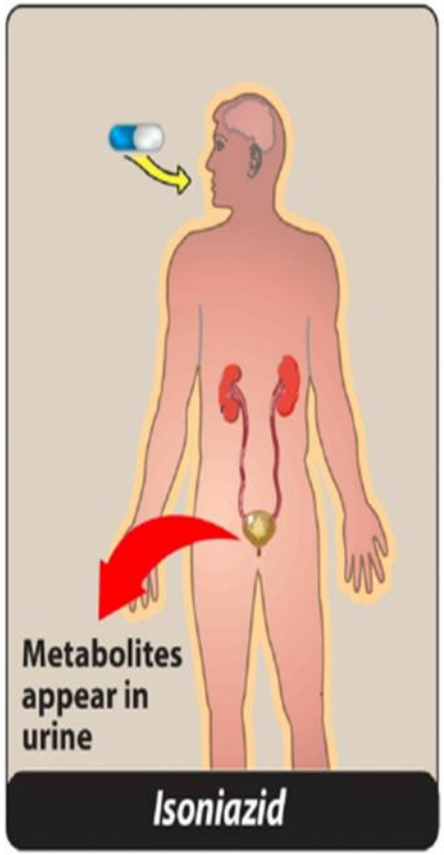

Figure 32.5 Administration and fate of *isoniazid*.

Adverse effects

Hepatitis is the most serious adverse effect associated with isoniazid. If hepatitis goes unrecognized, and if isoniazid is continued, it can be fatal. The incidence increases with age (greater than 35 years old), among patients who also take rifampin, or among those who drink alcohol daily. Peripheral neuropathy, manifesting as paresthesia of the hands and feet, appears to be due to a relative pyridoxine deficiency caused by isoniazid. This can be avoided by daily supplementation of pyridoxine (vitamin B6) Central nervous system (CNS) adverse effects can occur, including convulsions in patients prone to seizures.

Hypersensitivity reactions with isoniazid include rashes and fever. Because isoniazid inhibits the metabolism of carbamazepine and phenytoin, isoniazid can potentiate the adverse effects of these drugs (for example, nystagmus and ataxia).

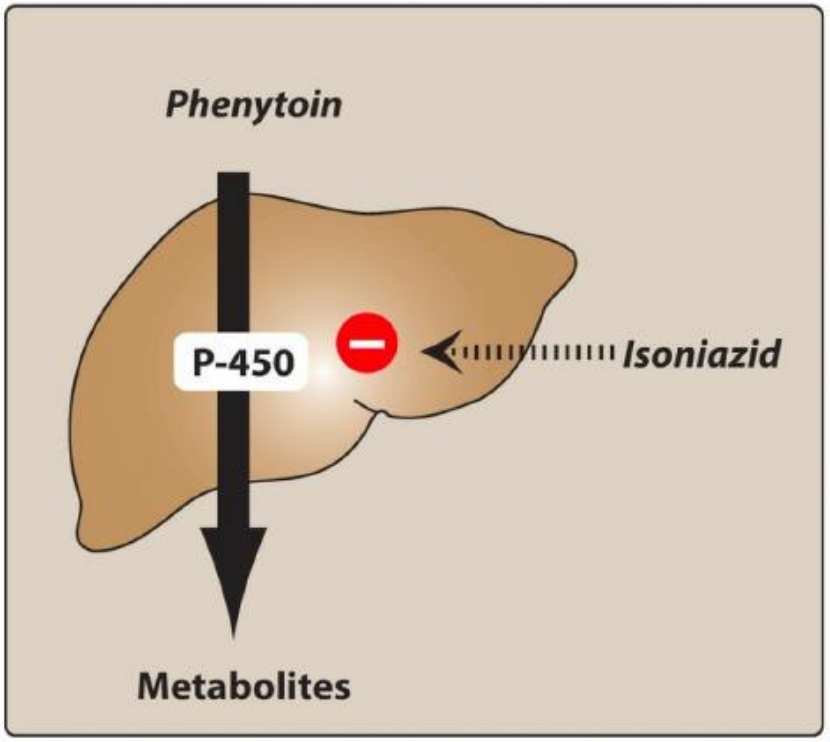

Figure 32.6 *Isoniazid* potentiates the adverse effects of *phenytoin*.

C. Rifamycins: rifampin, rifabutin, and rifapentine

Rifampin, rifabutin, and rifapentine are all considered rifamycins, a group of structurally similar macrocyclic antibiotics, which are first-line oral agents for tuberculosis.

1. Rifampin

Rifampin has broader antimicrobial activity than isoniazid and can be used as part of treatment for several different bacterial infections. Because resistant strains rapidly emerge during monotherapy, it is never given as a single agent in the treatment of active tuberculosis.

Mechanism of action

Rifampin blocks RNA transcription by interacting with the β subunit of mycobacterial DNA-dependent RNA polymerase.

Antimicrobial spectrum

Rifampin is bactericidal for both intracellular and extracellular mycobacteria, including M. tuberculosis, and NTM, such as M. kansasii and Mycobacterium avium complex (MAC). It is effective against many gram-positive and gram-negative organisms and is used prophylactically for individuals exposed to meningitis caused by meningococci or Haemophilus influenzae. Rifampin also is highly active against M. leprae.

Resistance

Resistance to rifampin is caused by mutations in the affinity of the bacterial DNA-dependent RNA polymerase gene for the drug.

Pharmacokinetics

Absorption is adequate after oral administration. Distribution of rifampin occurs to all body fluids and organs. Concentrations attained in the CSF are variable, often 10% to 20% of blood concentrations. The drug is taken up by the liver and undergoes enterohepatic recycling. Rifampin can induce hepatic cytochrome P450 enzymes and transporters, leading to numerous drug interactions. Unrelated to its effects on cytochrome P450 enzymes, rifampin undergoes autoinduction, leading to a shortened elimination half-life over the first 1 to 2 weeks of dosing. Elimination of rifampin and its metabolites is primarily through the bile and into the feces; a small percentage is cleared in the urine (Figure 32.7). [Note: Urine, feces, and other secretions have an orange-red color, so patients should be forewarned. Tears may even stain soft contact lenses orange-red.]

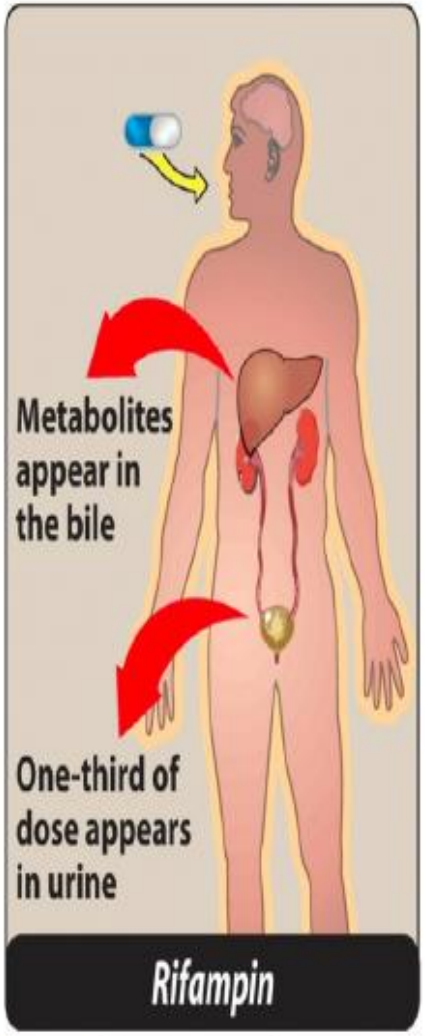

Figure 32.7 Administration and fate of *rifampin*. [Note: Patient should be warned that urine and tears may turn orange-red in color.]

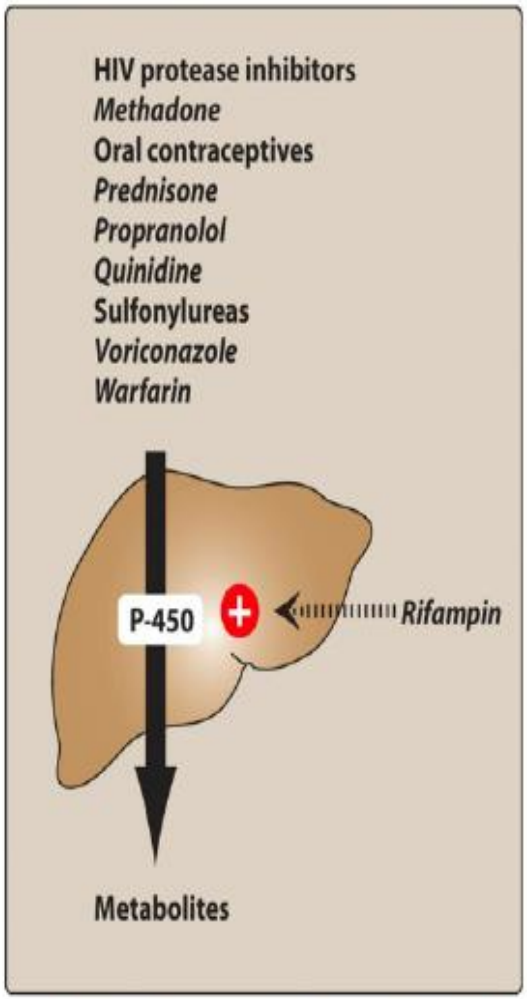

Figure 32.8 Induces cytochrome P450, which can decrease the half-lives of coadministered drugs that are metabolized by this system.

Adverse effects

Rifampin is generally well tolerated. The most common adverse reactions include nausea, vomiting, and rash. Hepatitis and death due to liver failure are rare. However, the drug should be used judiciously in older patients, alcoholics, or those with chronic liver disease. There is a modest increase in the incidence of hepatic dysfunction when rifampin is coadministered with isoniazid and pyrazinamide. When rifampin is dosed intermittently, especially with higher doses, a flu-like syndrome can occur, with fever, chills, and myalgia, sometimes extending to acute renal failure, hemolytic anemia, and shock.

Drug interactions

Because rifampin induces a number of phase I cytochrome P450 enzymes and phase II enzymes, it can decrease the half-lives of coadministered drugs that are metabolized by these enzymes (Figure 32.8). This may necessitate higher dosages for coadministered drugs, a switch to drugs less affected by rifampin, or replacement of rifampin with rifabutin.

2. Rifabutin

Rifabutin, a derivative of rifampin, is preferred for TB patients coinfected with the human immunodeficiency virus (HIV) who are receiving protease inhibitors or several of the nonnucleoside reverse transcriptase inhibitors. Rifabutin is a less potent inducer (approximately 40% less) of cytochrome P450 enzymes, thus lessening drug interactions. Rifabutin has adverse effects similar to those of rifampin but can also cause uveitis, skin hyperpigmentation, and neutropenia.

3. Rifapentine

Rifapentine has a longer half-life than that of rifampin. In combination with isoniazid, rifapentine may be used once weekly in patients with LTBI and in select HIV-negative patients with minimal pulmonary TB.

D. Pyrazinamide

Pyrazinamide is a synthetic, orally effective short-course agent used in combination with isoniazid, rifampin, and ethambutol. The precise mechanism of action is unclear.

Pyrazinamide must be enzymatically hydrolyzed by pyrazinamidase to pyrazinoic acid, which is the active form of the drug. Some resistant strains lack the pyrazinamidase enzyme. Pyrazinamide is active against tuberculosis bacilli in acidic lesions and in macrophages.

The drug is distributed throughout the body, penetrating the CSF. Pyrazinamide may contribute to liver toxicity. Uric acid retention is common but rarely precipitates a gouty attack. Most of the clinical benefit from pyrazinamide occurs early in treatment. Therefore, this drug is usually discontinued after 2 months of a 6-month regimen.

E. Ethambutol

Ethambutol is bacteriostatic and specific for mycobacteria. Ethambutol inhibits arabinosyl transferase—an enzyme important for the synthesis of the mycobacterial cell wall. Ethambutol is used in combination with pyrazinamide, isoniazid, and rifampin pending culture and susceptibility data. [Note: Ethambutol may be discontinued if the isolate is determined to be susceptible to isoniazid, rifampin, and pyrazinamide.

Ethambutol distributes well throughout the body. Penetration into the CNS is variable, and it is questionably adequate for tuberculous meningitis. Both the parent drug and its hepatic metabolites are primarily excreted in the urine. The most important adverse effect is optic neuritis, which results in diminished visual acuity and loss of ability to discriminate between red and green. The risk of optic neuritis increases with higher doses and in patients with renal impairment. Visual acuity and color discrimination should be tested prior to initiating therapy and periodically thereafter. Uric acid excretion is decreased by ethambutol, and caution should be exercised in patients with gout. The figure below summarizes some of the characteristics of first-line drugs.

DRUG	ADVERSE EFFECTS	COMMENTS
Ethambutol	Optic neuritis with blurred vision, red-green color blindness	Establish baseline visual acuity and color vision; test monthly.
Isoniazid	Hepatic enzyme elevation, hepatitis, peripheral neuropathy	Take baseline hepatic enzyme measurements; repeat if abnormal or patient is at risk or symptomatic. Clinically significant interaction with *phenytoin* and *carbamazepine*.
Pyrazinamide	Nausea, hepatitis, hyperuricemia, rash, joint ache, gout (rare)	Take baseline hepatic enzymes and uric acid measurements; repeat if abnormal or patient is at risk or symptomatic.
Rifampin	Hepatitis, GI upset, rash, flu-like syndrome, significant interaction with several drugs	Take baseline hepatic enzyme measurements and CBC; repeat if abnormal or patient is at risk or symptomatic. Warn patient that urine and tears may turn red-orange in color.

F. Alternate second-line drugs

Streptomycin, para-aminosalicylic acid, capreomycin, cycloserine, ethionamide, bedaquiline, fluoroquinolones, and macrolides are second-line TB drugs. In general, these agents are less effective and more toxic than the first-line agents. The figure below summarizes some of the characteristics of second-line drugs.

DRUG	ADVERSE EFFECTS	COMMENTS
Fluoroquinolones	GI intolerance, tendonitis, CNS toxicity including caffeine-like effects	Monitor LFTs, serum creatinine/BUN, QT interval prolongation. Avoid concomitant ingestion with antacids, multivitamins or drugs containing di- or trivalent cations.
Aminoglycosides, *Capreomycin*	Nephrotoxicity, ototoxicity	Not available orally. Monitor for vestibular, auditory and renal toxicity.
Macrolides	GI intolerance, tinnitus	Monitor LFTs, serum creatinine/BUN, QT interval prolongation. Monitor for drug interactions due to CYP inhibition (except *azithromycin*).
Ethionamide	GI intolerance, hepatotoxicity, hypothyroidism	Monitor LFTs, TSH. A majority of patients experience GI intolerance. Cross-resistance with *isoniazid* is possible.
Para-aminosalicylic acid (PAS)	GI intolerance, hepatotoxicity, hypothyroidism	Monitor LFTs, TSH. Patients with G6PD deficiency are at increased risk of hemolytic anemia.
Cycloserine	CNS toxicity	Close monitoring is needed for depression, anxiety, confusion, etc. Seizures may be exacerbated in patients with epilepsy. Monitor serum creatinine.

Figure 32.10 Some characteristics of second-line drugs used in treating tuberculosis. BUN = blood urea nitrogen; CNS = central nervous system; CYP = cytochrome; G6PD = glucose-6-phosphate dehydrogenase; GI = gastrointestinal; LFTs = liver function tests; TSH = thyroid-stimulating hormone.

1. Streptomycin

Streptomycin, an aminoglycoside antibiotic, was one of the first effective agents for TB. Its action appears to be greater against extracellular organisms. Infections due to streptomycin-resistant organisms may be treated with kanamycin or amikacin, to which these bacilli usually remain susceptible.

2. Para-aminosalicylic acid

Para-aminosalicylic acid (PAS) works via folic acid inhibition. While largely replaced by ethambutol for drug- susceptible TB, PAS remains an important component of many regimens for MDR-TB.

3. Capreomycin

This is a parenterally administered polypeptide that inhibits protein synthesis similar to aminoglycosides. Capreomycin is primarily reserved for the treatment of MDR-TB. Careful monitoring of renal function and hearing is necessary to minimize nephrotoxicity and ototoxicity, respectively.

4. Cycloserine

Cycloserine is an orally effective, tuberculostatic drug that disrupts D-alanine incorporation into the bacterial cell wall. It distributes well throughout body fluids, including the CSF. Cycloserine is primarily excreted unchanged in urine. Accumulation occurs with renal insufficiency. Adverse effects involve CNS disturbances (for example, lethargy, difficulty concentrating, anxiety, and suicidal tendencies), and seizures may occur.

5. Ethionamide

Ethionamide is a structural analog of isoniazid that also disrupts mycolic acid synthesis. The mechanism of action is not identical to isoniazid, but there is some overlap in the resistance patterns. Ethionamide is widely distributed throughout the body, including the CSF. Metabolism is extensive, most likely in the liver, to active and inactive metabolites. Adverse effects that limit its use include nausea, vomiting, and hepatotoxicity. Hypothyroidism, gynecomastia, alopecia, impotence, and CNS effects also have been reported.

6. Fluoroquinolones

The fluoroquinolones, specifically moxifloxacin and levofloxacin, have an important place in the treatment of multidrug-resistant tuberculosis. Some NTM also are susceptible.

7. Macrolides

The macrolides azithromycin and clarithromycin are included in regimens for several NTM infections, including MAC. Azithromycin may be preferred for patients at greater risk for drug interactions, since clarithromycin is both a substrate and inhibitor of cytochrome P450 enzymes.

8. Bedaquiline

Bedaquiline, a diarylquinoline, is an ATP synthase inhibitor. It is approved for the treatment of MDR-TB. Bedaquiline is administered orally, and it is active against many types of mycobacteria. Bedaquiline has a boxed warning for QT prolongation, and monitoring of the electrocardiogram is recommended. Elevations in liver enzymes have also been reported and liver function should be monitored during therapy. This agent is metabolized via CYP3A4, and administration with strong CYP3A4 inducers (for example, rifampin) should be avoided.

III. Drugs for Leprosy

Leprosy (or Hansen disease) is uncommon in the United States; however, worldwide, it is a much larger problem (Figure 32.11). Leprosy can be treated effectively with dapsone and rifampin (Figure 32.12).

A. Dapsone

Dapsone is structurally related to the sulfonamides and similarly inhibits dihydropteroate synthase in the folate synthesis pathway. It is bacteriostatic for M. leprae, and resistant strains may be encountered. Dapsone also is used in the treatment of pneumonia caused by Pneumocystis jirovecii in immunosuppressed patients. The drug is well absorbed from the gastrointestinal tract and is distributed throughout the body, with high concentrations in the skin. The parent drug undergoes hepatic acetylation. Both parent drug and metabolites are eliminated in the urine. Adverse reactions include hemolysis (especially in patients with glucose-6-phosphate dehydrogenase deficiency), methemoglobinemia, and peripheral neuropathy.

B. Clofazimine

Clofazimine is a phenazine dye. Its mechanism of action may involve binding to DNA, although alternative mechanisms have been proposed. Its redox properties may lead to the generation of cytotoxic oxygen radicals that are toxic to the bacteria. Clofazimine is bactericidal to M. leprae, and it has potentially useful activity against M. tuberculosis and NTM. The drug is recommended by the World Health Organization as part of a shorter regimen (9 to 12 months) for MDR-TB. Following oral absorption, clofazimine accumulates in tissues, allowing intermittent therapy but does not enter the CNS. Patients typically develop a pink to brownish-black discoloration of the skin and should be informed of this in advance. Eosinophilic and other forms of enteritis, sometimes requiring surgery, have been reported. Clofazimine has some anti-inflammatory and anti-immune activities. Thus, erythema nodosum leprosum may not develop in patients treated with this drug.

Fig.32.12 Patient with leprosy

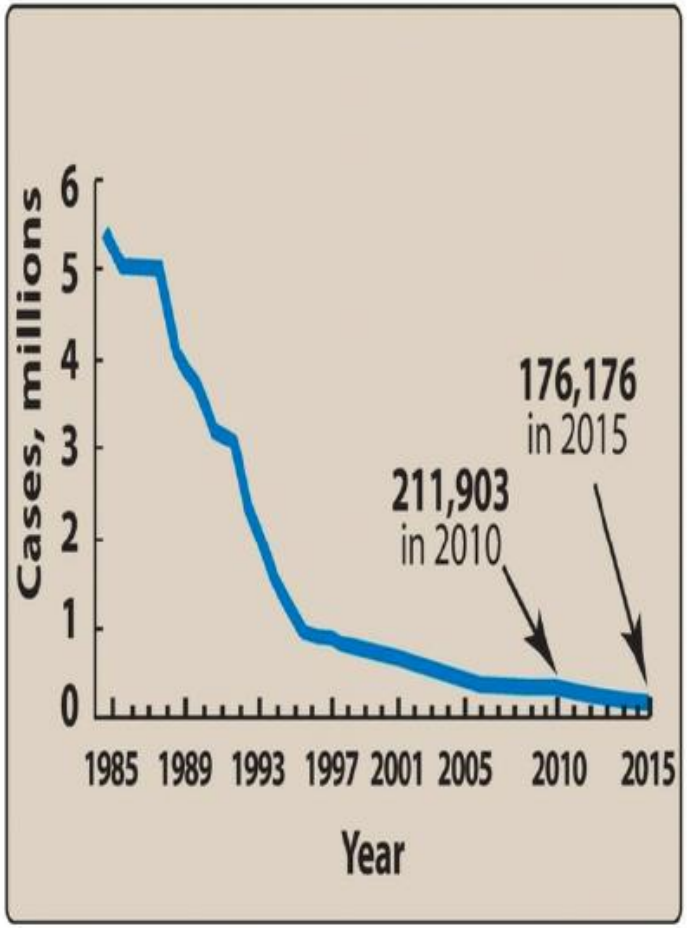

Figure 32.11 Reported prevalence of leprosy worldwide.