INTRODUCTION AND HISTORICAL PERSPECTIVE

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Various microorganisms have evolved specialized, and in many cases, unique mechanisms for evading host defenses. For organisms such as pneumococci and Haemophilus, the presence of a capsular coat allows the organism to evade phagocytosis and multiply unchecked in the extracellular fluid. The ingestion of the pneumococcus by the pursuing polymorphonuclear leucocyte (PMN) results in the subsequent death of this pathogen in the hydrogen peroxide-filled atmosphere of the phago-lysosome. Minute amounts of antibody directed towards the antigenic determinants of the capsular polysaccharide render the pneumococcus an easy target for the PMN. Thus, excellent protection against Streptococcus pneumoniae infection is provided for non-immune animals receiving injections of immune serum.

In the case of the "intracellular pathogens," the topic of the symposium on which this volume is based, there is a much different situation. These organisms are in many cases inadequately handled by the PMN, the body's first line of defense, and infection results in a mononuclear cell infiltrate characterized by lymphocytes and macrophages. Even these cells, a second line of defense, may prove inadequate to contain the bacterial invasion. Max Lurie, in his classic experiments on immunity to tuberculosis, used the anterior chamber of the rabbit eye as his culture vessel (1). When he injected Mycobacteria into the eye chamber of a normal rabbit along with macrophages obtained from a second normal rabbit, the bacilli were phagocytized. Instead of being killed, the organisms found the intracellular environment conducive to their growth. How these facultative intracellular pathogens manage to escape the onslaught of the macrophage armamentarium of enzymes, peroxides and superoxides is still a topic of much active investigation.
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Studies on the mechanism of immunity to intracellular pathogens remained largely unclarified during the first half of the twentieth century, as numerous investigators were unable to transfer immunity to the tubercle bacillus with serum. Yet, it was recognized as far back as 1891 by Koch (2) that infection with \textit{M. tuberculosis} sensitized the host to give a delayed-type hypersensitivity reaction to culture filtrates of the organism. Von Pirquet (3) recognized that other infectious agents could stimulate similar kinds of skin reactions and referred to them as the allergy of infection. It was noted that this type of "allergy" was different from other hypersensitivities which occurred in closer temporal sequence to application of the elicitin. Yet, the immunologic basis for this characteristic reaction was unknown until 1945, when Chase (4) was able to transfer tuberculin hypersensitivity in guinea pigs with peritoneal exudate cells. This observation laid the foundation for a concept of "cellular immunity" in which immune reactivity resided in cells, but not in serum. Considerable confusion reigned concerning the mechanisms involved, and popular concepts attributed the immunologic specificity of the reactions to cell-bound antibodies. Furthermore, the relationship between delayed hypersensitivity and immunity was hotly debated (5).

A major conceptual advance came in 1964 when Mackaness carried out a remarkable series of \textit{in vivo} studies using several bacteria, all of which had the capacity to grow in macrophages (6). These included \textit{Brucella}, \textit{Listeria}, and BCG, the attenuated \textit{Mycobacterium}. He showed that at various stages of infection with one of these organisms there was cross-protection against one of the other organisms which was antigenically unrelated. Furthermore, the onset of immunity correlated with the ability to elicit delayed hypersensitivity. In a most cleverly designed experiment he tested the ability of \textit{Listeria monocytogenes} to grow \textit{in vivo} in 1) groups of mice which had received BCG 14 weeks earlier; 2) those which had received the primary BCG infection but were given a second injection of BCG 3 days before the \textit{Listeria} infection; or 3) control mice. He found that growth of \textit{Listeria} was inhibited only in the animals which had received both doses of BCG. The hypothesis was formulated that there was a requirement for an antigenically specific elicitation of immunity to one intracellular pathogen, which could manifest itself as nonspecific resistance. The immunological mechanism behind these observations was clarified in 1969 by Mackaness (7), who proposed that specifically sensitized lymphocytes could activate macrophages to express nonspecific, enhanced bactericidal properties. David (8) and Bloom and Bennett (9) had already demonstrated \textit{in vitro} that lymphocytes sensitized to antigen, could elaborate soluble factors, when re-exposed to the antigen that caused inhibition of macrophage migration. Furthermore, it was recognized that the ability of lymphocytes to generate the factor was immunologically specific, and correlated with the ability of the donor animal to give a