IMMUNOLOGICAL REACTIONS
IN LEPROSY

THESIS

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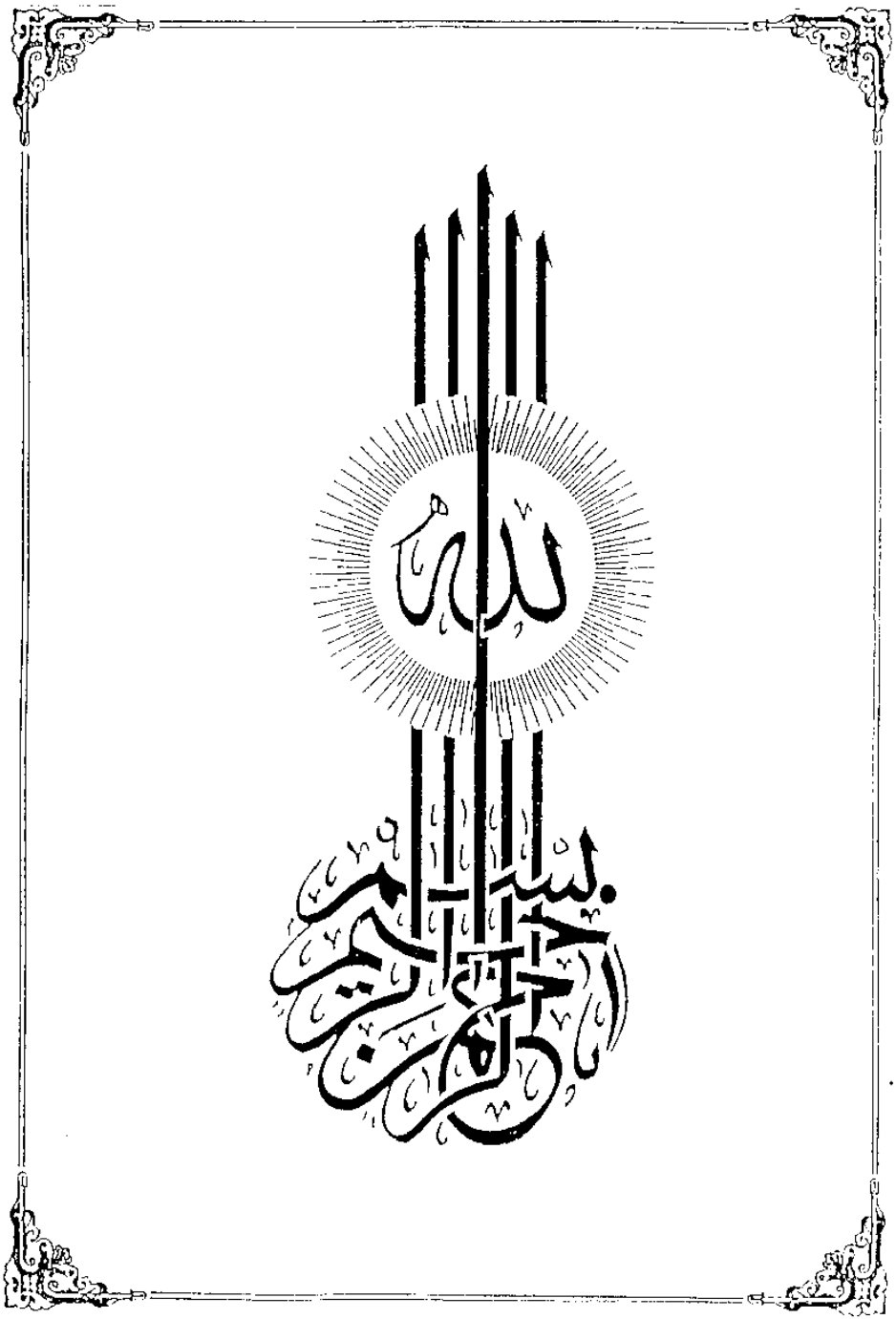

INTRODUCTION

Leprosy is a chronic wasting, contitutional, transmissible disease, characterized by certain well-recognized pathological and clinical manifestations . The disease is a slowely progressive bacterial infection caused by Mycobacterium leprae. It mainly attacks the skin, nerves , mucous membranes and some other organs. Moreover it shows a wide range of variation in morphology from patient to another.

Leprosy may to a great extent be described and considered as an immunological disease. When the defense acts properly,the individual will not show any clinical symptoms after infection. If resistance is inadequate the bacilli multiply with development of clinical disease, so , most symptoms of the disease are caused by immune reactions against various components of the bacillus.

Many factors as movement of population from country to country, and from rural areas to towns as well as the overall increase in endemic leprosy are bringing the disease into notice.

Leprosy is placed in the group of infectious disease in which the rate of transmission of the infecting agent is

very significantly higher than the disease attack rate. The most important factor in the transmission and progress of leprosy in subjects exposed to infection is the efficiency of the defence mechanism of the body especially the immune mechanisms which depend on many factors such as genetic, goegraphical, nutritional, climatic and racial , so the aim of this review is to illustrate the immunological reactions of leprosy.

HISTORICAL REVIEW

Leprosy a chronic contagious granulomatous disease primarily affecting the peripheral nervous system with secondary involvement of skin, mucosa of mouth and upper respiratory tract, reticuloendothelial system, eyes, bones and testis, (Jopling and Harman, 1979).

Leprosy is an ancient disease and has been the dread and horror of human-race for many centuries. The existence and spread of leprosy in the ancient times is difficult to determine .

Historically, the first full accounts of various forms of leprosy in the Far East came from India (Dhramendra, 1960) . They may have originated as early as 600 B.C. They described different kinds of skin lesions as well as peripheral nerve damage. The next records are of slightly later date from china (Cochrane, 1964).

Leprosy was known to the ancient Egyptians (El-Agad, 1979 and Awad 1979). The ancient Egyptian name of leprosy is " Khanso ". The disease was described in the Ebres papyrus. The date given was 1500 B.C. (Yeoli, 1955).

Opinions still differ widely as to the exact meaning of the " Leprosy" in the old and New testaments (Cochrane,1964).

In the Hebrew " Isaraath " scaly lesions on skin, cloth, leather or the walls of houses are associated with vitual defilement. Some of the references in the old testament may possibly have been to true leprosy, and the"lepra" of the New testament probably was the disease, for by that time elephantiasis Graecorum was known in the Midaterrenean Littoral.

In the Western world,no identifiable clinical descriptions of leprosy are known prior to the third century B.C., when its nodular form (Lepromatous type) were to be known to the physicians of Alexandria under the name elephantiasis, what Hippocrates and other ancient scholars called "lepra" was on undefined and non specific eruption of the skin. Andersen (1969) has suggested that the troops of Alexander The Great, returning from the India compain in 327-326 B.C., must have brought leprosy back with them. Pompey's soldiers returning from Egypt (62 B.C.) are said to have brought leprosy to Italy, and there are suggestions that Nubian

slaves had previously taken it with them into Egypt.

While the ancient literary allusions are often vague or misleading, definite evidence is provided by skeletal remains in which the typical bony erosions due to leprosy are seen in the nasal spine and alveolar process of the maxilla, and the first osteological evidence comes from Egypt, in a coptic mummy of the 5th century of our era (Cochrane, 1964).

According to Cochrane (1964) , leprosy reached its height in Europe between A.D. 1000 and A.D. 1400. The last outposts of leprosy in Europe were in Norway, a century ago. This decline of leprosy in Europe remained a historical puzzle.

Central and South America may have been free from leprosy before the Spaniards and Portuguess introduced it in the 16th century (Cochrane, 1964).

We are still ignorant of how leprosy has spread and of the reasons of its curiously uneven distribution from country to country , nor do we know for certain why leprosy has declined or disappeared in known foci in recent years.

THE IMMUNE RESPONSE

When an antigen enters the body, two different types of immunological reactions may occur :

The synthesis and release of free antibody into the blood and other body fluids (humoral antibody). This antibody acts for example by direct combination with, and neutralization of bacterial toxin, by coating bacteria to enhance their phagocytosis and so on.

The production of " sensitized " lymphocytes which have antibody-like molecules on their surface (cell-bound antibody). These are the effects of cell-mediated immunity expressed in such reactions as the rejection of skin transplants and the delayed hypersensitivity to tuberculin seen in individuals immune to tubercle infection (Roitt, 1977).

Primitive lymphoid cells from the bone marrow appear to be deferentiated into two small lymphocyte populations :

1. T-lymphocytes, processed by or in some way dependent on

the thymus, and responsible for cell mediated immunity .

2. B-lymphocytes, bursa-dependent, and concerned in the synthesis of circulating antibody (Roitt , 1977).

Both lymphocytes populations on appropriate stimulation by antigen proliferate and undergo morphological changes.

The B-lymphocytes develop into the plasma cell series the mature plasma cell is actively synthesizing and secreting antibody and has a well developed rough surfaced endoplasmic reticulum characteristic of a cell producing protein for export (Roitt, 1977).

T-lymphocytes on the other hand, transform to lymphoblasts which in the electron microscope are seen to have virtually no rough-surfaced endoplasmic reticulum although there are abundant free ribosomes, either single or as polysomes. These cells are concerned with the synthesis of their own components but do not secrete appreciable amounts of free antibody .

This high ribosome content makes them basophilic so that they show superficial resemblance to plasmoblasts in the

light microscope. However, no antibody can be detected in their cytoplasm using immunoflurescent methods (Roitt, 1977).

Cell-Mediated immune response :

The existance of the delayed -type hypersensitivity or cell-mediated immune responce has been known since the time of Jenner and Koch, but appreciation of its importance in disease, and perhaps more significantly in health, has only recently became possible. For many years, cell-mediated immunity has been associated with resistance to certain bacterial, mycotic and viral infections especially intracellular parasites.(Mehra and Bloom, 1979).

Another suggested role for the delayed-type hypersensitivity response, perhaps its primary function, is "surveillance", i.e. the rejection of cells in the body antigenically altered by neoplastic events (Thomas, 1979). Support for these possibilities came from many experiments but ,perhaps most impressively from the study of these conditions of man in which there was deficiency or suppression of this

immune response (Peterson et al., 1966 and Blaner, 1970) In addition, the cell-mediated immune response serves as the principal obstacle to successful organ and tissue transplantation as well as being involved in the pathogenesis of a number of autoimmune diseases of man and experimental animals (Bloom, 1971).

Katz and Benacerrof (1972) mentioned that T-lymphocytes when stimulated by an antigen, respond on one hand, by a clonal expansion and differentiation, and on the other hand by being activated to perform their specific function i.e., target cell killer, helper cells, etc.

Sensitized T-lymphocytes have been shown to produce more than one biologically active molecule when incubated with a specific antigen in vitro. One of them is migration inhibition factor (MIF) which acts on macrophage at least to prevent their normal imigration from a capillary tube (David, 1966). There are other factors produced by sensitized T-lymphocyte.

These factors are :-

- Interferon (Wheelcock, 1965).

- Blastogenic factor or mitogenic factor (Dumonde et al., (1968).
- Transfer factor (Lawrance, 1969).
- Complement (Permlann et al., 1969).
- Skin reactive factor (Turk, 1969).
- Chemotactic factor for monocytes (Ward et al., 1969).
- A factor highly cytotoxic to cancer cells (Dunmand et al., 1969).
- Proliferation inhibition factor and cloning inhibition factor , which inhibit proliferation of cultured cells (Good and Park, 1974).
- Osteoclast activating factor (Thaler et al., 1977) .

Production of MIF :

David et al.,(1964 b) found that when small numbers of peritoneal cells from sensitive guinea pigs(2.5%) where admixed with normal peritoneal cells, they were capable of inhibiting the migration of the mixture. Later, Bloom and Bennett in 1966 tried to find which cells type was responsible for this inhibition of

of migration in vitro. Thus, peritoneal exudate from tuberculin hypersensitive guinea pigs were separated into their component types, macrophage population of 0.5% or greater homogeneity and lymphocyte populations of greater than 94% purity.

They found that purified macrophages obtained from sensitized animals were not inhibited by purified protein derivatives (PPD). In contrast, purified peritoneal lymphocytes from the same exudate were able to inhibit the migration of normal macrophages. In these studies as few as 1%. sensitized lymphocytes were sufficient to inhibit the migration of population of normal unsensitized macrophages. Thus, in this system the lymphocyte possess the immunological information, the macrophage serving as an indicator cell that migrates. Macrophages did not seem to have specificity in this system. The fact that so few sensitized lymphocytes were able to inhibit the migration of normal macrophages suggested that this inhibition was not likely to be mediated by a direct lymphocyte- macrophage cytotoxicity but related by a soluble material elaborated by the lymphocytes .

To investigate this possibility, purified populations of sensitized peritoneal lymphocytes were incubated with or without PPD for various periods of time. After removal of the cells the supernates were used as the chamber media to study the migration of normal peritoneal exudate cells. It became clear that sensitized lymphocytes, upon interaction with specific antigen (PPD) elaborated a soluble factor which inhibited the migration of normal macrophages(Bloom and Bennet, 1966) . At the same time, David (1966) found that supernatants of sensitized lymph node lymphocytes cultured with specific hapten- protein conjugates were able to inhibite migration of normal macrophages. Similar results were obtained by Svejcar et al., (1967) ,Dunmonde (1967) and by Dunmonde et al.,(1968) in the capillary system.

The factor responsible for mediating this reaction in vitro was termed " migration inhibition factor " or MIF. This factor was detected as early as 6 hours after the lymphocytes were stimulated with PPD (Bennett and Bloom, 1967 ; Svejcar et al., 1969) and production continued for 4 days with daily changes of medium, suggesting continuous