CHAPTER II
REVIEW OF LITERATURE
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HISTORY

Tuberculosis is a disease of great Antiquity. What were almost certainly Tuberculosis lesions have been found in the vertebrae of neolithic man in Europe and of Egyptian mummies perhaps as early as 3700 B.C. (Morse et al, 1964).

In Chinese literature `Laoping' a disease of the lung, fits in with tuberculosis in its symptoms. Pulmonary Tuberculosis was described in India in 3000 B.C. in Rig Veda as `Yakshma' which very much confirms to the present description of consumption of Tuberculosis (Rao, 1972).

Franciscous Sylvius of Leyden (1614-1672) first employed the term `Tubercle' and stated that tubercles were often seen in the lungs of consumptives (Rao, 1972). In 1882 March 24 Robert Koch announced the Discovery of the Tubercle bacillus was a major break through in the History of Tuberculosis.

The morbidity and mortality of Tuberculosis diminished in developed countries after the discovery of Anti-tuberculous drugs Streptomycin in 1943 by Waksman, was soon followed by other drugs with
Anti-tuberculosis activity. Although in developing countries like India the situation remains grim (Sudre et al, 1992).

The emergence of drug resistant strains has reduced the efficacy of treatment almost to the level of pre-chemotherapy era (Grange, 1990). The appearance of AIDS leading to immunosuppression of the cellular immunity has further complicated the present situation.

**Epidemiology**

**Prevalence of infection:** Most people in the world were infected at some time in their lives (Groth-Peterson, 1959). Prevalence of infection is measured by the proportion of Tuberculin reactors in the total population at any point of time and usually expressed as a percentage.

Various study conducted in India at various places the final conclusion is (1) Infection rate increases with age and higher in males than females. (2) The difference can probably be explained by the fact that males in general lead a more active circle thus coming across more changes of acquiring infection. (3) Infection rate in general are more or less the same in urban and rural areas. In a recently conducted study in Chingleput district of Tamil Nadu Tuberculosis Prevention Trial reported as overall prevalence rate of infection 50% (Males 54%, females 46%).
Among males the infection rate rose rapidly up to the age of 25 years (Reaching 80%) whereas in females the rise continued up to 35 years (reaching 70%) (Gothi, 1982).

The prevalence of Dual Tuberculosis and HIV infection was estimated by applying the prevalence of tuberculosis infection in the 15-49 year age group to populations which are thought to be infected with HIV in this age group.

**Incidence of Infection:**

The incidence of infection calculated as non reactors at an earlier tuberculin testing who become reactors at a subsequent testing can be considered to have acquired tuberculous infection in the intervening period and incidence of infection is calculated per annum by expressing the letter as a percentage of the former. Adopting the same calculation a study conducted in 1980 by Tuberculosis Prevention Trial the age specific annual incidence of infection as follows - 3%, 4% and 6% per year for this age groups 1-4 years, 5 to 9 years and 10 to 14 years respectively.

In another International Study the annual incidence of infection of 1.5 to 2.5% for the countries of African region, 0.5 to 1.5% for countries in Central South America and Eastern Mediterranean region and 1 to 2.25
for countries in South east Asian and Western Pacific regions (Murray et al, 1990). The additional number of HIV related tuberculosis cases was obtained by applying a 10% of annual break down rate to the number of dually infected individual (Selwin et al, 1990).

**Incidence of disease**

In 1990 an estimated 8 million individuals developed Tuberculosis world wide. More than 4.5 million cases occurred in Asia. The highest incidence rate was observed in Africa. In Africa 20% of additional HIV related tuberculosis cases were reported.

**Mortality**

According to mortality projections there were 2.6 to 2.9 million death due to tuberculosis worldwide in 1990, the majority in China and South East Asia. Because of increasing number among HIV infected individuals especially in Africa.

**Tubercle Bacilli**

Four type of Myobacterium Tuberculosis are recognised, human, bovine, murine and Avian. The human and bovine are major clinical importance.
The Mycobacterium Tuberculosis is a straight or slightly curved rod 1-3\(\mu\) x 0.2 - 0.8\(\mu\) occurring singly in pairs or in small clumps.

The bacilli are non motile, non-sporing and non capsulated when stained by carbol fusion by the Ziehl-Neelsen method or by fluorescent dyes (auramine O, Rhodamine) the resist decolourisation by 25% Sulphuric Acid and Absolute Alcohol for 10 minutes (Acid and Alcohol fast).

Factors relevant to the development of Tuberculosis

1) Source of Infection:

The sputum is for the most important source of Tubercle bacilli, infected urine and discharge from sinuses etc. Patient positive on direct smear are much more infectious than those only positive on culture and individuals infected by them are likely to develop Clinical Tuberculosis (Rouillon et al, 1976).

A study based on tuberculin skin test reactor rate found that children in contact with sputum positive on direct smear cases showed a reactor rate of 65.2% children in contact with sputum positive on culture cases a rate of 26.8% and children in contact with spectrum negative on culture cases a rate of 17.8%. A group of non contacts showed a reactor rate of 22.1% (Brain Shaw, 1954).
The principal sources of infection are smear positive cases. The main groups at special risk of disease are household and other close contacts of active tuberculosis and persons with inactive tuberculosis or fibrotic lesions (Ian Sutherland, 1988).

The effective treatment rapidly reduces infectivity in most cases if probably lost within 2 weeks (Rouillon et al, 1976). Children with primary Pulmonary Tuberculosis without sputum are not an infectious risk of any importance (Styblo, 1978).

**Virulence of Tubercle bacilli**

The human tubercle bacilli isolated in South India have a diminished virulence for guinea pigs and probably for man compared both with strain isolated in Britain and with other strains prevalent in India. The maximal number of strains with diminished virulence occurs in South India (Mitchison, 1964).

**Defence of host**

1) **Genetic:** Eskimos and Australian aerovigines are also probably much more susceptible than people of European origin (Grzybowski et al, 1976; Abrahams, 1975). In New York, American Negros who have long been exposed to tuberculosis and often live in poor environmental
conditions had a tuberculosis morbidity 4 times higher than whites (Katz and Kunofsky, 1960). The prevalence of tuberculosis among blacks is known to be about twice that among whites (William et al, 1990).

2) Physiological factors

Age and Sex: In the developing countries the majority of infected individuals are below 50 years of age. In the developed countries it is very low among those less than 50 years old but not still high in the relatively large older age group (Sudre et al, 1992). A study conducted by Bhaskara Reddy et al (1975) 28.5% of tuberculosis was in the age group of 0-9 years and 20% in the age group of 30-39 years group. The ratio of male to female was 2:1.

Environmental factors

Nutrition: Protein and fats are usually considered important protective foods. Malnutrition predispose to Tuberculosis Infection.

Housing condition: Over crowding increases the chances of infection but poor housing conditions probably also lowers the resistance to the disease.

Toxic factors: The relatively high incidence of tuberculosis in Alcoholics is well known (Smith and Palmer, 1976). In patients of both sexes with Pulmonary Tuberculosis.
Over the age of 30 years in a highly significant deficiency of non-smokers and light smokers and an excess of moderate and heavy smokers compared to controls of the same age group suffering from other diseases (Lowe, 1956).

Doll and Peto (1976) have shown that mortality from Pulmonary Tuberculosis among doctors increased significantly with the number of cigarettes smoked.

Corticosteroid drugs and other immunosuppressants may lower resistance to the disease tuberculosis is a well known complication in patient's on long term corticosteroid drugs especially if those are given in large doses.

**Influence of other diseases**

Any debilitating disease may predispose to tuberculosis. The association with Diabetes is particularly notorious and the outlook of patients with both diseases before chemotherapy became available was grim (Turner-Warwick and Margaret, 1957). The incidence of tuberculosis in diabetic patients is 2.6% that is about 3 times higher than the average tuberculosis morbidity in the U.S. between 1920 and 1929 inclusive (Banyai, 1930).
A study conducted by Patel et al (1977) shown Tuberculosis was found to be in 5.77% in 4349 cases of diabetics.

Tuberculosis may complicate neoplastic disease or result from its treatment with chemotherapy (Kaplan et al, 1974). The risk of developing pulmonary tuberculosis after partial gastrectomy is was known (Thorn et al, 1956).

Since the discovery of Human Immunodeficiency Virus (HIV) in mid 1981 the prevalence of tuberculosis and HIV infection is on the rise (Mohanty and Baskar, 1995). It is estimated that 4% of global tuberculosis is HIV related and 10% of those having dual (HIV + TB) develop active tuberculosis (WHO, 1991).

It is estimated that more than 3 million people are dually infected with tubercle bacillus and HIV in the world, 2.4 million in Sub-Saharan Africa alone (Kochi, 1991). In an Indian study conducted by Shivlal (1992) estimated that 600,000 HIV infected individuals in India. Another Indian study says the hospital admission of tuberculosis in HIV infected individual increased from 2.56% in 1988 to 10-15% in 1993-1994 (Mohanty and Baskar, 1995).
Extrapulmonary involvement occurs frequently and earlier than other opportunistic infections especially in individuals dually infected with HIV and tubercle bacillus and is more difficult to diagnose than pulmonary tuberculosis (Arora et al, 1995).

**Primary Pulmonary Tuberculosis**

**Primary focus:** It is initial lesion produced by tubercle bacilli in any tissue.

**Primary or Ghon complex:** Includes both the primary focus and homogenous lesions in draining lymph nodes. The primary complex most commonly occurs in the lung but also may develop in the skin, intestine, genital tract and tonsils (Stead, 1967).

**Pathology:**

The primary lesion is subpleural, in children it may occur in any part of the lung through the adolescents and young adults there is some bias towards the upper zones (Daniel et al, 1948). When the tubercle bacilli are first deposited in an alveolus, an acute inflammatory reaction ensues in the tissue with phagocytosis of bacilli by polymorphonuclear leukocytes. These are incapable of killing the mycobacteria and are replaced by macrophages. Bacilli rapidly carried by macrophages to the regional
lymph nodes. In both the local and lymph node sites activation of epitheloid cell and Langhan's giant cell granuloma develops.

Coagulative necrosis (caseation) with in the granuloma occurs at about the time that cutaneous hypersensitivity to tuberculoprotein is demonstrable so liking its pathogenesis with developed hypersensitivity phenomena (Bertrong, 1970; Lucas, 1988).

The classical pathological manifestations of tuberculosis may be found in varying proportion they consist of a granulomatous lesion containing epitheloid cells derived from macrophages, Langahn's giant cells with multiple nuclei also derived from macrophages, lymphocytes and varying degree of fibrosis (Sutton and Weiss, 1966). The peculiarly chessy form of necrosis found of tuberculosis is known as caseation and the caseous tissue may latter become calcified. If the lesion progress the caseous tissue owing to factors which are not well understood may become liquified to form purulent material. This material may be discharged into the air passages resulting in cavitation of the lesion.

On the basis of morphological data correlation seems to exist between the cellular composition of the lesions and the most resistance to tuberculosis. One pole of the histological spectrum shows lesions containing lymphocytes and epitheloid cells, patients with such
lesions shows early reduction of the bacterial load in the sputum with treatment and localised lesions on x-ray.

The opposite pole presents lesions with polymorphonuclear leukocytes and macrophages containing mycobacteria, undifferentiated histocytes are also present. These lesions correlate clinically with patients who shows a poor response to treatment have persistent mycobacteria in the sputum and also disseminated lesions. The intermediate region of this spectrum shows characteristics of both polar forms (Lenzini et al, 1977).

Ridley and Ridley (1987) classified the tuberculosis as follows on the basis of histological criteria:

<table>
<thead>
<tr>
<th>Main cell type</th>
<th>Necrosis</th>
<th>Bacilli</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a Ec organized</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>1b EC (or) IEC</td>
<td>Fibrinoid</td>
<td>Rare</td>
</tr>
<tr>
<td>2a IEC</td>
<td>Homogenous eosinophilic no nuclear debris</td>
<td>Scanty</td>
</tr>
<tr>
<td>2b Undifferentiated</td>
<td>Basophilia PMN</td>
<td>1-2+</td>
</tr>
<tr>
<td>3a Macrophages</td>
<td>Coarse nuclear debris basophilic Extensive</td>
<td>2-3+</td>
</tr>
<tr>
<td>3b Scanty macrophages</td>
<td>Coarse eosinophilic vary Extensive</td>
<td>Over 3+</td>
</tr>
</tbody>
</table>

EC : Mature Epitheloid cell
PMN : Polymorphonuclear leukocyte
IEC : Immature epitheloid cells.
Fate of the primary complex: (Richard et al, 1980)

Primary Focus + Lymphnode (Ghon complex)

Healing
(calcification)
Easy generalization
Progressive primary
Tuberculosis

Abortive (minute lesions in any organ system)
Progressive (Acute Miliary Tuberculosis)

Fibrosis + calcification
Organ Tuberculosis

Reactivation

Reactivation
Simon's foci
Organ Tuberculosis

Lymphnode Tuberculosis
Chronic Pulmonary Tuberculosis
Late generalized Tuberculosis

Rapidly progressive
(progressive acute miliary Tuberculosis)

Late discrete generalization

Symptoms:
The great majority of primary tuberculous infections are probably symptomless, at least in adolescents and young adult. A proportion may experience a brief febrile incident at the time of tuberculin conversion
which is passed off as 'influenza' or one of the brief fevers which are relatively common in childhood.

If infection is a severe one or host resistance is low the child may appear to be vaguely unwell with reduced appetite, fretfulness and failure to gain weight. Normally cough is unusual.

Physical signs:

In most cases there are no detectable abnormal physical signs where the lesions is severe or extensive there may be the appearance of general debility. The child may be thin, pale and fretful. The hair may be loss grossly than usual. In the chest there are usually no detectable physical signs, but sometimes there may be a few local crepitations over a large lung component of the primary complex (Daniel et al, 1948).

Post Primary Pulmonary Tuberculosis

Post primary pulmonary tuberculosis is by far the most important type of tuberculosis partly because it is much the most frequent and partly because the resulting positive sputum is the main source of infection and responsible for the persistence of the disease in the community.
Pathogenesis

One of the distinctive characteristics of tuberculosis is the existence of a latent stage of the disease represented by apparently healed primary lesions resulting from the first infection with tubercle bacilli. In some individuals the primary lesions progress without apparent interruption into active stage, namely the clinical disease tuberculosis. In others they heal without the development of 'progressive primary tuberculosis' and indeed often without any illness having been noted in the individual. Those in whom the primary lesions heal are believed to have some immunity against a fresh infection. The latent stage may last indefinitely or be followed perhaps after many years, by active tuberculosis. Tuberculosis occurring some while after a primary infection may either be the result of the reintroduction of tubercle bacilli into the body by a fresh infection (Exogenous tuberculosis) or may represent the result of a reactivation of tubercle bacilli which have been dormant in the body since the primary infection (endogenous tuberculosis) (Sutherland et al, 1982).

Pathology:

Tuberculosis commonly involves the posterior segment of the upper lobe of the apical segment of the lower lobe. The most likely reason for this predilection is the decreased blood flow but relatively good ventilation of the upper lobe in the upright position. This results in a high
mean alveolar O2 tension than the lower lobes, this favouring the growth of tubercle bacilli (Bates et al, 1971; Corper et al, 1927).

The histopathological lesions vary from the patient to patient and within the same lungs.

Pre-exudative phase:

On which there is vasodilatation with swelling of the cells lining the alveoli with appropriate staining methods numerous bacilli may be demonstrated and those are often intracellular.

This is frequently succeeded by an exudative phase - in which vasodilatation, oedema, fibrinous exudate, histocytes, polymorphonuclear cells and lymphocytes occur in varying proportions.

Bacilli is varying quantities are present in the exudative lesions mainly outside cells.

In most cases the exudative lesions proceeds to caseation. The inflammatory cellular elements and often those of the lung tissue also become more homogenous, loose their identity and gradually merge into the cheesy substance which gives the name to the process caseation is
nearly always preceded by an increase in the number of bacilli and it is probably largely a hypersensitive phenomenon.

Around the edge of the caseation develop the so called productive lesions. Consisting initially of macrophages derived from the blood and local histocytes both of which later evolve into the characteristic cells with a large pale nucleus known as the epitheloid cell. A number of those cells may fuse to form characteristic Langhan's giant cell with multiple nuclei distributed around the periphery. There is often infiltration with lymphocytes and sclerosis gradually develops. The epitheloid cells and giant cells may be aggregated into clumps to form the classical tubercles.

Of the lesion regrets the productive and sclerotic elements gradually replace the exudative lesion. Fibrosis may increase around the periphery of the lesion and gradually invade it.

Cerebral fibrosis may also occur caseous material may be reabsorbed may often becomes walled off by fibrous tissue and calcified.

If the lesion progress the caseous material liquefies and discharged into a bronchus so that a cavity forms in the previously necrotic area. The hair of the cavity is usually lined by softened caseous material containing...
very numerous bacilli the greatest concentration of the latter being near the surface of the caseous, presumably owing to a better oxygen supply.

**Pinner classified cavities as follows:**

1) Small multiple cavities in densely infiltrated parenchyma mouth eaten areas honey combing.

2) More or less sharply defined round or slightly oval cavities either with a perifocal inflammation (or) with thin walled outlined borders.

3) Irregularly shaped cavities with dense thick walls.

**Symptoms:**

Symptoms of Pulmonary Tuberculosis do not form a clear cut syndrome. They are common to many non tuberculous conditions, intrathoracic as also extrathoracic. One of the points in the history which may make tuberculosis a possibility is the gradual onset of the symptoms over weeks or months. General symptoms or constitutional symptoms.

These are due to liberation of products from disease foci into the blood stream and include lassitude, loss of appetite, loss of weight, fever, night sweats are classical symptoms of tuberculosis.
A study conducted by Krishnaswamy et al (1977) 25% of patients had loss of appetite, 16% had loss of weight, 52% of patients had fever.

Some times patient complaint mainly of mental symptoms such as irritability and difficulty in concentrating in work.

**Respiratory Symptoms:**

Cough is the most common and almost always first to appear. A study conducted by Krishnaswamy et al (1977) the highest prevalent symptom observed is cough (35%) which was complained by the largest number of patients (92%). In another study, cough is by far one of the most important single symptom, not only is it the most frequent symptom above and in combinations (Banerji and Andersen, 1963). There is nothing specific about sputum in tuberculosis, sputum may be mucoid, purulent or blood stained.

Hemoptysis is a classical and very important diagnostic evidence in pulmonary tuberculosis. Pamra et al in 1970 found more than half of their patient with a history of hemoptysis to be tuberculosis concluded that tuberculosis is the most frequent cause of hemoptysis in all age groups. Heller (1946) found about 15% of his tuberculous cases had hemoptysis during their illness corresponding figures of 30% by Rao (1960).
Chest pain is the common symptom. In a study 20% of patients had chest pain. Dyspnoea also is another common symptom.

**Physical signs:**

The general condition in pulmonary tuberculosis may be excellent. But in advanced cases pallor and cachexia is present.

They also have pyrexia which is more in the evening and tachycardia and tachypnoea in advanced cases. Clubbing of fingers to an important degree is unusual except in chronic disease with purulent sputum.

In the chest there are often no physical signs. The most common abnormality consists of post tussive crepitations in the upper zones or apices. Physical signs of consolidation and fibrocavitary disease may occur. Localised ronchi can occur in severe tuberculous bronchitis.

**Miliary Tuberculosis:**

Miliary Tuberculosis results from massive hematogenous dissemination of tubercle bacilli from an established focus producing numerous lesions of approximately the same age and size in many organs of the body. The large numbers of granulomas which result are
likened in appearance to millet seed hence the name miliary tuberculosis (Chapman and Whorton, 1946).

Pathogenesis:

Caseous foci responsible for hematogenous spread are generally derived from reactivated old caseous lesions located principally in the lung, lymph node, bone, central nervous system, adrenals and genitourinary tract. Simultaneous reactivation of anatomically unrelated foci in multiple organs and lymph nodes occurred in 54% of cases (Proudfoot et al, 1969).

Disseminated tuberculosis may be divided into 3 broad groups.

1) Acute miliary tuberculosis associated with brisk tissue and cellular reaction to the invading bacillus

2) Fulminating non-reactive disease

3) Chronic miliary tuberculosis, associated with reduced or atypical cellular reaction, cryptic miliary tuberculosis (Cameron, 1974).

Predisposing factors

Chronic alcoholism is one of the important predisposing factor (54% patients). The other predisposing factors such as prolonged steroid therapy, previous gastrectomy, diabetes mellitus, carcinoma and blood dyscrasia were infrequent (8%) (Arthur et al, 1973).
Pathology:

A consequence of hematogenous dissemination of mycobacterium tuberculosis results in widespread millet seed size (1-2 mm in diameter) visceral tubercles occurs. These lesions consist of clumps of epitheloid cells, lymphocytes and Langhan's cells often with caseation (Rajeswari et al, 1993).

Clinical features

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anorexia, weight loss</td>
<td>87%</td>
</tr>
<tr>
<td>Fever</td>
<td>85%</td>
</tr>
<tr>
<td>Cough</td>
<td>69%</td>
</tr>
<tr>
<td>Night sweats</td>
<td>63%</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>29%</td>
</tr>
<tr>
<td>Pleuritic chest pain</td>
<td>18%</td>
</tr>
<tr>
<td>Stiff neck and head ache</td>
<td>16%</td>
</tr>
<tr>
<td>Abdominal pain and swelling</td>
<td>13%</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>12%</td>
</tr>
<tr>
<td>Urinary symptoms</td>
<td>6%</td>
</tr>
</tbody>
</table>

Clinical findings

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever (&gt; 98° F)</td>
<td>85%</td>
</tr>
<tr>
<td>Rales and ronchi</td>
<td>51%</td>
</tr>
<tr>
<td>Clear lungs</td>
<td>36%</td>
</tr>
<tr>
<td>Hepatosplenomegaly</td>
<td>31%</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>15%</td>
</tr>
</tbody>
</table>
Stupor/coma 15%
Meningism 13%
Splenomegaly 11%
Jaundice 9%
Ascites 4%

Extrapulmonary Tuberculosis

In India the non pulmonary tuberculous cases are about 5 to 8% of the total freshly diagnosed tuberculous cases.

Tuberculosis of lymph nodes:

Tuberculous lymphadenitis continues to be a major health problem in our country. It is one of the commonest manifestation of extrapulmonary tuberculosis (Madhusudanmurthy, 1976). It usually affects adolescent and young adult females (10-29 years). Among children it commonly affects infants and toddlers (0-5 years).

Pathology:

Caseating type: If defence mechanism of host is overwhelmed, the lymph node consisting of a central caseation necrosis, surrounded by epitheloid cells lymphocytes and giant cells of Langhan's type.

Non-caseating type: If defence mechanism is not adequate the reaction is hyperplastic with an irregular arrangement of tuberculous giant cells, endotheloid cells and lymphocytes. These nodes resemble
the nodes of Hodgkin's disease both clinically and microscopically that the condition is called the pseudolymphadenomatous variety of tuberculous lymphadenitis.

Clinical features:

Tuberculous lymphadenitis is common in young adults 20-40 years of age. It is relatively uncommon at the extremes of life. Cervical and supraclavicular nodes were nearly always involved (94%). Involvement of more than one site was relatively uncommon a single site have involved in 18% of cases (Summers and McNicol, 1980).

In an Indian study of 40 cases of Tuberculous lymphadenitis lymphnode of cervical group were affected in 70%, multiple sites in 12.5%, axillary group in 12.5% and inguinal nodes were affected in 5%. Matting and caseation were the usual mode of presentation and there were present in 62% and 25% of cases respectively. Other cases presented with either discrete lymphadenopathy with other features of Tuberculosis or with non healing ulcers or sinus (Nanda et al, 1986).

Tuberculous adenitis is seen in the following stages:

1) Glands enlarged firm and discrete
2) The glands are firm for the most part but the largest one shows periadenitis and may show early softening in the centre.
3) There is cold abscess formation without skin involvement.

4) There is skin involvement shown by adherence and redness.

5) The cases is one of some standing which has been treated unsuccessfully and there are sinuses, recurrent abscesses or abscesses in calcified nodes.

Abdominal Tuberculosis:

Abdominal Tuberculosis was made in 1643 when two autopsy on Louis XIII showed ulcerative intestinal lesions associated with large pulmonary cavity (Paustian, 1976).

Incidence: The frequency of intestinal involvement secondary to pulmonary tuberculosis varies from 1 to 90% and the incidence of isolated or primary tuberculosis different series reported varies from 0.02 to 5.1% (Chuttani, 1970; Pimparker and Donde, 1974; Tribedi and Gupta, 1941).

Pathogenesis

Ingestion of tubercle bacilli, Intestinal tuberculosis came result from ingestion of contaminated food and milk or secondary infection of the gut may result from swallowing of infectious sputum in patient with pulmonary and laryngeal tuberculosis.

Following ingestion the bacilli pass through the stomach into small intestine. The lipid capsule protects the bacteria from digestion by gastric
acid. In the intestine, infection is more likely at sites where there is abundant lymphoid tissue, increased physiologic stasis, increased rate of water and electrolyte absorptives and minimal digestive activity.

Hematogenous spread from an extra intestinal focus of infection

Blood have dissemination and infection may occur from primary phase of pulmonary tuberculosis and in miliary tuberculosis.

Infected bile:

Sequestration of the bacilli by the liver and excretion in bile is a potential source of infection.

Extension from adjacent organs

Enteric tuberculosis may result from extension of infection from adjacent organs e.g. female adnexa.

Histopathogenesis

Whatever the route of infection the submucosa in initially involved resulting in thickening due to edema, cellular infiltration, lymphatic hyperplasia formation of tubercles and fibrosis. The serosa is involved later by direct continuity or by way of lymphatic channels. This is followed by invasion of mesentric lymph nodes through the lymphatic
channels. In the later stages, the bowel, mesentry and lymph nodes are all involved and form the thick fixed mass.

Pathology

Gross appearance: Tuberculous enteritis is classified as ulcerative hypertrophic or ulcerohypertrophic.

Ulcerative form: This is most probably the result of deprivation of blood supply due to an endarteritis. The disease segment exhibits moderate induration with an increase in mesentric fat.

The mucosa shown single or multiple transverse and circumferential ulcers. The margins are irregular and the bases snaggy or nodular. The serosa is often studded with nodules.

Hypertrophic form: The mesentry, lymphnode and bowel wall are thickened and matted together. This form is due to a florid inflammatory fibroblastic reaction in the submucosa and subserosa layers.

Ulcerohypertrophic form: This is a combination of ulcerative and hypertrophic forms. This form exhibits various combinations of ulcers, nodularity, pseudopolyps, hyperplasia and stenosis.
**Microscopic findings:** Caseating granuloma are the histological hallmark of tuberculosis. Acid-fast bacilli are occasionally seen. Ulcers usually do not penetrate beyond the muscularis propria. In late stages a variable degree of fibrosis may be seen.

**Clinical features**

Tuberculosis can affect any part of the gastrointestinal tract. The ileum and ileo cecal region are most commonly involved followed by the colon. The male and female ratio is approximately equal women in 2\textsuperscript{nd} and 3\textsuperscript{rd} decade.

The symptoms are usually non specific the most frequent having abdominal pain, weight loss, fever, nausea and barbarygmi. Other common symptoms are vomiting, anorexia, post prandial abdominal pain, abdominal distension and night sweats, constipation and diarrhoea each occur in about a fifth of the cases.

In an Indian study of 25 patients of abdominal tuberculosis 92% had obstruction and 8% had perforation (Abraham and Fersosh, 1992; Habibullah et al, 1977).
Tuberculous peritonitis

Tuberculous peritonitis is usually associated with a tuberculous focus elsewhere in the body. The spread to the peritoneum may be hematogenous, via the lymphatics or directly by contiguous spread from affected bowel loops and lymph nodes.

The parietal and visceral surfaces of the peritoneum are studded with small tubercles, about 1.3 mm in size on histopathology caseased granulomas and Langhans giant cells are seen. Initially the peritonitis is associated with ascites later fibrosis set in the finally bowel loops become matted together and adhere to the patients.

Clinically this form of tuberculosis usually occurs in young adults. The onset is insidious and patients have symptoms of fever, vague abdominal pain, abdominal distention and weight loss for more than 3-4 months prior to presentation. The abdomen may be distended and has doughy feel. An abdominal lump due to matted bowel loops and omentum may be felt. Ascites is usually detected (Singh et al, 1969).

Central Nervous System - Tuberculosis

Robert Whytes in 1968 published the first clinical description of tuberculous meningitis (TBM) in his monograph on 'Dropsy in the brain' in children of all the manifestation of tuberculosis, meningitis is
undoubtedly the most serious. Fatality rate of tuberculous meningitis still remain considerably high as compared to that (Dastur et al, 1970).

Incidence of tuberculous meningitis varies from 1-4% of total inpatient admission in different parts of India (Rao, 1972). In a study done by Udani et al (1970) tuberculous meningitis comprises 29.02% of total cases of tuberculosis.

Tuberculous meningitis can occur at any age. But more common in children under the age of 5 years.

Pathogenesis:

Tuberculous meningitis is never a primary manifestation. But always occurs as a result of secondary hematogenous spread from the site of primary extracranial tuberculous lesion which is frequently in the lungs. It usually occurs within the first 6-12 months after the primary infection.

Predisposing factors

1) Malnutrition 2) poor socio-economic status 3) overcrowded surrounding 4) antecedent infection with measles and pertussis 5) Head injury.
As a result of hematogenous dissemination the tubercle bacilli are lodged principally at two sites. (1) Leptomeninges (2) Brain parenchyma. The miliary tubercles in the leptomeninges are most frequently on the lateral aspect of parietal and temporal lobes on either side of the sylvian fissure and along the blood vessels of these sites. Parenchymatous lesions in the brain are located at 3 sites

1) Superficial part of the brain - Rich focus
2) Base of the brain - in the subthalamic and subputaminal region
3) Along the superolateral surface.

It is frequently a basal tuberculoma which may be single or multiple, small cortical granulomatous foci burst out in the leptomeninges. This explain the predominant basal location of the exudate. The exudate may be scanty usually is very copious, thick and adhere in nature. The exudate has predilection for the interpeduncular fossa, over the floor of 3rd ventricle around the optic chiasma, distal ends of the internal carotid artery and proximal portion of the middle meningeal artery. The exudate extends backwards over the pins and cerebellum and occupies cisterna ambiens and cisterna pontis forming collar which compress the brain stem and emerging 3rd cranial nerve and the medullo cerebellar angles where the Foramine of Laschka open.
The blockage of CSF pathways is responsible for the internal hydrocephalus.

**Parenchymal changes:**

Dastur and Lalita (1973) described six main gross parenchymal changes.

1) Ventriculitis
2) Border zone encephalitis
3) Infarction
4) Internal hydrocephalus
5) Diffuse oedema
6) Tuberculoma

**Clinical features:**


1) Meningeal Exudate gives rise to meningeal signs; cranial nerve palsy and hydrocephalus.
2) Lesions in the brain parenchyma course alteration of sensorium, seizures, hypothalamic symptoms and brainstem disturbances.
3) Arteritis causes vascular obstruction and focal neurological deficit.
4) Allergy and hypersensitivity cause oedema of the brain.
The clinical manifestations may be grouped into three stages (High and Nelson, 1975).

**Stage I:** Symptomatology is non-specific and diagnosis is difficult to establish. This stage lasts for 1-2 weeks.

**Stage II:** Appearance of definitive neurologic sign, lasts for about 2 weeks.

**Stage III:** The stage of coma. This stage lasts for 1-2 weeks. In India it may be prolonged for 1-6 months.

The presenting symptoms reported in various series (Udani and Bhat, 1974; Benakappa et al, 1975) are fever in 80-90% of cases, convulsions in 50-60% of patients, vomiting in 40-45% and altered sensorium in 20-45%.

Tuberculous meningitis clinically involves the basal meninges it gives rise to cranial nerve palsies most commonly III, VI, VII and VIII. Papilloedema may occur without co-existing hydrocephalus. An intense vasculitis complicates the meningitis gives rise to infarcts in the central nervous system and hence variety of neurological defects which include hemiplegic, decerebrate rigidity, cerebellar signs, involuntary movements, hypothalamic disorders, spinal cord syndromes and in children dystonic, behaviour problems as well.
Tuberculomas may be asymptomatic or may present with signs and symptoms of a space-occupying lesions depending on their size and location (Girling et al, 1988).

**Skeletal Tuberculosis**

Skeletal tuberculosis is the second most commonest orthopaedic problem in India and in the other countries of the world. Bone and joint tuberculosis remains one of the most important crippling diseases worldwide. Spinal lesions are the most frequent and may cause severe deformities with serious complications. In a 6 months survey all tuberculosis notifications in England and Wales in 1983 bone and joint tuberculosis occurred in 9.0% of 1097 patients of Indian, Pakistani or Bangladeshi ethnic origin but only 2.4% of 1668 of white ethnic origin. Spinal lesions being the commonest in all ethnic groups.

Skeletal tuberculosis has classically reported to develop within 2-3 years of primary infection usually but not necessarily as a result of blood borne infection (Crofton and Douglas, 1981).

**Tuberculosis of the spine**

The incidence of tuberculosis of spine 44% of total bone and joint tuberculosis. It usually starts in early childhood, during adolescence or
in early adult life. The commonest site of involvement is thoracolumbar region.

**Four types of tuberculosis spine recognised:**

1) Central or Juvenil type in which the lesion start in the centre of the body and spread to the entire body resulting in collapse and deformity.

2) Epiphyseal or adult type in which the infection begins in the upper or lower epiphyseal plate near the intervertebral disc.

3) The anterior or peripheral type which also occurs in adults and in which the initial lesion is beneath the anterior longitudinal ligament.

4) The last type which is rare, attacks one or other of the vertebral appendages and most commonly the transverse process.

**Pathology**

Once the primary lesion sets in the vertebral body the bone destruction leads to formation of a cold abscess. The abscess may remains localised and give rise to paraplegic or it may become wondering or migratory.

**Clinical features**

These may be considerable variation in the clinical findings at the time of presentation. In many patients these are very few symptoms or signs, back pain and tenderness over the affected area being the most
common limitation of spinal movement associated with muscular spasm and mild kyphosis may be found in examination. General symptoms such as fever, night sweats and weight loss may occur and those may be evidence of tuberculosis elsewhere. In developing countries like India cases are often diagnosed at more advanced stage with a high proportion of patients having marked kyphosis, abscess or sinus and severe myelopathy.

Tuberculosis of the Genitourinary Tract

Tuberculosis of the genito-urinary tract was usually the last of various manifestations of tuberculous infection and that a period of years average 8 to 10 years (Gloor, 1946). The incidence of genito-urinary tuberculosis varies. Kaswan et al (1982) reported a series of autopsy examination on 736 tubercular cases who had 4 of received chemotherapy. They found genitourinary involvement in 117 (16%) of cases whereas it was 7% in those who received antitubercular drugs.

Mygind (1960) found that tubercle bacilluria is demonstrable in 2% of patients with pulmonary tuberculosis. Singh et al (1975) studied 36 cases of pulmonary tuberculosis in India and showed that 3 cases (8.3%) had urine culture positive for AFB.
Genitourinary tuberculosis common between 16-40 years and preponderance of males (63.6%) and females (36.4%) (Borthwick, 1956).

Pathogenesis

The tubercle bacilli produce earliest lesions in the kidney are usually bilateral and found in relation to the glomeruli of the cortex after post primary bacillaemia. The lesion may be healed or encysted. The encysted lesions may reactivated at any time.

After reactivation the cortical lesions may ulcerate into the renal tube and give rise to tubercle bacilluria. The cortical focus may spread directly or the lymphatics to the tubules of the pyramids especially in the papilla. So the papilla is a tendency to necrosis and cavity formation when this has ulcerated into the renal pelvis, the infection can spread to the ureter, bladder and in the male to genitalia (Medlar, 1926).

In the ureter which shows mucus or submucous tubercles and later fibrous tissue infiltration. The ureter may become thickened and strictures are common. In the bladder hyperaemia at the ureteric orifice in often followed by the appearance of numerous greyish-yellow tubercles. Those may coalesce spread and produce ulceration when healing occurs the fibrous tissue tends to contract producing reduction in bladder capacity which may be severe so called systolic bladder.
Tuberculous epididymitis was found 70% of patients with renal tuberculosis. The pathogenesis of tuberculous epididymities is a sequel of a renal one.

Clinical features

The presenting symptoms are increased frequency of urine 50% of patients, renal pain 4.6% of patients, hematuria 7.4%, painful hematuria 3.7% retention of urine 0.6%. 29.9% of patients did not have any symptoms they were presented with unexplained albuminuria or pyuria (Borthwick, 1956). In the involvement of the epididymis patients will have frequent nocturnal emissions which may be blood stained and dysuria. On examination epididymis shows induration enlargement and nodularity especially at the lower pole.

Female Genital Tuberculosis:

The incidence of female genital tuberculosis varies. Incidence in dependent upon the geographic location and the extent of investigatory procedures and techniques employed for the diagnosis. In a postmortem autopsy study the incidence of genital tuberculosis was 10-12% of pulmonary tuberculosis (Auerbeck and Martin, 1942).

In another study 13% of genital tuberculosis in patient with pulmonary tuberculosis by using endometrial biopsy and laparotomy,
the same authors used laproscopy, hysterosalpingography and endometrial aspiration cytology and culture along with histopathological study their found 24% of genital tuberculosis in patient with pulmonary tuberculosis (Tripathy and Tripathy, 1981).

The mode of infection occurs one by primary infection and secondary infection. The primary infection of genital tract is rare. Secondary infection by hematogenous dissemination from the extra genital primary foci is common one. The initial involvement involves the fallopian tube which is the one involved in 100% of all genital tract tuberculosis. From here the infection spreads to endometrium and ovaries.

Pathology

The pathology is same as other organs. The serosal surface of tubes usually studded with tubercles. In the advanced stage the tubes are markedly thickened and firm, the were adhere to the neighbouring bowels and form pelvic masses. The inner side of the tube contains caseous material.
Clinical features

Genital tuberculosis is very common in the second and third decade. The commonest presentation are infertility, menstrual disturbances, abdominal pain and leucorrhoea or combination of these.

In a study found 5-10% of patients with infertility due to tuberculous endometrities. The commonest menstrual abnormality noticed is amenorrhoea 60% of patients and the other abnormalities are oligomenorrhoea and menorrhagia (Tripathy and Tripathy, 1991).

Tuberculous pericarditis

Before the advent of antituberculous chemotherapy, tuberculous pericarditis was reported to be almost invariably fatal, either in the acute stage or as a result of subsequent constriction (Harvey and Whitehill, 1937).

In almost all countries in which reliable epidemiological data are available, pericarditis is a rare form of tuberculosis for example, were only 0.5% cases among 3002 notifications of tuberculosis in England and males during the first 6 months of 1983.

In marked contrast in Transkei and the surrounding regions of South East Africa it was for many years been recognised as one of the
commonest causes of the clinical picture of congestive heart failure (Schrire 1959; Gelford, 1957). In a current study, 383 cases were diagnosed during a period of 4 years in a population of about 3 million people (Strang et al, 1987).

Fibrocaseous material, blood stained fluid or a combination of the two within the pericardial space interfere with ventricular filling to produce the signs or symptoms. In the transfer study only a small proportion of patients had evidence of concomitant active pulmonary tuberculosis and of seems likely that in the majority of cases infection is blood borne or reaches the pericardium.

Clinical findings

The clinical and radiographic features are often nonspecific and very greatly in severity. They include dyspnoea on exertion and at rest if there is tamponade chest pain, raised JVP (most marked when more in constriction), pulsus paradoxus, tachycardia, hepatomegaly and ascities. Large effusion if the develop slowly may cause circulatory embarrassment. Whereas small effusion if they develop rapidly may cause tamponade an acute clinical emergency characterized in addition to the above features by severe hypotension, a low pulse pressure and poor perfusion of vital organs.
Diagnosis of Tuberculosis

The diagnosis of tuberculous still largely depends upon clinical, radiological and bacteriological evidence (Nassau et al, 1976).

1. Clinical features

The most important clue to the tuberculous disease is contact with a known case of tuberculosis. However, such history is available in only 20-30% of cases (Abdolghader and Jack, 1985). The clinical features of the disease are not specific; the disease is often initially unrecognised particularly because of its relatively low rate of occurrence but also because of the frequent absence of classic clinical symptoms.

2. Radiological evidence

In an economically developed country in which radiological facilities are readily available, in developing countries like ours the facility for x-ray is not available in most of the rural areas (Alka Agarwal and Moudgil, 1989). X-ray findings have been estimated as atypical in more than 30% of patients with tuberculosis in developed countries (Jeffrey et al, 1980). Chest skiagram provides only a probable diagnosis but not the exact diagnosis (Sachan et al, 1994). A normal chest x-ray almost although not completely excludes pulmonary tuberculosis, because small radiological lesions are readily missed (Yerushalmy, 1953; Cochrane and Garland, 1952).
3. **Biological evidence of Tuberculosis:**

This has been further divided as follows by Ayush Gupta et al, 1993.

I) **Direct methods:**

These methods detect either the bacilli or their DNA

a) Bacteriological methods: (1) smear examination and culture method (traditional and radiometric)

b) Techniques of molecular biology. DNA hybridization technique and polymerase chain reaction (PCR)

II) **Indirect methods:**

a) Serology: Methods include Radioimmunoassay (RIA), Latex Agglutination, Circulating Immune Complexes (CIC) and Enzyme Linked Immunosorbent Assay (ELISA).

b) Demonstration of Biological Products: Adenosine Deaminase (ADA) Estimation, Tuberculostearic Acid and Bromide partition test.

The histological examination of specimens obtained by pleural biopsy (Fibroptic Bronchoscopy (FOB), Bronchoalveolar Lavage (BAL), Transabdominal Lung Biopsy (TALB) and Fine Needle Aspiration Cytology (FNAC) can be categorized either into direct (demonstration of bacilli) or indirect method (demonstration of Granulomas etc.)
Smear Examination:

This simple, inexpensive and already in use throughout the world. It cannot be applied to the diagnosis of Extrapulmonary or other forms of tuberculosis in which patients usually do not have positive sputum smears (Daniel, 1990). Sputum is positive for AFB only in the open cases. Moreover sputum examination often gives false negative results if the number of AFB is low. At least 105 acid fast bacilli/ml of the sputum are required for detection on a stained smear (Bates, 1979). The specificity of positive sputum smears is high but not 100% the sensitivity of direct sputum smears are surprisingly limited it is probably in the rate of 25% to 60% (Boyd and Marr, 1975). Aber et al (1980) in general African laboratories sensitivity ranged from 8.8 to 46.4% and specificity from 83.6 to 100%.

Culture method

The culture of myobacterium tuberculosis by traditional methods takes 6-8 weeks of the diagnosis of tuberculosis is delayed, it leads to increased morbidity and in some cases mortality (e.g. Tuberculous meningitis) (Charpin et al, 1990).

The radiometric method (BACTEC) detecting bacterial growth is about a week. Park et al (1984) used this method in 1000 clinical specimens 59 of there were positive for mycobacterium. BACTEC
picked up 55 while culture in LJ medium there were only 25. However more important was that the time taken for detection was significantly less by radiometric method compared to the traditional culture (7 days for smear positive mycobacterium tuberculosis by BACTEC compared to 18 days by LJ media).

But this technique is to expensive and too technologically complex for widespread applications in laboratories is developing countries which a high prevalence of tuberculosis (Jain, 1996).

DNA Hybridization technique

Recent development in the field of molecular genetics of mycobacteria have made it possible to identify particular sequences of DNA that are specific for individual mycobacterial species. Based on this Chia-C-Pao et al (1988) have used a M-tuberculosis probe in 441 uncultured specimens and detected mycobacterial squamous in 30.4% specimens compared to only 19% positivity on culture. The level of detection and specificity of the test depends on the sequence of the probe. However the disadvantage is in term of the poor sensitivity (104 AFB/ml) and high cost.
Polymerase Chain Reaction (PCR)

The polymerase chain reaction can be used for amplification of DNA before nucleic acid probes are used for specific identification. It is a recent and the most sensitive and specific method for the diagnosis of tuberculosis. Noel et al (1989) used PCR in 35 clinical specimens and detected M tuberculosis in 15 specimens 2 more than by smear and culture. Keneko et al (1990) found PCR positive in 5 out of 6 patients with Tuberculous meningitis. However the high sensitivity is its biggest disadvantage as contamination from the environment may give a false positive result as shown by (Shanker et al, 1991). The PCR is not freely available at present. At present time the technology is too complex for application in developing countries.

Adenosine Deaminase (ADA) Estimation

This is an enzyme of purine metabolism. The level of this enzyme is 10 times higher in lymphocytes than red blood cells, and activity is more in T cells than B cells (Nishida et al, 1980). The activity of ADA is related to lymphocyte proliferation and differentiation i.e. it is more in rapidly proliferating and immature lymphocytes. Therefore whenever there is cell mediated immune response to an antigenic stimuli the ADA levels are the highest. ADA is measured by the calorimetric methods of Guisti (1974).
Maritz et al (1982) found that ADA could not distinguish between tuberculous and metapneumonic pleural effusion and this indicating that the test had poor sensitivity and specificity.

Large studies by Malan et al (1984) and Ribera et al (1987) have analysed CSF ADA in tuberculous meningitis patients found that sensitivity is 63-100% but a poor specificity to around 84%. Because of low specificity this test is not very popular.

Tuberculosteric Acid (TBSA)

Tuberculosteric Acid is found in the cell wall of mycobacterium. It also present in Actinomycetes. It is identified by gas chromatography or mass spectrophotometry. It is a costly investigation and requires complex analytical equipment. Larson et al (1979) used it in 6 patients who were smear positive and found 5 of them to be positive for TBSA. Most of the work in this field has been done by French et al (1987) who found a sensitivity of > 95% and a specificity of > 99% in their clinical material. A very high sensitivity and specificity has also found in patients with tuberculous meningitis by French (1987). However due to the complex technique and costly equipment required for the estimation of TBSA is seldom used in the diagnosis of tuberculosis.
Bromide partition test

The partition of bromide ion between serum and CSF after a loading dose reflects the integrity of the blood brain barrier. Either by direct chemical measurement or by using an isotopic tracer, the ratio of bromide in serum to bromide in CSF in simultaneous samples may be estimated. Taylor et al (1954) found value < 1.6 to be characteristic of tuberculous meningitis. In subsequent studies the sensitivity and specificity have been found to be near 90%. However it may be false positive in herpes simplex, hysteria, mumps, measles, pyogenic meningitis and hypothyroidism with the availability of better tests, this test have been given up (Nicol and Fawns, 1958 and Mandal et al, 1972).

Tuberculin Testing

It is of limited value especially in India where due to mandatory BCG vaccination in infancy and very high environmental exposure. Majority of the adults are tuberculin positive. It is however of use as supportive evidence especially when along with the clinical picture either it is strongly positive (induration > 20 mm) and/or there is necrosis or ulceration).

Tuberculin testing has a poor sensitivity and specificity and false negative test is seen in patients with chronic renal failure. Viral infections, malnutrition, sarcoidosis lymphoma. HIV infection
disseminated tuberculosis and patients on steroid or immunosuppressive agents.

**Serology of Tuberculosis**

In view of the problem and limitation of the above mentioned tests and poor accessibility of suitable material for laboratory examination is various extrapulmonary tuberculosis. So there is need for a quick and simple test for the diagnosis of tuberculosis. In such a way serology of tuberculosis developed. The basic principle of the serological tests are either to detect the antigen i.e. some component of the mycobacteria or to detect specific antibody produced by the host as a part of its mounting an immunological reaction to the presence of mycobacteria (Samuel et al, 1985).

Sputum microscopy fails to provide a diagnosis in smear negative patients in children with pulmonary disease as well as extrapulmonary form of disease. For this group a reliable serologic test could provide to be extremely useful.

**Immune Response**

Mycobacterial infections involve multiple infections of bacterial components with the defense system of the host, leading to humoral and cellular immune reactions (Chaparas, 1982).
The cellular response such as the delayed hypersensitivity induced by injection of tuberculin, plays a key role in antituberculosis immunity (Collins and Mackaness, 1970; Youmans, 1975). This is a complex process involving antigen processing, TH lymphocyte stimulation by antigen presenting cells and production of lymphokines, which promote phagocyte activation and half of intracellular bacterial proliferation (Crowle and May, 1981).

**Humoral immune response**

Tuberculous infection produce antibody it plays a secondary role in the host defence against mycobacteria, measuring the antimycobacterial antibody level provides important information about the evolution of tuberculous process (Grange, 1984). Earlier reports indicated that absolute levels of IgG and IgA class of antibodies were elevated in cases with active tuberculosis (Grange et al, 1980). Alarcon-Segovia and Fishbein (1973), Gatner and Anderson, (1980) found that significant range of IgM class during tuberculous infection. Bhatnagar et al (1977) found that only IgA class levels were significantly increased.

Recently IgE antibodies have also been shown to be elevated in patients with tuberculosis (Papiha et al, 1985). Levels of IgA, IgG and IgM were found to be elevated prior to institution of chemotherapy in
Indian subjects, while on therapy levels of IgA and IgG declined in those who responded to therapy but not in those who failed to respond (Singh et al, 1984).

As in other bacterial infections it appears that in response to tubercular infection there is a short lived synthesis of IgM followed by a predominance of IgG antibodies.

**Antigen of M Tuberculosis**

The performance of various serologic tests requires the standardisation of antigens which are to be used for detection of antibody in the most. Preparation of such antigens has been the biggest stumbling block in the field of tuberculosis serology.

Logically the simplest approach would be to use the whole bacillus as an antigen. Good results were obtained by an immunofluorescent test using whole bacillus as an antigen after the surface lipids had been removed by phenol or organic solvents (Nassau and Merrick, 1977). However these tests can only detect those antigens which are expressed on the surface of bacillus.

Old tuberculin (OT) and purified protein derivative (PPD) have been used extensively as antigens in the serodiagnosis of tuberculosis.
There preparations consist of a hundred or more antigens in different stages of denaturation but many important antigens are lost due to autolysis and subsequent autoclaving of the cultures (Harboe, 1981). In an attempt to improve the specificity of skin test, Seibert (1949) obtained 3 protein (A, B and C) and 2 polysaccharide fractions (I & II) by sequential precipitation with acetic acid and ethanol at various concentrations. The protein fractions were found to have contain multiple antigens by immunoelectrophoresis but most of these were shared by both fractions (Daniel and Affronti, 1973).

Since protein molecules have general antigenic determinants (epitopes) it is difficult to prepare pure antigens. Some epitopes are species specific while others are shared among species (Chapars, 1985) and there may both be present on the same molecule, thereby leading to cross reactions. This realisation has led to the search for a single species specific antigen of M tuberculosis, the detection of which may reliably indicate the diagnosis of tuberculosis.

Stanford (1973) demonstrated four groups of soluble antigens in ultrasonically disintegrated fractions of mycobacteria by immunodiffusion. Group I consist of 5 antigens that are detected in all mycobacterial species. Group II consist of 3 antigens which are restricted to the slowly growing species. Group III antigens are present
in rapidly growing species and are 4 in number. Group III antigens are restricted to individual species and vary from 2 to 8 in number depending in the species. Ultrasonicates of M tuberculosis are found to contain 6 group IV antigens and minor variations in the distribution of these species specific antigens occurs as in other mycobacterial species.

**Antigen A60**

This antigen A60 isolated in 1986 by Cocito and Vanlineden. This antigen is a major component of mycobacterial cytoplasm. Antigen A60 is the main thermostable macromolecular antigen family and main component if old tuberculin and purified protein derivative (Harboe, 1981).

Antigen A60 is isolated by excultion chromatography and affinity chromatography by Cocito and Vanlineden (1986) from cytoplasm of M. novis BCG. Antigen A60 was the less mobile polymer in the reference system developed by Closs et al (1980).

It is composed of proteins, carbohydrates and lipids in roughly equal amounts (Fabre et al, 1986) with the molecular weight ranging from 1 to 10 millions and the main component of reference tuberculin (Harboe, 1981).
ELISA

A variety of methods have been employed for detection of antibodies in tuberculosis (TB) sera, directed again a variety of mycobacterial antigens, such as agglutination, precipitation or complement fixation. However most of these assays lacked the requisite sensitivity and/or specificity. Considerable efforts were spent in correlating the clinical status and these tests but to reliable correlations could be established (Popp, 1971).

Recently binding assays that is Radiommunoassays and Enzyme Linked Immunosorbent Assay (ELISA) have replaced the above techniques which employ physical characteristics like agglutination, precipitation etc. These new assays detect the binding of antibody to antigen directly and hence theoretically can detect all kinds of antibodies (Samuel et al, 1983). Radio-immunoassay is highly sensitive but has several drawbacks short half life of reagents, problems of waste disposal requirement of costly equipment for counting radioactivity. On the other hand ELISA is as sensitive as RIA and employs non isotopic label and unless other comes second disadvantages inherent in RIA. Among the serodiagnosis tests for tuberculosis the ELISA is considered the best method (Narayanan et al, 1983; Kalish et al, 1983).
In 1972 Engvall and Perlmann described the highly sensitive and reproducible technique of enzymes linked immunosorbent assay. This technique does not require sophisticated instrumentation, and the reagents that employ it are inexpensive.

Although radioimmunoassays are sensitive and objective they require expensive gamma counting equipment and expose personnel to radiation hazards (Chaparas, 1985). ELISA has also been used in sputum, cerebrospinal fluid in patients with Tuberculous meningitis, pleural and ascitic fluid. The test has also given encouraging results in patients with intestinal tuberculosis and in those with bone and joint tuberculosis. ELISA does not require sophisticated instrumentation and can be used reliably in the field situation in developing countries (Daniel et al, 1986).

ELISA is less extensive, sensitive and technically simple and also it can measure class specific antibodies and the technique requires only minute quantities of serum with additional advantage of quantitating antibodies by testing serum at single dilution (Young et al, 1980). Because of its reproducibility assured has the potentially of providing a powerful tool for intensive tuberculous case finding activity which can lead to successful implantation of tuberculosis control programmers in developing countries (Acharyulu et al, 1987).
ELISA of tuberculosis is a potentially valuable technique (Daniel and Debanne, 1987). In particular the use of antigen A60 provided high diagnostic value than using other antigens (Cocito, 1991).

ELISA in clinical diagnosis

Charpin et al (1990) analysed IgG, IgM measurements by using A60 antigen in 83 patients they found the sensitivity, specificity and positive predictive value of IgG measurements equal to 48%, 81% and 50% respectively. Using IgM measurements these parameters were equal to 76%, 98% and 95% respectively. Combining the results of IgG and IgM measurements, sensitivity, specificity and positive predictive value were equal to 68%, 100% and 10% respectively. Thus the ELISA described here can greatly facilitate the diagnosis of tuberculosis in patients with negative smears.

Raheman et al (1988) by using a dual antigen (Antigen cytosolic fraction from M.tuberculosis and antigen 100 from M.bovis) analysed IgG level in samples of 169 sera found a specificity of 100% and sensitivity of 0.974 while the gain in the certainty of diagnosis was 1.974 only slightly less than the ideal value of 2.00.
In 1989 Maes based on interspecific highly purified antigen 60. The ELISA has been found to be useful and detects either or both IgG and IgM antibodies against mycobacterium. IgM appears initially and IgG appears after about 4 to 6 months of the infection persists or progress. The test is mostly positive with 90% to 95% reliability in cases of active infections of pulmonary and extrapulmonary tuberculosis. Delacourt et al (1993) conclude that antigen A60 IgG measurement is a rapid and low cost technique that enhances the diagnosis of clinically active tuberculosis in children and may distinguish recent infection without disease from infection with disease.

Gupta et al in 1995 analysed IgM, IgA and IgG antibodies against Antigen A60 found that very good sensitivity (91.6%) and specificity (90.0%) of the test when combined IgA and IgG antibody fibres are considered, to detects cases of adult tuberculosis. The role of IgM estimation can be restricted to the detection of cases of reactivation of tuberculosis.

Alifano et al (1996) by using Antigen A60 by ELISA method measure IgG and IgM in 216 subjects 88 healthy volunteers, 44 patients suffering from non tuberculous lung disease and 15 subjects with patients healed pulmonary tuberculosis constituted the control population. 69 patients with active pulmonary tuberculosis were
examined, the sensitivity of IgG test was 73.9% in pulmonary tuberculosis, the specificity of the test was 95.9%, for the IgA test observed a sensitivity of 72.5% and specificity of 93.9%. Combination of the two tests increased the sensitivity to 84.0% the specificity decreased to 92.5%. In conclusion the combined use of evaluation of anti A60 IgG and IgA increases the accuracy of serological diagnosis of pulmonary tuberculosis.

ELISA has also been used in sputum, cerebrospinal fluid in patients with TBM, pleural and ascitic fluid. This test has also given encouraging results in patients with intestinal tuberculosis and in those with bone and joint tuberculosis.

A study conducted by Gandhi et al (1986) in 22 patients of intestinal tuberculosis found to be a sensitive test as it was positive in all 22 patients (100%) with intestinal tuberculosis. It is specificity was 85%. The test is easy to perform and may be recommended for the serological diagnosis of intestinal tuberculosis.

Basker et al (1993) found ELISA test is mostly positive with 90 t9 95% reliability in cases of active pulmonary and extrapulmonary tuberculosis. It has no relation with the BCG vaccination or with the mantoux test reaction.
In a study conducted by Srivastava et al in 1994 in TBM patients the detection of IgG antibodies in CSF and sera found 90% of proven cases of TBM in CSF 75% in sera. In patients clinically suspected to have TBM, antibodies in CSF and sera were present in 87.5% and 70.8% respectively. Whereas in control group antibodies were present in only one serum sample and in none of the CSF samples. So the study concluded ELISA test is a sensitive and specific test for the diagnosis of TBM.

Stroebel et al (1982) by using ELISA test analysed mycobacterial antibody level in patients with bone and joint tuberculosis. They found the sensitivity of the assay is 94% and the specificity was 100%. So they concluded that ELISA test is not only sensitive enough but also specific enough to be used for the rapid serodiagnosis of extrapulmonary infection due to M.Tuberculosis.

Wilkins and Ivanyi (1990) mycobacterial antibodies by using ELISA in various form of extrapulmonary tuberculous patients the result showed positivity 70-80% unrelated to the organ localization of the disease. They also concluded that serological test would have obviated the need for the majority of biopsies and allowed to start chemotherapy at the earliest. They also found it could also have prevented the treatment
of 14 of the 15 patients inappropriately treated tuberculosis. Fadda et al in 1992 ELISA assay based on A60 from M.Bovis BCG was used to quantitate specific antimycobacterial antibodies in 250 sera from 133 subjects. 90 Tuberculosis cases and 43 controls were negative suggesting the specificity of this assay. In subjects with secondary pulmonary tuberculosis a correlation was observed between the antimycobacterial antibody and culture positivity. In fact positive ELISA assays were found in 88.8% of patients with positive cultures for M.tuberculosis and in 45% of culture negative tuberculosis patients under therapy. According to this results the A60 ELISA assay useful in monitoring the efficacy of antimycobacterial drugs. In pulmonary tuberculosis cases with positive cultures for M.tuberculosis higher levels of specific antimycobacterial IgG were found after therapy.

Kalish et al in 1983 using ELISA test then analysed IgG antibody in patient with active pulmonary tuberculosis and non tuberculosis pulmonary disease. They found ELISA test to distinguish patients with active pulmonary tuberculosis from patient with other non tuberculous pulmonary disease.

Sachan et al in 1994 estimated Antigen A60 specific IgG levels were determined by ELISA method in 66 pulmonary tuberculosis patients and 32 healthy individuals. The bacillary content of sputum and
radiological extent of the disease were found to be correlated with the IgG varies at the time of initiation of chemotherapy and after 6 months of therapy. They found to have a significant fall in the IgG levels in pulmonary tuberculosis patients after 6 months of chemotherapy. So it can be used for follow up of the response of therapy.

The ELISA test study as mentioned above found to have very sensitive and used for rapid diagnosis of tuberculosis. However latter on found that it has some disadvantages. The increased sensitivity has shown that almost every way has detectable antibody to M.Tuberculosis, so it is diagnostic potential is limited. Undan et al in 1992 found that detection of IgG antibodies against antigen A60 has 67% sensitivity, 90% specificity and 81% positive predictive values. It has been decided that these values have no superiority compared to the sputum examination. It was also found that sensitivity of antigen A60 ELISA IgG test is very low (22%) in the condition of primary preliminary tuberculosis cases where direct sputum microscopy sensitivity is also very low.

The lack of specificity was thought due to use of Crude antigen. Subsequently within the advent of improved technology purified antigen are used for to increase the specificity. Varies purified antigen are used to improve the sensitivity. However Daniel and Debanne (1987)
found that irrespective of the type of antigens ELISA test and other assay could not detect more than 95% of the patients.

In an Indian study conducted by Chanderasekaran et al (1996) found that by using A60 antigen based on ELISA the sensitivity, specificity and accuracy were 48.3%, 92.0% and 71.3% respectively. They also found that there is a significant overlap of antibody levels between patient and control groups has been observed in their study (8.5 to 16%) and almost 50% of the smear positive show low antibody levels there can be motility of these serodiagnostic test as the diagnosis of pulmonary tuberculosis. So they concluded that these test till needs an extensive evaluation and it should be interpreted with caution.

With this background this study has been undertaken to find out the Diagnostic Utility of the ELISA test for detection of antimycobacterial IgG and IgM in human tuberculosis.