INTRODUCTION
Introduction

Tuberculosis is an ancient disease which causes human sufferings and carries a social stigma because of its prevalence in underprivileged populations of the developing world. Recent upsurge of tuberculosis in American cities however suggests that *Mycobacterium tuberculosis*, the causal organism of tuberculosis, is omnipresent and may infect people in developing as well as developed countries. This organism is a slow-growing acid-fast bacillus transmitted primarily by the respiratory route. It can cause disease in most organs, but pulmonary tuberculosis is most common. It is believed that *M. tuberculosis* invaded the human population from cattle during the domestication of farm animals approximately 10,000–15,000 years ago. Accounts of tuberculosis can be found in the writings of the ancient Egyptians and in those of the Greek physician Hippocrates. Remnants of the disease have been found even in mummies dating back to 3700 BC.

*M. tuberculosis* infections are acquired through inhalation of infective bacilli. Once in the lung, the bacteria are internalized by alveolar macrophages. If the alveolar macrophages fail to kill the bacteria, the bacteria may lie dormant or grow inside the macrophages, thus starting infection foci. The success or failure of the infection is determined at the level of the macrophage that acts as the host cell for the microbe. The bacterium enters the host macrophage by phagocytosis and, instead of being delivered to lysosomes and digested, the bacterium arrests the normal progression of its phagosome to endosome. On the other hand, recruitment of macrophages and lymphocytes to the site of infection by the host immune system builds the granuloma that prevents the spread of infection. While granuloma prevents metastasis of the infection, it also protects the bacterium from the immune response and is probably responsible for the persistence and therefore latent nature of the infection. Clinical disease develops when this immune-mediated restriction is abrogated as a result of immune suppression, often years after the primary infection. At
Introduction

this time, the granuloma caseates and spills its contents into the lungs, and is transmitted as an aerosol generated by coughing.

These observations raise certain pertinent questions: what is the difference between the response of those who succumb to disease and those in whom the infection remains dormant? Again, why the immune response against *M. tuberculosis* is capable of containing the infection but not abrogating it?

It is quite evident that *M. tuberculosis* has developed mechanisms for evading elimination by host immune system. Thus, it is crucial to understand the key elements of host immune system which determine the development of protective immunity as well as about the ways and means adopted by the bacteria to evade them in order to design new strategies for prevention and treatment of tuberculosis.

The aim of the present study is to characterize the changes that take place in the macrophages immediately after infection with *M. tuberculosis*. A great number of animal experimental models have been proposed to investigate the mechanisms involved in the host response against this intracellular pathogen. Studies of airway infection in guinea pigs and rabbits, as well as in mice intravenously infected with *M. bovis* BCG or *M. tuberculosis* have made an important contribution to our understanding of the virulence, pathogenesis and the immunology of mycobacterial infections. But very little is known about the initial inflammatory process induced by the first contact with the Mycobacteria and the relevance of leukocyte which accumulated at the site of infection. In the present study we investigated the early changes that took place after intra-peritoneal administration of *M. tuberculosis* in C57/Bl6 mouse. Leukocytes, which accumulated in
response to \textit{M. tuberculosis} in first 48 hours, have been characterized. Early changes occurring in \textit{vivo} have been compared with the changes occurring in response to \textit{M. tuberculosis} in peritoneal leukocytes in cell culture. Taken together these results define the direct effects of \textit{M. tuberculosis} on various leukocyte sub-populations, as well as the changes that occur in \textit{vivo}, reflecting overall effect of migration pattern of leukocyte population and interplay of various soluble factors produced in response to \textit{M. tuberculosis}. 