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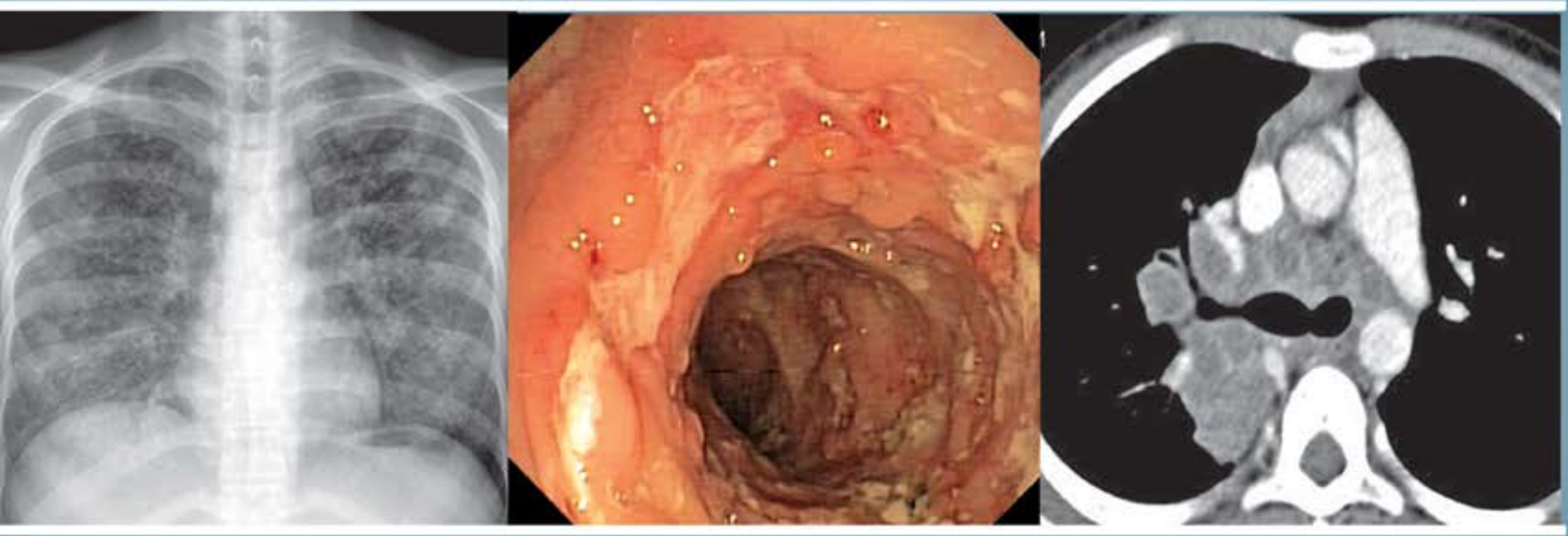
5TH EDITION

Essentials of Tuberculosis in Children



Rakesh Lodha
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CHAPTER

4

Mycobacterium tuberculosis

Sarman Singh, Amit Singh, Jitendra Singh, K Gopinath, Ashok Rattan

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INTRODUCTION

The genus *Mycobacterium* includes species of bacteria responsible for tuberculosis (TB) and leprosy, diseases of antiquity, which still affect millions. Before the COVID-19 pandemic, from a single infectious agent, TB was the largest cause of death, which ranks above human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS)[1,2] (WHO 2021). Worldwide, in 2019, around 10.0 million (range, 8.9–11.0 million) people fell ill with TB, a number that has been declining very slowly in recent years. India tops the list by having the highest burden of infected people (WHO 2021).[1,2] Initially, the main cause of the increased rate of death was the HIV pandemic, which has allowed TB to reemerge so dramatically.[1-3] In 2019, an estimated 1.2 million (range, 1.1–1.3 million) TB deaths occurred among HIV-negative people (a reduction from 1.7 million in 2000) while 208,000 deaths happened (range, 177,000–242,000) among HIV-positive people (a reduction from 678,000 in 2000).[1-3]

Robert Koch, a physician from Wolstein, Germany, demonstrated that TB is caused by a prokaryote. He was able to isolate pure culture of tubercle bacilli and inoculated them into healthy mice and guinea pigs, which eventually became diseased with the pathogen. **Box 1** gives Koch's postulates. Thus, a far-reaching discovery emerged after centuries of ignorance. Koch published his findings on April 10, 1882, after presenting these on March 24, 1882.[4]

The bacterium was named *Mycobacterium* (Greek, Mykes, Fungus; bacterium; small rods) in 1896 by Lehmann and Neumann in reference to the mold-like pellicles formed by the bacteria on liquid medium. At that time, the genus contained only two species, *Mycobacterium tuberculosis (MTB)* and *Mycobacterium leprae*.

BOX 1: Koch's postulates.

- The bacterium should be constantly associated with the lesion of the disease
- It should be possible to isolate the bacterium in pure culture from the lesion
- Inoculation of such pure culture into suitable laboratory animals should reproduce the lesions of the disease
- It should be possible to reisolate the bacterium in pure culture from the lesions produced in the experimental animals

Mycobacterium tuberculosis is clinically the most important member of the *Mycobacterium tuberculosis* complex (MTC). The MTC includes *MTB, M. africanum, M. bovis, M. microti, M. canettii, M. caprae, M. pinnipedii, M. suricattae, M. mungi, M. dassie,* and *Mycobacterium oryx*. The members of this complex are closely related as seen by deoxyribonucleic acid (DNA) homology.[5] Each of them, however, does possess signature sequences, which can be differentiated by sequencing after polymerase chain reaction (PCR) amplification of specific hypervariable regions in the gene coding for the 16S ribosomal RNA (rRNA).[6,7] But for all practical purposes, the degree of homology between the species of the complex suggests that the members of this complex might be more properly considered serovars or pathovars of the same species rather than 11 different species. Disease caused by *M. bovis* and *M. africanum* is clinically indistinguishable from classical TB and treatment is the same for all the infections. *M. microti* causes a TB-like disease but is not considered pathogenic for humans while Bacillus Calmette–Guérin (BCG) is essentially nonpathogenic for humans.

Mainly, *M. caprae* has been identified in central Europe, where it sometimes has been isolated from the tuberculous lesions of cattle, pigs, red deer, and wild boars. In few cases, its isolation from humans has also been described.[8] Other members of MTC are *M. pinnipedii, M. suricattae, M. mungi, M. dassie,* and *M. oryx*, which can infect seals, meerkats, mongoose, dassie, and the Bovidae family, respectively.[9-11]

TAXONOMY

Mycobacterium is the only genus in the family Mycobacteriaceae. The high guanine + cytosine (GC) ratio in the DNA of mycobacteria (62–70%) is similar to that of other mycolic acid-producing bacteria—*Nocardia* (60–69%), *Rhodococcus* (59–69%), and *Corynebacterium* (51–59%).

This similarity may support the consolidation of these genera into a single family.[12] The genus *Mycobacterium* is responsible for more suffering worldwide than all other bacterial genera combined. Currently, there are more than 170 recognized species of Mycobacteria.[13] This genus contains obligate pathogenic, opportunistic, and saprophytic species. According to Bergey's manual of determinative bacteriology, mycobacteria are classified in the category II (gram-positive bacteria having cell wall) with the following classification:

- *Division:* Prokaryote
- *Subdivision:* Protophyta
- *Class:* Schizomycetes
- *Order:* Actinomycetales
- *Family:* Mycobacteriaceae
- *Genus: Mycobacterium*

Mycobacteria have been classified into fast- and slow-growing species by the seemingly arbitrary criteria of whether or not they produce visible growth on subculture in 7 days. Recently, however, this criterion was shown to be remarkably valid taxonomically: all slow-growing species have only one operon whereas all fast-growing species have two. A phylogenetic analysis based on the 16S rRNA sequences placed the fast- and slow-growing species into two clear and separate branches of the evolutionary tree[14] **(Table 1)**.

DESCRIPTION OF THE GENUS

The mycobacteria are nonmotile, nonspore forming, slightly curved or straight bacilli, 0.2–0.6 by 1–10-µm in size, sometimes branching. Filamentous or mycelium-like growth may occur, but it is easily fragmented into rods or coccoid elements **(Fig. 1A)**.

Mycobacteria have a unique cell wall responsible for its virulence, diagnostic staining, and treatment. The cell wall has high (>60%) lipid content that includes a waxy coat

TABLE 1: Classification on the basis of growth rate (also *see* **Figs. 1A to E**).

Slow-growing mycobacteria	*Rapid-growing mycobacteria*	*Species that do not have special nutritional requirements*	*Species with special growth requirements*
M. tuberculosis complex	*M. fortuitum* complex	*M. marinum*	*M. paratuberculosis*
	M. fortuitum	*M. ulcerans*	*M. haemophilum*
M. tuberculosis	*M. chelonei* subspecies *chelonei*	*M. malmoense*	*M. lepraemurium*
M. bovis	*M. chelonei* subspecies *abscessus*		*M. leprae*
M. africanum			
M. microti *M. avium* complex	Nonphotochromogenic		
M. avium	*M. agri*		
M. intracellulare	*M. chitae*		
M. xenopi *M. scrofulaceum* complex	*M. smegmatis* *M. parafortuitum* complex		
M. scrofulaceum	*M. parafortuitum*		
M. simiae	*M. aurum*		
	M. diernhoferi		
	M. vaccae		
M. gordonae complex	*M. neoaurum* Thermotolerant strains		
M. gordonae	*M. flavescens*		
M. szulgai	*M. phlei*		
M. asiaticum *M. kansasii* complex	*M. thermoresistible* Bovine farcy		
M. kansasii	*M. farcinogens*		
M. gastri *M. terrae* complex	*M. senegalense*		
M. terrae			
M. nonchronogenium			
M. triviale			

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consisting of four major components: mycolic acids, cord factor, wax D, and sulfatides. The mycolic acids of mycobacteria are unique alpha-branched chains of hydroxyl-fatty acids. These are strong hydrophobic and significant determinants of virulence, as they prevent attack on mycobacteria by cationic proteins, lysozymes, and oxygen radicals in the phagocytic cells.

They also protect the extracellular organisms from complement attack. The waxes make up 50% of the dry weight of the cell envelope. The cord factor is another constituent responsible for serpentine growth of the organism. It is toxic to mammalian cells and is also an inhibitor of polymorphonuclear cell migration. The cord factor is most abundant in the virulent strain of *MTB*. The robust cell wall also provides resistance to killing by acidic and alkaline compounds, osmotic lysis via complement, and resistance to common antibiotics.

Staining Reaction

The high lipid content of the cell wall provides unusual impermeability to aniline dyes and stains. Mycobacteria, therefore, are not readily stained by the Gram stain. Special staining procedures are applied to promote the uptake of a strong dye but once the mycobacteria have taken the stain, they are not easily decolorized even with acid-alcohol. This resistance to decolorization is called acid fastness. The property of acid fastness is not absolute and may be partly or completely lost at some stage of growth by some proportion of the cells of some species of mycobacteria. Cells of the fast-growing mycobacteria may be <10% acid fast.

Koch (1882) stained the tubercle bacilli with hot alkaline methylene blue as the primary stain and vesuvin as the decolorizer and counter stain.[4] Ehrlich (1882) discovered 3% acid-fast property of the bacteria and stained the bacilli with hot fuchsin in the presence of aniline oil as a mordant and destaining with a dilute mineral oil. Ziehl (1883) changed the mordant to phenol and Neelsen (1884) combined the dye and mordant to form carbol fuchsin. Thus, the acid-fast staining technique, although pioneered by Ehrlich, is now known as the Ziehl–Neelsen (ZN) method and has remained essentially unchanged since 1884 **(Figs. 1B to D)**.

Decolorization with alcohol and cold staining techniques as well as the use of fluorescent dyes (e.g., Auramin-O) to visualize the mycobacteria have also been developed **(Fig. 1E)**. It is not possible to differentiate *MTB* from other acid-fast atypical mycobacteria. The property of acid fastness, however, is not unique to mycobacteria. It is shared with *Nocardia*, volutin granules of *Corynebacteria*, *Legionella micdadei*, bacterial and fungal spores, and cysts of the protozoan *Cryptosporidium* species, if only 1% acid is used to decolorize.

Mycobacterial Species

The primary mycobacteriosis throughout the world is TB. Its prevalence and severity prompted the studies of Robert Koch and others on its etiology that culminated in the discovery of the tubercle bacilli in 1882. Before the end of the century, the bovine, avian, reptilian, piscine, and saprophytic varieties of mycobacteria had also been described. Despite sporadic reports of isolation of many varieties of nontuberculous mycobacteria (NTM) from clinical specimens, only *MTB* and *M. bovis* were taken seriously as a cause of human disease,[15] while these isolates were given dismissive epithets such as "atypical," "pseudotubercular," and "tuberculoid" bacilli. Also, as their classification was in chaos, they were dubbed "anonymous" mycobacteria. Interest in their role as pathogens of man commenced in earnest in the 1950s with the description of two distinct diseases, namely swimming pool granuloma and Buruli ulcer caused by *M. marinum* and *M. ulcerans*, respectively. Their etiological role has also been demonstrated in causation of the TB-like pulmonary disease.[16]

The "atypical" mycobacteria isolated from clinical material have been called by many names—paratubercle, pseudotubercle, anonymous, atypical, nontuberculous (NTM), environmental, opportunistic, tuberculoid, and mycobacteria other than tubercle (MOTT) bacilli. The diseases associated with them have been termed—pseudotuberculosis, mycobacteriosis, nontuberculous, mycobacterial infection, and TB due to one of the specific mycobacteria by species name.

None of the proposed names is without criticism but the most appropriate and least offensive, is NTM.[15] Certainly, atypical, anonymous, and unclassified are no longer acceptable as each of the species is typical, for the genus *Mycobacteria*, when analyzed microbiologically and since species-specific names have been designated, opportunistic is also not entirely appropriate[16,17] but usually referred to describe such infections in immunocompromised persons.[18] It is also not right to call the disease "tuberculosis" because of the pronounced differences between the two infections in pathogenesis, epidemiology, prognosis, and response to treatment. The drug susceptibility of NTM, as measured by tetrazolium microplate assay, showed that the pattern of drug susceptibility is grossly different in NTM from *MTB* **(Fig. 2)**. Runyon[19] provided early leadership in the classification of these mycobacteria and on the basis of type of colony, rate of growth, pigment production, and simple biochemical reactions, he divided them into four groups. Subsequent workers have suggested different biochemical tests and high-performance liquid chromatography (HPLC) analysis of species-specific mycolic acids in order to improve the identification of isolates, but the basic format has remained unchanged. From the clinical point

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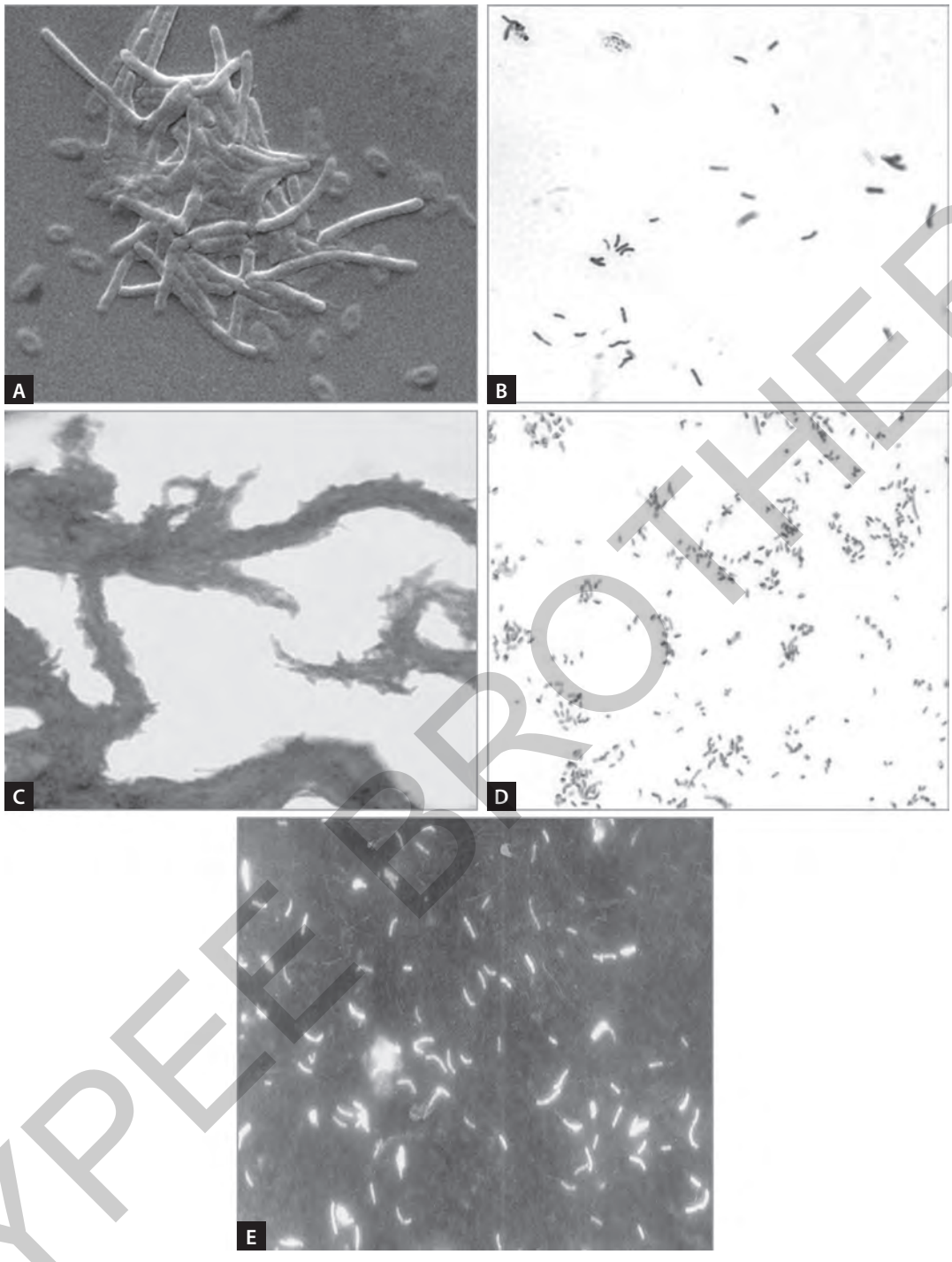

Figs. 1A to E: (A) Scanning electron microscopical observation of *M. tuberculosis*; (B) Ziehl–Neelsen (ZN)-stained *M. tuberculosis* cells; (C) Typical serpentine growth (cord factor) of *M. tuberculosis* culture grown in egg-based media (Lowenstein–Jensen medium); (D) ZN-stained cells harvested from liquid culture (Middlebrook 7H9 broth); (E) Auramine–rhodamine (AR)-stained *M. tuberculosis* cells. The fluorescent staining method has higher sensitivity over the ZN method. *[For color version (Figs. B to E), see Plate 1].*

of view, however, these mycobacteria are divisible into three groups:

1. Obligate human pathogens
2. Species that have been definitely shown to cause human disease under certain circumstances
3. Those that rarely, if ever, do so

Opportunistic infections due to MOTT or NTM have been on the increase, mainly as a consequence of the AIDS epidemic.[20-22] Among the mycobacterial species often implicated in NTM infections are *M. avium, M. intracellulare complex, M. fortuitum, M. chelonae, M. abscesses, M. kansasii, M. celatum,* and *M. xenopi.*[17,20,22,23]

Habitat

Mycobacteria are not members of the normal bacterial flora of man, but *M. smegmatis* and *M. gastri* can sometimes

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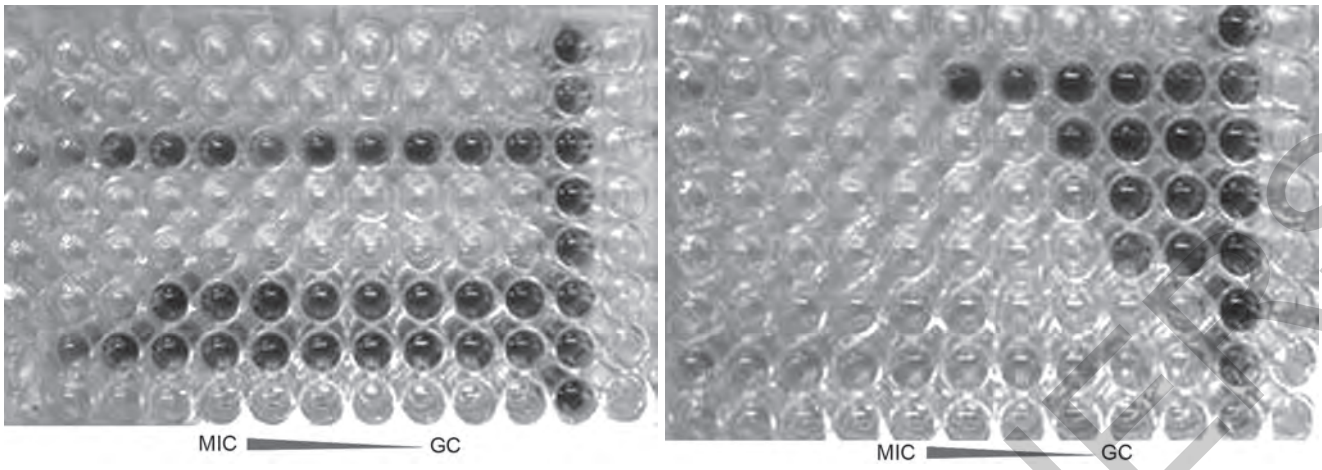

Fig. 2: Antimycobacterial drug susceptibility by tetrazolium microplate assay. This method is rapid and quantitative but feasible only in the center with biocontainment facility. *(For color version, see Plate 1).*

be isolated from the smegma and gastric contents, respectively.[24]

Mycobacterium tuberculosis is clearly not typical of the mycobacteria since the majority of these species are essentially environmental saprophytes and do not cause disease or rarely do so. Thus, *MTB* has been described as being the *Wayward Son of Honorable Parents.* The implication is that *MTB* probably evolved from an environmental organism to become the most successful bacterial pathogen of all time utilizing successful strategies to invade and persist within macrophages with phases of dormancy.

Mycobacteria are most widely known as the cause of dreadful diseases. Less well known is their role as thriving members of environmental ecosystems. In fact, a large variety of complex organic, synthetic, and degradative processes have been described recently for free-living soil mycobacteria. Mycobacteria synthesize a variety of steroid hormones from cholesterol.[25] Various simple and complex hydrocarbons and other organics can be degraded and these activities could be useful in pollution control.[26]

Cultural Characteristics

The mycobacteria are aerobic nonencapsulated, nonspore-forming, and nonmotile bacilli. The *MTB* is one of the slowest growing (generation time in animal tissues ~24 hours) mycobacteria. Colony morphology varies among the species, *MTB* forms rough colonies with bacilli compacted into curving strands (serpentine cords). In contrast, *M. avium* complex usually forms smooth transparent colonies with the bacilli arranged in no definite pattern. Robert Koch isolated the organism on heat-coagulated sheep serum culture medium devised by John Tyndall. Nocard later introduced glycerol–beef broth, which Koch used for his studies on tuberculin.

Mycobacteria are strictly aerobic and grow more slowly than most bacterial pathogens. The generation time of the mycobacteria is >12 hours. *MTB* has the longest replication time of 20–22 hours. The growth of *MTB* is enhanced by an atmosphere of CO_2 between 5 and 10% for the first few weeks of incubation. Mycobacterium requires a pH between 6.5 and 6.8 for the growth medium and grows better at higher humidity.

Isolation of mycobacterium poses a special problem for the laboratory. Mycobacteria require a prolonged time for replication (approximately 15–22 hours), whereas the generation time of other bacteria present in the specimen may be as short as 20–30 minutes. This disproportionate rate of growth between mycobacteria and other bacteria may result in rapid accumulation of metabolic acids that liquefy the culture medium, making it unsatisfactory for the recovery of mycobacteria. Therefore, the successful isolation of mycobacteria depends upon the selective suppression of contaminating bacteria.

Egg-based solid media such as Lowenstein–Jensen or American Trudeau Society medium are very rich and contain phospholipids and proteins that tend to bind and/or neutralize toxic products in clinical specimens. They have been used for primary isolation of *MTB* from the clinical samples and they also tend to yield a higher percentage of positive results in comparison to agar-based isolation media. Because of its luxuriant growth on egg media, *MTB* has been termed "eugonic."

Agar-based media are prepared from semisynthetic basal medium and are enriched with defined supplement. Since the medium is transparent, it permits early microscopic detection of the colonies. Growth of *MTB* on agar-based medium such as Middlebrook 7H10 is enhanced by the presence of 5–10% of CO_2 in the incubation atmosphere **(Fig. 3A)**. The medium should be made selective by incorporation of various antibiotics. For the best results, both agar- and egg-based media should be used for primary isolation of mycobacteria. Most strains of mycobacteria causing human disease can be isolated using media of two different basal compositions. Diffusible pigment is seldom

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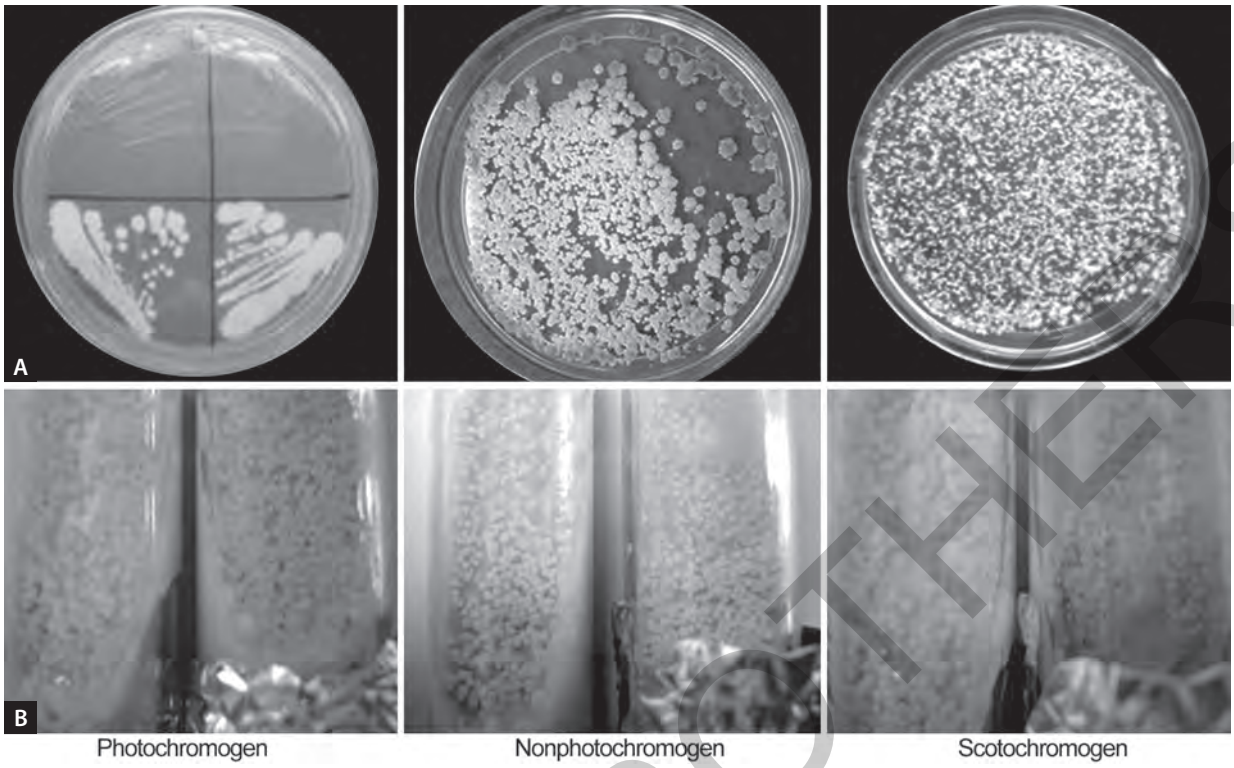

Figs. 3A and B: (A) *Mycobacterium smegmatis* cultured in Middlebrook 7H10 agar and incubated at 37°C for 5 days; (B) Mycobacterial colony and phenotypic appearance on Lowenstein–Jensen medium incubated at 30–37°C in the presence or absence of light. *(For color version, see Plate 2).*

present, but colonies of some species are regularly, variably yellow or orange. Some species require light to form pigments (photochromogens) and other form pigment in either the light or dark (scotochromogens) **(Fig. 3B)**.

It is true that *MTB* is best isolated from clinical specimens on rich and fairly complex media such as Middlebrook 7H9, BACTEC-MGIT960, and MB-Bact-240 **(Figs. 4A to C)**, but the apparent fastidiousness of some such isolates may be consequence of their injury by conditions in host tissue or by the treatment employed for processing the clinical specimen. Once isolated, *MTB* is capable of adapting to grow on extremely simple medium, i.e., one containing a simple source of carbon and nitrogen plus some buffer salts and trace elements. A visible mass multiplication can be seen in Middlebrook 7H9 broth **(Fig. 4C)**.

Mycobacterial Envelope

The cell envelope essentially distinguishes species of *Mycobacterium* genus from other prokaryotes. Mycobacteria, in general, give a weakly positive response to the Gram stain but are phylogenetically more closely related to gram-positive bacteria. Based on the recent developments in the knowledge of the ultrastructure and chemistry of mycobacteria, the mycobacterial cell envelope possesses three structural components: (1) capsule, (2) cell wall, and (3) plasma membrane.[27] This skeleton provides osmotic protection from the outside environment and also helps in transportation of ions and molecules beside the mechanical support and shape to the bacteria.

Mycobacterial Capsule

The outermost compartment of the cell envelope consists of a mixture of polysaccharides, proteins, and lipids and is called capsule. The earliest mention of mycobacterial capsules was by Chapman in 1959, who called the space between the phagosomal membrane of the infected cell and the wall of the enclosed *Mycobacterium* a capsular space or halo. Chemically, a clear distinction between the wall-associated compounds and capsular constituents has not been possible so far and many substances are found in more than one envelope compartment. However, electron microscopic studies have proved existence of capsule in mycobacteria. It is also established now that most part of the capsule is lost from the mycobacteria during the conventional processing of the samples for microscopy. Most of the species of mycobacteria are known to possess the capsule, but the thickness varies from species to species. The ratio of protein to polysaccharides varies, according to the species. For example, the major constituents in *MTB*, *M. kansasii*, and *M. gastri* are polysaccharides while *M. phlei* and *M. smegmatis* consist mainly of proteins.[23]

The major polysaccharides of mycobacterial capsule consist of mainly the glucan (an arabino-mannan) and a mannan. Small amounts of other oligo- and polysaccharides

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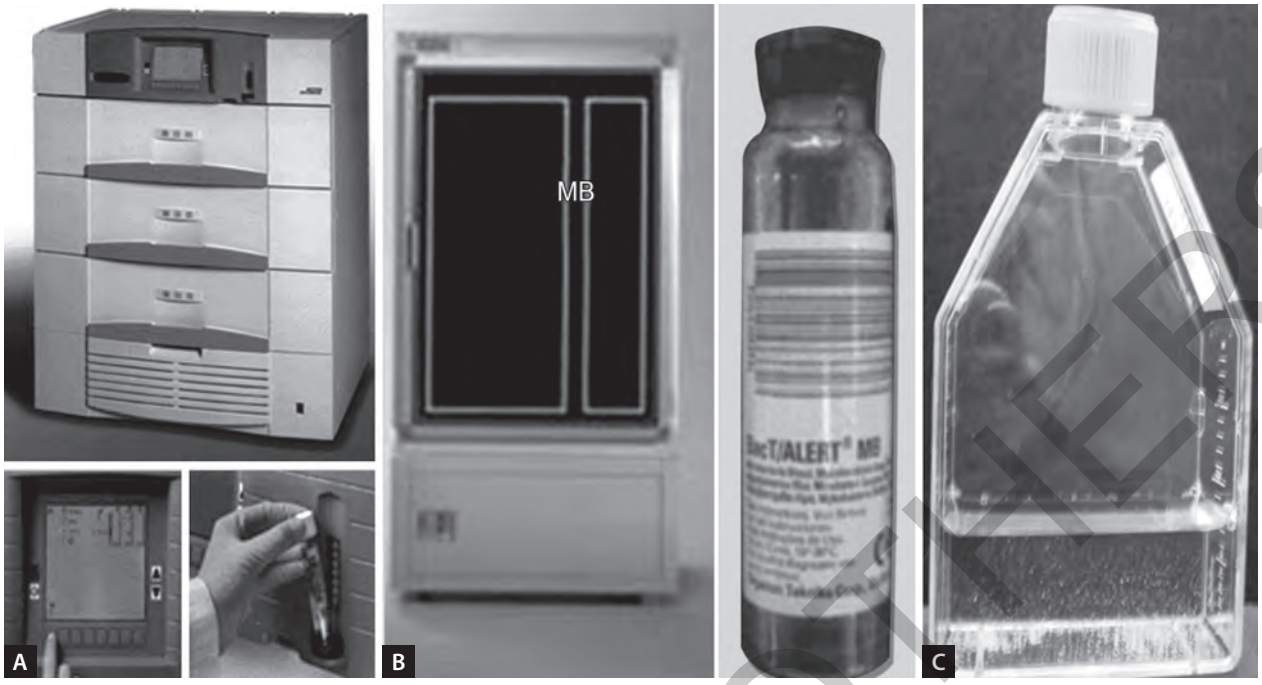

Figs. 4A to C: Middlebrook 7H9 broth containing OADC (oleic acid, dextrose, catalase) with antibiotic mixture (PANTA—polymyxin, amphotericin, nalidixic acid, trimethoprim, and azlocillin) to prevent other contaminants is being used in automated culture system with higher sensitivity. The growth rate of *Mycobacterium tuberculosis* is faster (12–17 days) than the solid (22–30 days), egg-based Lowenstein–Jensen (27–45 days) culture methods. (A) BACTEC MGIT-960 (Mycobacterial Growth Indicator Tube, Becton Dickinson, USA) growth detection based on fluorescence; (B) MB-BacT-240 (Biomerieux, France) growth detection based on colorimetry; (C) Laboratory mass multiplication of *Mycobacterium tuberculosis* in Middlebrook 7H9 broth. *(For color version, see Plate 2)*.

are also found, which are still not characterized. The capsular proteins are complex mixture of polypeptides. These include superoxide dismutase, alanine dehydrogenase, glutamine synthetase, alcohol dehydrogenase, and thioredoxine. Even though traditionally the mycobacteria have been considered to be surrounded by "thick waxy coat," the recent findings are that the capsule indeed consists of mainly carbohydrates and proteins and the lipid constituents are only 2–5%. The mycobacterial lipopolysaccharide (LPS), lipoarabinomannan (LAM), a major bioactive constituent of mycobacterial cell wall, is not detectable from the capsule. Various phospholipids and some species-specific lipids (e.g., dimycocerosate of phthiocerol) and type-specific lipids of *MTB*, such as phenolic glycolipid (PGL) and lipooligosaccharides, are present on its surface; others such as trehalose dimycolates occur in the inner compartments of the capsule.[27]

The role of mycobacterial capsule in pathogenesis is important at least for the first steps of internalization of bacteria, though not absolute. The capsule plays an important role in adhesion and penetration into the host cell through various cell receptors, binding proteins, and adhesion molecules.

Cell Wall Core

The cell wall core is defined as the insoluble matrix of the mycobacterial cell wall after the removal of all soluble proteins, lipids, and carbohydrates. It is composed of three covalently attached macromolecules. The outermost, the mycolic acids, are 70- to 90-carbon-containing, branched fatty acids which form an outer lipid layer in some ways similar to the classical outer membrane of gram-negative bacteria. The mycolic acids are esterified to the middle component, arabinogalactan (AG), a polymer composed primarily of D-galactofuranosyl and D-arabinofuranosyl residues. AG is connected via a linker disaccharide, α-L-rhamnosyl-(1→3)-α-D-*N*-acetyl-glucosaminosyl-1-phosphate, to the six position of a muramic acid residue in the peptidoglycan. The peptidoglycan is the innermost of the three cell wall core macromolecules:[27]

1. *Peptidoglycan:* It is the innermost layer adjacent to the plasma membrane and is analogous to other bacteria such as *Escherichia coli*. It is composed of glycan to which the tetrapeptide is attached which in turn is cross-linked.
2. *Linker disaccharide:* Carbon 6 of about 10% of muramic acid residues provide the point of attachment of peptidoglycan to polysaccharide, AG, via a linker disaccharide phosphate. This structure is unique to mycobacteria and *Nocardia*.
3. *Arabinogalactan:* It is attached to a simple linker disaccharide unit and is a complex polysaccharide. Mycolic acids are attached to the five positions of the terminal AG.

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Plasma Membrane

In ultrathin sections, the plasma membrane occurs as classical bilayers with two electron-dense layers separated by a transparent layer.[27] This appearance, coupled with their known chemical composition,[27] indicates that these are normal biological membranes. Mycobacterial membranes do, however, have some distinctive components, notably the LPS LAM, lipomannan, and phosphatidylinositol.[28] The appearance of mycobacterial plasma membrane is not symmetrical and the outer, electron-dense layer is thicker than the inner layer. This asymmetry is lost when cells are killed before fixation. There is electron cytochemical evidence that the extra thickness is associated with carbohydrate and possible candidate molecules are phosphatidylinositol mannosides of LAM. There appears to be space between outer of the plasma membrane and the inner layer of cell wall. If we hypothesize that the walls of *MTB* form permeability barriers somewhat analogous to the outer membranes of gram-negative bacteria, then the space between the outer leaflet of the membrane and the wall forms a compartment analogous to the periplasmic space of the gram-negative bacteria.

Associated Molecules of the Cell Wall

Lipoarabinomannan

Lipoarabinomannan is a phosphatidylinositol-anchored lipoglycan composed of a manna core with oligoarabinosyl-containing side chains. It is found in all mycobacteria including *MTB*. While LAM lacks covalent association with the cell wall core, it is nonetheless a crucial part of cell envelope also. LAM is a molecule of profound interest and importance with diverse biological activities. It has properties analogous to gram-negative O-antigenic LPS such as nonspecific suppression of T-lymphocyte activation and inhibition of antigenic responsiveness of human peripheral blood leukocytes and inhibits antigenic-presenting cells. LAM also inhibits interferon-γ-mediated activation of macrophages. Thus, it may be implicated in the interaction of the pathogen and the host cell in the downregulation of T-cell responses of various types. It may be a harbinger of bad immunity (i.e., immunopathogenesis). In addition, it is a major B-cell immunogen.[29] Three general classes of LAM have been described: (1) ManLAM, from the virulent strains Erdman and $H_{37}Rv$; (2) Phosphor-myo-inositol-capped LAM (PILAM) found in rapidly growing mycobacteria, *M. smegmatis*, and *M. fortuitum*; and (3) AraLAM which was described in *M. chelonae*. Although there is significant heterogeneity between LAM molecules with respect to glycosylation and acylation, differences in biological activity between the major classes of LAM have been attributed to heavy mannose capping.

Trehalose-based Glycolipids

Trehalose is a simple disaccharide of glucose similar in some ways to common table sugar, which is found free and bearing various fatty acyl groups in *MTB* and other mycobacteria. These acylated trehaloses are associated via hydrophobic interactions with the mycolic acids of cell wall core and thus are on the outside edge of cell envelope. The most studied among these is trehalose dimycolate, commonly known as the cord factor. Various biological activities have been described, most of them seemingly related to their ability to induce cytokine-mediated events, such as systemic toxicity, antitumor activity, and macrophage release of chemotactic factors.

Another important class of lipids based on trehalose is the sulfatides. In these molecules, trehalose is sulfated at two position and acylated with array of specialized fatty acids. Its association with virulence has been demonstrated in guinea pigs. The biological activities of the sulfatides have been proposed as an antagonist of the fusion of the secondary lysosomes with phagosomes or phagosome activation, thus promoting intracellular survival of pathogen.[30]

Cell Envelope Proteins

Some of the proteins of mycobacteria are preferentially associated with the cell wall and are powerful immunogens. A 23-kilodalton (kDA) protein appears to be tightly, although noncovalently, associated with peptidoglycan. A 59-kDa protein has been identified as the porin and the 65-kDa protein is the heat shock protein which acts as the molecular chaperon. Bioinformatic analysis of the *MTB* genome predicts >65 lipoproteins of "cell envelope" origin, some of which were identified previously as "secreted" proteins, or enzymes involved in cell wall biogenesis. Besides these, there are 17 conserved MmpL and MmpS proteins and >600 other "putative" membrane proteins.

Metabolic Biosynthesis

Most mycobacteria are prototropic, i.e., they are going to grow in a media containing only inorganic salts plus a source of carbon. Occasional fastidious strains, however, are encountered, which could represent naturally occurring auxotrophic mutants. Optimal growth in synthetic medium is generally obtained with asparagine and glutamine for nitrogen and glycerol for carbon. Latency seen in pathogenic mycobacteria is explained by the metabolic shutdown in the mycobacteria which is triggered and regulated by the host immune system. Though no clear genetic basis of dormancy and reactivation has been described, it is expected to be genetically programmed and controlled by the intracellular signaling pathway.

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Essentials of Tuberculosis in Children

Salient Features

- The fifth edition of this book on tuberculosis in children is being presented after an interval of more than 10 years. Significant changes have occurred in the understanding of the pathogenesis, diagnosis, and treatment of tuberculosis in children during this period
- Fully revised by the experts in the field, incorporating recent advances in tuberculosis in children
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