INTRODUCTION

Tuberculosis is a chronic bacterial infection caused by two species of bacterium *Mycobacterium tuberculosis* and rarely by *Mycobacterium bovis* characterised by the formation of granulomas in infected tissues and by florid cell-mediated hypersensitivity. In the absence of effective treatment, a chronic wasting course is usual and death ultimately supervenes in most cases.

In the 16th century, Frascatorices first postulated that tuberculosis was caused by small particle, the *Contagium vivum* which could be carried in the air from person to person. Not everyone, however, believed that tuberculosis was a communicable disease, and there was strong support for the alternative theory that heredity was the main causative factor. But subsequent generations of physicians from Galen onwards, confirmed that persons who had been in close contact with consumptive often developed the same illness. Finally Robert Koch applied himself to this task and in 1882 the elusive microbe was identified. No other disease has challenged and occupied the greatest minds in medicine and science from Hippocrates through Koch to an unprecedented degree. This disease currently remains the largest single infectious cause of death in the developing countries. Approximately one third of world's population is infected with *M. tuberculosis* and is at risk to develop the disease. The vast majority of people suffering from tuberculosis live in developing countries and it is the cause of almost one fifth of all deaths in adults, one fourth of all available deaths and approximately 7% of all deaths in developing countries.

M. tuberculosis is generally always initiated by inhalation of infected material, rarely by ingestion and more rarely by cutaneous inoculation (Prosector's wart). The number of bacilli excreted by most infected persons is no large; however, patients with laryngeal tuberculosis, endobronchial disease, recent transbronchial spread of tuberculosis and extensive cavitary pulmonary disease are often highly contagious. Infectiousness correlates with the number of organisms in the expectorated sputum, extent of pulmonary disease and frequency

of-caugh. Most-patients become noninfectious within two weeks after the institution of appropriate chemotherapy.

The usual infecting inoculum is not more than one to three organisms which reach the alveoli. They are then ingested by macrophages and transported to the regional lymph nodes which can be identified as pulmonary tuberculosis. It may be minimal infiltrate to extensive cavitation. If spread of the organism is not contained at the level of regional lymph nodes, then tubercle bacilli reach the blood stream and wide spread dissemination ensues. Disseminated tuberculosis may result in miliary or meningeal tuberculosis. Miliary tuberculosis is apt to be more culminating in children than in adults. Lesions develop synchronously throughout the body. The appearance of these lesions suggested millet seeds; hence the name miliary tuberculosis. The leptomeninges are relatively frequently seeded by organisms which disseminate during primary infection. Pleurisy with effusion results when the pleural space is seeded with *M. tuberculosis.* There are different types of extrapulmonary tuberculosis involving different organs like kidneys, bones, meninges etc.

There are two stages in which the infection may cause clinical disease

1. Primary tuberculosis in which the tubercle bacilli invade a host, having no specific immunity; at this stage the disease most commonly heals spontaneously, but it may progress to clinical disease if immune mechanism fails.
2. Post primary or adult tuberculosis (often erroneously called 're-infection tuberculosis') which is the result of progress of infection years later in spite of specific immunity.

In 1993 WHO declared tuberculosis as a global emergency. Teeming millions are groaning today under the relentless ravage of tuberculosis. In developing countries like India especially North Eastern part of India, enjoying no exemption. The Pulmonary tuberculosis (PTB) in Gurkhas has been reported to be higher as early as in 1964 (Large). The etiology of the disease is very well known. It is due to the tubercle bacillus *Mycobacterium tuberculosis* the one of more than 30 well- characterised and many unclassified member of the genus *Mycobacterium.* The clinical presentation of the disease depends on the host immune response to the offending agents. But what is not clearly understood

that infection with *M. tuberculosis* does not necessarily develop overt tuberculosis. It can infect a host and then be immediately eliminated (no infection), become dormant indefinitely inside the host (latent infection) or cause disease soon (primary tuberculosis) or many years (reactivation tuberculosis) after the infection. Only a small portion of individual infected with *M. tuberculosis* develop disease and most of those infected remain disease free. Following *M. tuberculosis* infection of the immunologically normal host, there is a 5% risk of developing tuberculosis during the first year and a 5% additional risk spread over the lifetime of the host (Centre for Disease Control, 1992).

After a continuous decline for over 70 years, in the mid 80's tuberculosis emerged in epidemic form hastened by the onset of AIDS. WHO predicts 90 million new case of tuberculosis will occur between 1990-2000. 30 million people are expected to die of tuberculosis by the end of this decade. Aging, diseases such as diabetes mellitus and HIV infection, and our socio-economic condition are some of the factors which are responsible for weakening the immune system of the infected individuals and tip the balance in favour of microbe. Unravelling this is of great importance both for understanding the immune mechanisms in PTB and developing future immunological strategies to control it, especially on the face of emergence of drug-resistant forms of the bacillus.

The unique feature characterising human tuberculosis is its pathogenesis. The pathogenesis of tuberculosis involves cell-mediated immune responses against *M. tuberculosis*. The cell involved in tuberculosis immunology and pathogenesis include mainly T cells (α/β, γ/δ, CD4, CD8), macrophages and secondarily B cells. T cells play a crucial role because they constitute the element which trigger the subsequent immune events. Tuberculin skin testing is the simple method to see whether an individual is infected and sensitized with *M. tuberculosis*, is clearly a proliferation of T cells subsets. In patients with PTB, PPD skin test are negative at the time of diagnosis in 20-25% of cases. Even when the reactions are technically positive, there often barely exceed the cut point.

Hypergammaglobulinemia is a well described concomitant of tuberculosis.

So, we can't ignore the role of B cells also. Tuberculosis pleurisy also presents an interesting phenomenon from an immunological point of view.

The role of genetic factors as determinants of the risk of tuberculosis has been established in humans by virtue of twin studies and in murine models by cloning of the gene for BCG resistance. The Human Leucocyte Antigen (HLA) is a group of genes where lurk some crippling diseases like ankylosing spondylitis, SLE, rheumatoids arthritis, tuberculosis and may be many other diseases which are still in dark.

HLA, the small part of chromosome number 6, comes in two stretches, called Class I and Class II. The class one antigen consists of 3 loci HLA-A, B and C. Antigen defined by these loci are expressed mostly on the cell membranes of leucocyte. The Class II loci specifies antigen on B cells.

T cell response to proteins is directed against different epitopes of an antigenic protein. The T cell will target which epitope of the antigen depend upon the gene product of the patient through Ir genes (Beneceraff *et al*, 1972). So an exact definition of the influence of HLA- linked genes is delineation of T cell mechanisms is of critical importance. In the context of how to protect people against infection with *M. tuberculosis* and /or against developing tuberculosis, Bacillus Calmette Guerin (BCG) remains the controversial of all the currently used vaccines. If we can characterise that particularly which protein (antigen) could draw out a strong cell mediated immune response (CMI) that may be a better candidate for vaccination. While characterising a protein for T cell activity, it is important to consider the context of HLA phenotype of the subject concerned.

Reference study reveals that there is no one or two gene products which are universally responsible for the disease and moreover, not a single datum is available on the HLA antigen frequencies in the population of Eastern and North Eastern India.

Justifications for taking this study :

1. According to the report of WHO tuberculosis is an epidemic in the Eastern -Hill Region of India specially Darjeeling district.

2. Incidence of the disease is fairly high (in a survey conducted by the author)
3. The population studied consisted of many endogamous, inbreed caste groups with desperate genetic make up, both in anthropological, anthropometric and HLA polymorphism.

Thus it is appropriate to study a population which is an admixture of different major groups and wherein most of the individuals have been exposed to tubercle bacilli. Furthermore, the knowledge of HLA association promise new ways of treatment when the era of molecular medicine arrives.

In view of the above in the present investigation different parameters have been studied.

1. To evaluate the association of HLA Class I and Class II antigens in the patient with pulmonary tuberculosis and their various clinical groups and pleural effusive patients;
2. To understand the role of T cells/macrophages in the pathogenesis of pulmonary tuberculosis;
3. To investigate the incidence of the types and sub-types of lymphocytes of pleural effusion;
4. To evaluate the degree of antibody mediated immune response by quantitative estimation of immunoglobulins like IgM and IgG; and
5. To evaluate the degree of cell mediated immune response *in vitro* by using PHA.