INSIGHT TO TUBERCULOSIS
GLOBAL BURDEN OF TUBERCULOSIS

Tuberculosis has plagued mankind since prehistoric times and is still an important cause of morbidity and mortality, with particularly devastating effects in countries with high population density. Tuberculosis results from an infection caused with *Mycobacterium tuberculosis* and the WHO estimates that perhaps as much as one third of the world population or approximately 1.9 billion people are infected with *Mycobacterium tuberculosis*. Each year, there are 8-10 million new cases of tuberculosis and about 2-3 million deaths due to it. Indeed tuberculosis is the leading cause of death in adults due to a single infectious agent and accounts for approximately 26% of all preventable adult deaths in the world. (1)

Tuberculosis has also reemerged as an important health problem in many developed countries. For example the number of tuberculosis cases reported in USA between 1985 and 1992, increased by 20%. In many of the countries re-emergence of tuberculosis has been accompanied by outbreaks of tuberculosis caused by *Mycobacterium tuberculosis* strains that are resistant to many of the commonly used anti-tuberculosis drugs, like Rifampacin, Ethambutanol.

For the immediate health perspective, keys to controlling the spread of tuberculosis includes the rapid diagnosis of tuberculosis and prompt initiation of effective chemotherapy and proper infection control procedure. With about one third of the world's population infected with *M. tuberculosis* a need of a fast and accurate method of diagnosis of patients suffering from tuberculosis to treat them for cure is necessary.

However, having one third of the people infected with *M. tuberculosis* does not mean that all of them will develop tuberculosis. It is observed that only about 10 % of the infected persons get the disease during their lifetimes, and some of these cases develop as many as 40-50 years after initial infection event. This is because the clinical manifestations of the disease are actually the result of a long series of interaction between the mycobacterium and the host immune system. Two key aspect of this is

> Tubercle bacilli survives and replicates within the host’s phagocytic cells, primarily within macrophages without being affected by the immune system of the host and
Much of the disease process, as well as immunity to the disease, are dependent on the host’s immune response to mycobacterium. It is therefore important to understand the interactions of mycobacterium and the host cells leading to protection as well as the diseased state.

Classification and Characteristics of Mycobacteria

The Mycobacteria belong to the family Mycobacteriaceae comprising the genus Mycobacterium. Mycobacteria are aerobic, nonmotile, slow-growing, rod-shaped bacteria that are characteristically acid and alcohol fast implying that after staining with a dye such as basic fuchsin they resist decolourisation with acidified alcohol and with strong mineral acids. (2)

The genus Mycobacterium was introduced by Lehmann and Neumann in 1896 to accommodate the causal agents of Leprosy and Tuberculosis (3), bacteria that had previously been classified as Bacterium leprae and Bacterium tuberculosis respectively. Over the years the genus has grown in size and stature and now contains about 71 species. (4)

Mycobacteria form slightly curved or straight rods (0.2-0.6x 1.0-10 μm) with occasional branches. Extensively branched filaments may occur but they readily fragment into rods and coccoid elements. Aerial hyphae are normally absent. The organisms are nonmotile and do not form endospores, spores or capsules. They are usually considered Gram positive but are not readily stained by Gram's method. (4)

The primary cell wall structure consists of plasma membrane, which is supported by a peptidoglycan backbone, which protects the cell against the osmotic pressure of the interior. Attached to the peptidoglycan backbone is the arabinogalactan layer and esterified mycolytic acids. Associated with the cell wall are a number of free lipids, glycolipids and proteins (5). Mycobacteria show the presence of meso-diaminopimelic acid, arabinose and galactose in their cell walls along with peptidoglycan. They produce straight chain saturated and unsaturated fatty acids and nontuberculostearic acid, phosphatidyl inositol, mannosides and dehydrogenated menaquinones with nine isoprene units. Mycobacteria have a guanine + cytosine (G+C) DNA base ratios in the range of 62-70 mol%. Their cell walls contain mycolic acids which are relatively complex having a high molecular weight (C60-C90 fatty acids), lack
components having more than two points of unsaturation in the molecule and on pyrolysis release C22 to C26 straight chain saturated fatty acids.

Most species of Mycobacteria form more than one kind of colony, but colonies of some species, such as *M. tuberculosis*, are mostly rough while that of some, such as *M. intercellulare* are commonly smooth. Mycobacteria, generally, grow slowly with generation times ranging from 2 hrs to more than 20 hrs. Most species adapt readily to growth on very simple substrates using ammonia or amino acids as nitrogen source and glycerol as carbon source in the presence of mineral salts. (4,5)

Most mycobacterial species are free-living in soil and water but the major ecological niche for some is the diseased tissue of the warm-blooded host. Mycobacteria can be grouped on the basis of their growth rates as so-called rapid-growers and slow growers. Rapid-growers include strains of those species which, under optimal nutrient and temperature regimes, produce, grossly visible colonies on solid media within seven days, whereas their slow growing counterparts require a week or more to form such colonies under comparable conditions.

Mycobacteria cause a variety of diseases in humans as well as in animals. In humans the two major diseases caused are - Tuberculosis (TB) and Leprosy, which affect millions of people world-wide. The causative agents of these two diseases are *M. tuberculosis* and *M. leprae* respectively. Both of these diseases are curable using proper treatment and care.
OVERVIEW OF CLINICAL MANIFESTATION OF TUBERCULOSIS

The clinical manifestation of infection with Mycobacterium tuberculosis is quite varied and depends on a number of identified factors (as listed below)

Table 1: Factors contributing to the varied clinical manifestation of tuberculosis

<table>
<thead>
<tr>
<th>Host factors</th>
<th>Microbial factors</th>
<th>Host-microbe interaction</th>
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<tr>
<td>Age</td>
<td>Virulence of organism</td>
<td>Sites of involvement</td>
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<td>Like lungs, stomach,</td>
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<td>reproductive organs</td>
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<td>Immune status</td>
<td>Predilection (tropism) specific</td>
<td>Severity of disease</td>
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<td>Specific immunodeficiency</td>
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<td>Genetic factors</td>
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<td>Coexisting Diseases</td>
<td>Bacterial load</td>
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<td>Immunization with BCG</td>
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Among generally healthy persons, infection with M. tuberculosis is highly likely to be asymptomatic. Data is suggestive of the fact that the lifetime risk of developing clinically evident pulmonary tuberculosis after being infected is approximately 10%, with a 90% likelihood of the infection remaining latent. (1). Only tuberculin skin test positivity indicates the presence of the organism in persons with latent infections or exposure to the same. In a specific subpopulation, for example in persons with immunodeficiency states or infants, the proportions who develop evident tuberculosis disease are much higher (6)

The most obvious and important factor influencing the clinical features of tuberculosis is the site involvement. Prior to the beginning of infection with HIV, approximately 85% of the reported cases of tuberculosis were limited to the lungs, with the remaining 15% involving only nonpulmonary sites or both pulmonary and non pulmonary sites. (7) (Figure 1). This proportional distribution is substantially different among persons with HIV infection. In a large retrospective study of tuberculosis
in patients with advance HIV infection, it was reported that 38% had only pulmonary involvement, 30% had extrapulmonary sites, and 32% had both pulmonary and nonpulmonary involvement (8).

The multiplicity of sites in HIV- infected persons is due to the fact that the immune system of such individuals are impaired in its ability to contain infection with M. tuberculosis. Included in this category are infants, the elderly, and persons with primary or secondary immunodeficiency states resulting from coexisting diseases or malnutrition.

**Pulmonary Tuberculosis**

Cough is the most common symptom of pulmonary tuberculosis. Early in the course of illness, cough may be non-productive, but subsequently, as inflammation and tissue necrosis ensue, sputum is usually produced. Inflammation of the lung parenchyma adjacent to a pleural surface may cause pleuritic pain. It may also occur spontaneously, often causing chest pain and Dyspnea. Dyspnea (difficulty in breathing) as a result of parenchymal lung involvement is unusual unless there is extensive disease. Tuberculosis may, however, cause severe respiratory failure. (9)
Hemoptysis (blood in cough) may also be presenting symptoms but does not necessarily indicate an active tuberculous process.

**Extrapulmonary tuberculosis**
Extra pulmonary tuberculosis accounts for approximately 15% of newly reported cases of tuberculosis. (1) Extrapulmonary tuberculosis is more of a diagnostic and therapeutic problem in comparison to pulmonary tuberculosis. In addition, it involves relatively inaccessible sites, and because of the nature of the sites involved, fewer bacilli can cause much greater tissue damage. The relative frequencies of tuberculosis at various sites without immunocompromise are shown in figure 1.

**Types of Extrapulmonary tuberculosis.**

**Disseminated tuberculosis**
Disseminated or miliary tuberculosis occurs because of inadequacy of host defenses in containing tuberculous infection. This failure of containment may occur in either latent or recently acquired tuberculous infection. The term miliary is derived from the visual similarity of the lesion to millet seeds. Grossly, these lesions are 1-2mm in diameter yellowish nodules that, histologically, are granulomas. Although disseminated tuberculosis nearly involves the lungs, it is considered among the extrapulmonary form of the disease because of the multiplicity of organs affected. (10)

**Lymph node tuberculosis**
Tuberculous lymphadenitis usually presents as painless swelling of one or more lymph nodes. The nodes most commonly involved are those of the posterior or anterior cervical chair or those in the supraclavicular fossa. Frequently, the process is bilateral, and other non contiguous groups of nodes can be involved (11). At least the nodes are discrete and the overlaying skin is normal. With continuing disease, the nodes may become matted and the overlying skin inflamed. Rupture of the node can result in formation of sinus tract, which may be difficult to heal. Intrathoracic adenopathy may compress bronchi, causing lung infection and perhaps bronchiectasis.

**Pleural tuberculosis**
The epidemiology of pleural tuberculosis parallels that of the overall pattern for tuberculosis, with the disease being more common among
males and increasing in incidence with increasing age between 5yrs and 45yrs. (12). There are two mechanisms by which the pleural space becomes involved in tuberculosis, and the difference in pathogenesis results in different clinical manifestation, approaches to diagnosis, treatment and sequel. Early in the course of tuberculosis infection, a few organisms may gain access to the pleural space, and in presence of cell-mediated immunity, they can cause a hypersensitivity response. (13). Commonly this form of tuberculosis goes unnoticed and the process resolves spontaneously. In some patients however, tuberculous involvement of the pleura is manifested as an acute illness with fever and pleuritic pain. If the effusion is large enough, Dyspnea may occur, although the effusions generally are small and rarely bilateral. The diagnosis of pleural tuberculosis is generally established by analysis of pleural fluid and/or pleural biopsy.

The second variety of tuberculous involvement of the pleura is a true empyema (pus in the pleura). This condition is much less common than tuberculous pleurisy with effusion and results from a large number of organism spilling into the pleural space, usually by the rupture of a cavity or an adjacent parenchymal focus via a bronchopleural fistula. (14). A tuberculous empyema is usually associated with evident pulmonary parenchymal disease on chest films and air may be seen in pleural space.

Genitourinary tuberculosis
As with pleural tuberculosis the epideomolgic patterns parallels that of tuberculosis in general except that the incidence is generally nearly equal in men and women. The pathogenesis appears to be one seeding in the kidney at the time of the initial infection and bacillemia. In patients with genitourinary tuberculosis, local symptoms are predominant, and systemic symptoms are less common. (15) Dysuria, hematuria, and frequent urination are common, and flank pain may also be noted. Genital involvement without renal tuberculosis is more common in women than in men. Diagnosis of isolated genital lesions usually requires biopsy. Because the differential diagnosis often includes neoplasia as well as other infectious processes.

Skeletal Tuberculosis
Osteoarticular tuberculosis results from endogenous reactivation of foci of infection seeded from paravertbral lymph nodes, which has been postulated to account for the common localization of spinal tuberculosis
to the lower thoracic and upper lumbar vertebrae. (16). After beginning in
the subchondral region on the bone, the infection spreads to involve the
cartilage, synovium, and joint space. This produces the typical findings of
metaphyseal erosion and cysts and the loss of cartilage, with narrowing of
the joint space.
Confirmation of diagnosis is obtained by aspiration of joint fluid or
periarticular abscesses or by biopsy and microbiologic evaluation.

Central nervous system Tuberculosis
Meningitis is the most frequent form of central nervous system
tuberculosis, solitary or multiple tuberculomas occur less commonly. The
epidemologic pattern of tuberculosis of the central nervous system is quite
different from either pulmonary or other forms of extrapulmonary
tuberculosis in that the peak incidence is in children of the age group 0-4
year. (17) Central nervous system involvement, especially tuberculomas,
seems to occur with greater frequency among HIV infected persons.
Meningitis presumably can result from direct meningeal seeding and
proliferation during a tuberculous bacillemia either at the time of initial
infection or at the time of breakdown of an old parameningeal focus with
rupture into the subarachnoid space. The consequences of the
subarachnoid space contamination include diffuse meningitis, a localized
arthritis, encephalitis, or myelitis. The other major central nervous system
form of tuberculosis, the tuberculoma, presents a more subtle clinical
picture than tuberculous meningitis. (18) The usual presentation is that of
a slowly growing focal lesion, although a few patients have increased
intracranial pressure and no focal findings.

Abdominal tuberculosis
Tuberculosis can involve any intra-abdominal organ as well as the
peritoneum. The age distribution of abdominal tuberculosis shows a
relatively higher incidence in young adults and a second peak in older
persons. Males and females have similar incidence. Abdominal
tuberculosis presumably results from seeding at the time of initial
infection and then late progression to clinical disease. Peritonitis can also
be caused by rupture of tuberculous lymph nodes within the abdomen.
Intestinal tuberculosis may also result from ingested tubercle bacilli with
direct implantation in the gut. The clinical manifestations of abdominal
tuberculosis depend on the areas of involvement. In the gut itself,
tuberculosis may occur in any location from the mouth to anus, although
lesions proximal to terminal ileum are unusual. The most common sites of involvement are terminal ileum and the cecum, with other portions of the colon and rectum involved less frequently. (19)

**Pericardial tuberculosis**
The descriptive epidemiology of pericardial tuberculosis is well defined, but in general the disease tends to occur among older persons, with approximately 50% of patients being older than 55 years. (10) The pericardium may become involved during the initial bacillemia, with early progression to clinically evident disease or recrudescence following a quiescent period. Hematogenous seeding may also occur during the course of endogenous reactivation. Alternatively, there may be direct extension of an adjacent focus of disease into pericardium. This focus may be in lung parenchyma, pleura, or tracheobrochial lymph nodes. The most common form or stage of tuberculous percarditis is characterized by pericardial effusion with pericardial thickening or epicardial involvement. (20)

**EPIDEMIOLOGY OF TUBERCULOSIS**
Robert Koch identified *Mycobacterium tuberculosis* as the causative agent of tuberculosis in 1882. (21). But archaeological evidence has indicated that TB has afflicted humans for thousands of years before that. About

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**Percentage of Tuberculosis Cases Reported World wide**

- **23%** west pacific region
- **36%** Africa
- **10%** America
- **6%** Eastern Mediterranean
- **18%** Europe
- **7%** South East Asian

WHO Report 2000
one third of the world's total population is infected with *M. tuberculosis* but only about 10% of those infected, develop active disease. (1) Tuberculosis infects about 6-8 million people worldwide and causes 2-3 million deaths annually causing the largest number of deaths by any single infectious agent in a year. It is estimated that TB will kill 30 million people this decade (1) and considering the potential danger of a global epidemic, WHO declared a global emergency against TB in 1993. (22)

**Epidemiological model of tuberculosis**

Disease due to tuberculosis in population is influenced by three distinct risks: the risk of an individual in the community being infected with tubercle bacilli within a given period, the risk of disease following shortly after such infection, and the risk of disease occurring long after the original infection owing to the reactivation of latent bacilli. Most of the disease burden from tuberculosis is suffered by those living in developing countries, but in the recent past, the disease has become one of the major causes of morbidity and mortality in the non-developed countries.

Disease is generally thought to develop in an individual as a consequence of one of the three processes: progression of primary infection, exogenous, or endogenous reactivation.

At some time after birth, an individual may be infected with *M. tuberculosis* for the first time. This infection is usually acquired through air borne organisms from someone who has active pulmonary tuberculosis. The age at which this primary infection is acquired depends on how common active tuberculosis is in the community. Following primary infection, a small proportion of individuals develop progressive primary disease. Most people do not develop disease following infection and are assumed to mount an effective immune response to the initial infection that limits proliferation of the bacilli and leads to long-lasting partial immunity both to further infection and to reactivation of latent bacilli remaining from the original infection. Such individuals can be identified by a positive response to a tuberculin skin test.

At later stages, the immunity of persons who have been previously infected may wane, and they are then at risk of developing active tuberculosis as a consequence of either exogenous reinfection or endogenous reactivation of latent bacilli.
Trends in tuberculosis rates
Until recently rates of tuberculosis in developed countries had shown large and consistent declines for many decades. Although it is likely that effective chemotherapy speeded the decline, the major decreases occurred before effective therapy. (24)

TB is now the leading cause of death among HIV positive people and accounts for one third of AIDS deaths worldwide. It is estimated that by the end of the year 2000, HIV infection will cause nearly 1.5 million cases of TB that otherwise would not have occurred. (1) When one calculates that nearly 31 million people world-wide were HIV positive in 1997, (25) and almost one half were believed to be infected with TB, the implications of TB control are enormous. The emergence of multiple drug-resistant (MDR) isolates of *M.tuberculosis* and subsequent MDR-TB outbreaks increasing the human morbidity and mortality has worsened the situation even more. (1)

India is estimated to have nearly one third of the world's TB patients. Among the AIDS patients in India too, the most prevalent cause of death is due to TB infection. Tuberculosis (pulmonary and extrapulmonary) was found to be the major opportunistic infection affecting 62% of the cases.
In 1997 alone, of the 390 AIDS cases analyzed, tuberculosis (pulmonary and extrapulmonary) accounted for 56.5% of the total cases. An increasing trend was observed with tuberculosis from 58% in 1986-1992 to 68.5% in 1995. (26)

PATHOLOGY OF TUBERCULOSIS

PATHOGENESIS OF MYCOBACTERIA
Mycobacteria causing disease in animals and human beings can be divided into two types as - pathogenic mycobacteria like *M.tuberculosis* and *M.bovis* and environmental saprophytes like *M.avium, M.scrofulaceum, M.kansaii* etc. Mycobacterial disease shows variability in their clinical features, course and outcome depending on the host's immune responsiveness. The best example of this is leprosy, which shows a wide "spectrum" of clinical manifestation of the disease with very strong immune reactivity at one end and specific anergy at the other end. (2).

Pulmonary tuberculosis can be contacted through droplet aerosol containing 2-3 bacilli. Once several bacilli are inhaled, less than 10% of it will reach the respiratory bronchioles and alveoli while most will settle in the upper respiratory tract. Bacteria that arrive in deep lung are phagocytosed by alveolar macrophages and are either killed or survive to initiate the infection. (3). Over the next 2-3 weeks, surviving organisms multiply and kill the host macrophages, which is followed by mycobacterial release and subsequent infection of additional host cells. Granulomatous focal lesions, composed of macrophage derived epitheloid giant cells and lymphocytes, begin to form. Generally, the process of granuloma formation serves as an effective means for containing pathogens, preventing their continued growth and dissemination. While granuloma formation is quite effective defense, even contained *M.tuberculosis* organisms in the granuloma are not always completely non-infectious. After 4-5 weeks of progressive infection, microscopic granulomas enlarge, as individual foci expand they coalesce. This results in relatively large areas of necrotic debris surrounded by multinucleated giant cells. A cellular zone of fibroblasts, lymphocytes and monocytes surrounds these granulomas or tubercles. (2, 3) Although *M.tuberculosis* bacilli are unable to multiply within these caseous tissues, due to acidic pH, low availability of oxygen and presence of toxic fatty acids, some organisms may remain dormant there for decades. If the macrophages
containing ingested but viable bacilli escape from the granuloma via the intrapulmonary lymphatic channels, rapid spread of infection to the regional lymph nodes occurs. The lung tissues are destroyed leading to pulmonary damage and spread of organisms via the lymphatics and blood. As disease progresses further, the semisolid caseous center of granuloma begins to soften and liquefy, providing a rich and oxygenated environment for extracellular mycobacteria to replicate. Enlarged lymph nodes can rupture into adjacent airways, releasing liquefied necrotic material and causing tubercular bronchopneumonia.

ENTRY AND SURVIVAL OF MYCOBACTERIUM TUBERCULOSIS IN MONONUCLEAR PHAGOCYTES

Electron microscopy studies have shown that entry of \textit{M. tuberculosis} into human macrophages resembles conventional receptor mediated phagocytosis in which phagocyte psuedopods move circumferentially around the bacterium and fuse at their distal tip, leaving the bacterium in membrane-bound vacuole or phagosome (27). Mycobacteria use several specific macrophage receptors to enter the host macrophages. \textit{M. tuberculosis} uses the complement receptor type 1 and 3 for entry. Mycobacteria may also attach to macrophages through the fibronectin and vitronectin receptors. Entry of \textit{M. tuberculosis} via the complement receptor (CR) pathway provide the bacterium safe passage into mononuclear phagocytes by allowing it to avoid the toxic consequences of the oxidative burst. (28). Once the bacteria are phagocytosed into the macrophages inside phagosomes, the fusion of phagosomes with lysosomes and degradation of bacteria will follow. Inside the macrophages, mycobacterial survival and growth depends on the ability of the organism to avoid destruction by host lysosomal enzymes, reactive oxygen intermediates (ROI) and reactive nitrogen intermediates (RNI) which are the characteristics of the host's protective response against intracellular pathogens. (29). There are reports, which indicate that the mycobacteria inhibit the phagosome-lysosome fusion in order to survive. \textit{M. tuberculosis} appears to have the ability to disrupt the normal functioning of phagosomes by preventing them from developing into acidic hydrolase-rich compartments. This is confirmed by the absence of proton-ATPase in vacuolar membranes, the presence of which is responsible for acidification of phagosomes.

Survival strategies of mycobacteria also include use of receptors for entry, by which they do not activate the bactericidal activity of macrophages. Mannose receptor of macrophages is used as a portal of entry by pathogenic and non-pathogenic mycobacteria. This receptor also
internalizes soluble and particulate ligands by endocytic and phagocytic pathways respectively. Recent studies indicate that phagocytosis of pathogenic, as well as non-pathogenic mycobacteria through this receptor do not trigger production of ROI like $\text{[O]}^2$. (29) On exposure to mycobacteria, macrophages release cytokines that can enhance the non-specific protective host response, which includes production
RECEPTOR-LIGAND INTERACTIONS THAT MEDIATE PHAGOCYTOSIS OF M. TUBERCULOSIS BY PHAGOSOMES

Adapted from Tuberculosis, Pathogenesis, Protection, And Control Editor Barry R. Bloom
of ROI and RNI. Glycolipids and carbohydrate components of mycobacterial cell wall may interfere at different stages of this process by modulating the release of macrophage-derived cytokines, blocking the activation of macrophages or inhibiting the action or reactive metabolites. Lipoarabinomannan (LAM) is a heterogeneous mixture of arabinose and mannose containing phosphorylated lipopolysaccharide in mycobacterial cell walls. The arabinose termini of LAM from *M. tuberculosis* appear to be capped with additional inositol phosphates (AraLAM). The difference in capping affects the macrophage responses. LAM is a potent inducer of Tumor Necrosis Factor (TNF-α) in human and murine macrophages, TNF-α is an important component of the early host response to mycobacteria, which synergies with T cell derived gamma Interferon (IFN-γ) to stimulate bactericidal mechanisms. However, the activity of LAM from virulent and avirulent *M. tuberculosis* differs in that the one from virulent strain is about 100 fold less potent in inducing secretion of TNF-α than the one from avirulent strain. In general, AraLAM is about 100 fold more potent in inducing TNFα production by macrophages compared to ManLAM. Similar activity is seen with respect to Interleukin-1 (IL-1), Interleukin-10 (IL-10), NO and chemokine induction. AraLAM also activates the transcription factor NF-κB in murine macrophages to a larger extent when compared to similar activity of ManLAM. LAM from avirulent strains of *M. tuberculosis* increases the expression of c-fos gene and cytokines which are involved in the early activation of macrophages and which stimulate the production of RNI. The failure of LAM from *M. tuberculosis* to stimulate these early events in macrophage activation enables the organism to multiply within the infected macrophages and hence are important determinants in virulence of mycobacteria. LAM from *M. tuberculosis* block the activation of murine and human macrophages at several levels. The activation of macrophages is induced by T cell-derived IFN-γ. LAM inhibits protein kinase C, which plays a key role in the signal transduction pathway, triggering macrophage activation and the respiratory burst. Furthermore, LAM blocks the transcriptional activation of other IFN-γ regulated genes in human macrophages, including the MHC class II genes. This down regulation of the function of macrophages contributes to the non-specific inhibitory effect of LAM on proliferating T Cell. Other cell wall components like the glycolipid fractions of *M. tuberculosis* inhibit the activation of protein kinase C and the release of ROI thus blocking macrophage activation. Cell wall glycolipids may also enhance the
survival of resident mycobacteria within macrophages after macrophage activation by T cell derived cytokines. The carbohydrate components of *M. tuberculosis* LAM are effective scavengers of ROI.