MONOCYTE FUNCTION IN PATIENTS WITH LIVER CIRRHOSIS ITS RELATION TO URINARY TRACT INFECTION

Thesis

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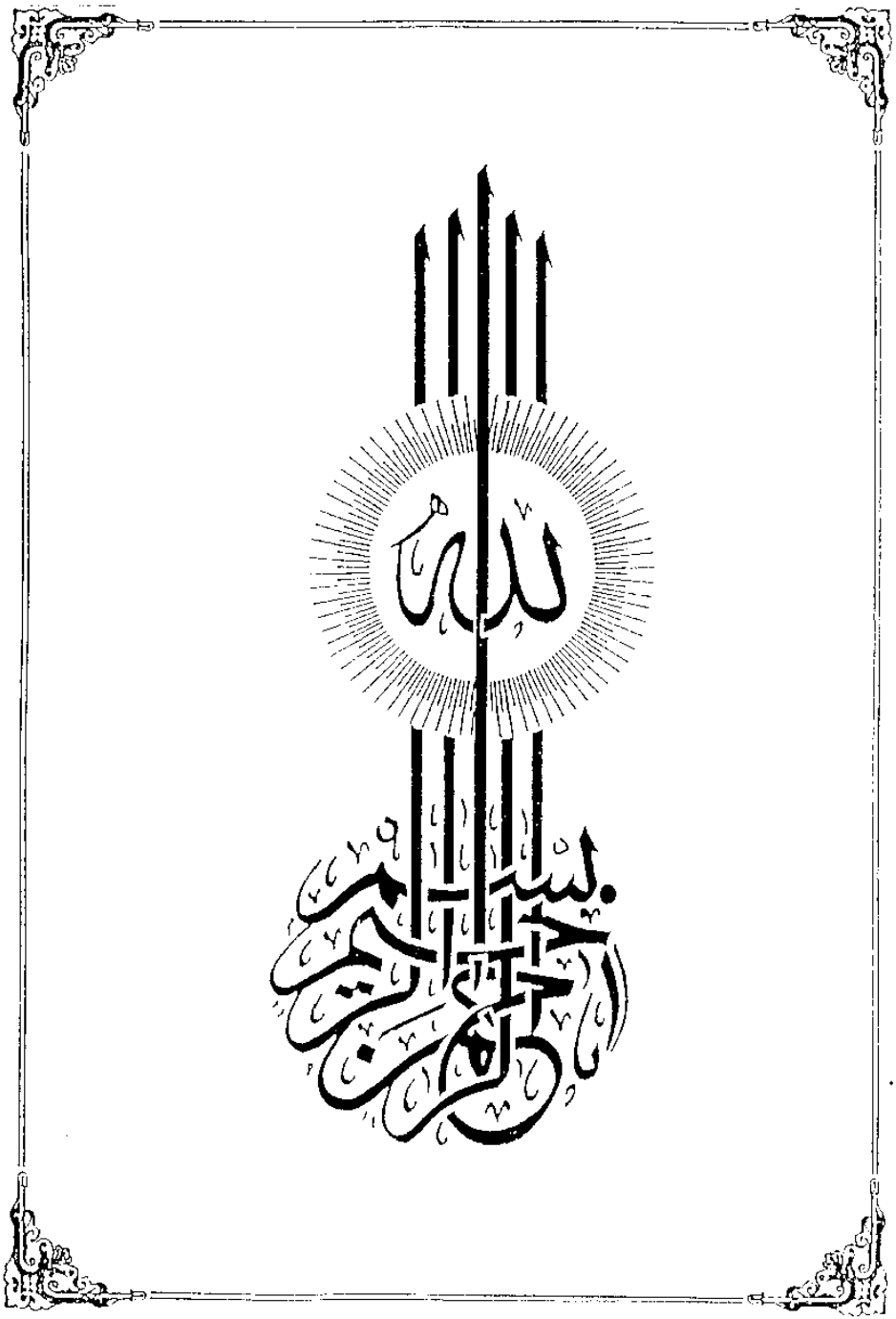

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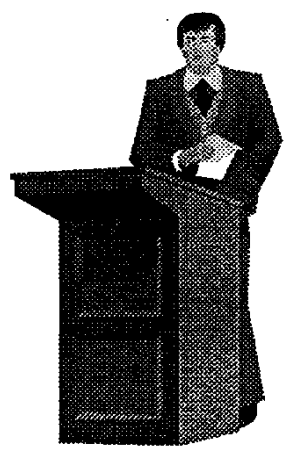


INTRODUCTION AND AIM OF THE WORK

Bacterial infection is responsible for up to a quarter of the deaths of patients with liver cirrhosis, either directly due to the infection or by precipitation of encephalopathy, gastrointestinal haemorrhage or renal failure **(Gerg-Holdstock et al., 1982)**.

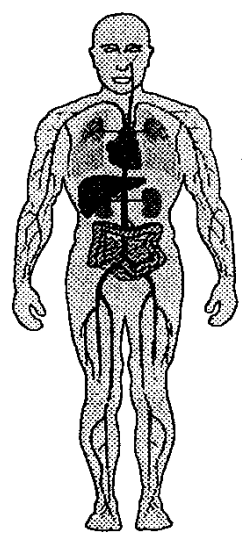
The renal infection occurs in up to 40% of patients admitted to hospital with cirrhosis especially patients with impaired monocyte macrophage function **(Rimola et al., 1984)**. This is because monocytes have several roles in defence against infection including chemotaxis, phagocytosis, intracellular killing and secretory functions which include the production of complement factors **(Hassner et al., 1981)**.

Renal infection has been implicated as the source of bacteremia and of episodes of spontaneous bacterial peritonitis.

Aim of the Work

The aim of this work is to study the monocytes functions in patients with liver cirrhosis in relation to urinary tract infection.

REVIEW OF LITERATURE



REVIEW OF LITERATURE

Monocytes and Macrophages

The work of Metchnikoff with wandering mesodermal cells in starfish larvae established the existence of specialized host cells adapted to serve a protective role through ingestion and removal of invading micro-ogranisms **(Metchnikoff 1884; Chernyak and Tauber, 1988)**. In mammals, the phagocytic cells of Metchnikoff exist as neutrophils and macrophages. The latter are extraordinarily versatile cells that play a central role in specific immunity as well as in non-specific aspects of host defence. In the specific immune response macrophages present antigen to lymphocytes and serve as supportive 'accessory' cells to lymphocytes, which is accomplished at least partly through release of soluble factors. Their capacity to ingest and kill invading micro-organisms is fundamental to their non-specific protective function, and they release an enormous number of factors involved in host defence and inflammation. This broad array of essential functions places macrophages at the centre of the contemporary concept of immunity.

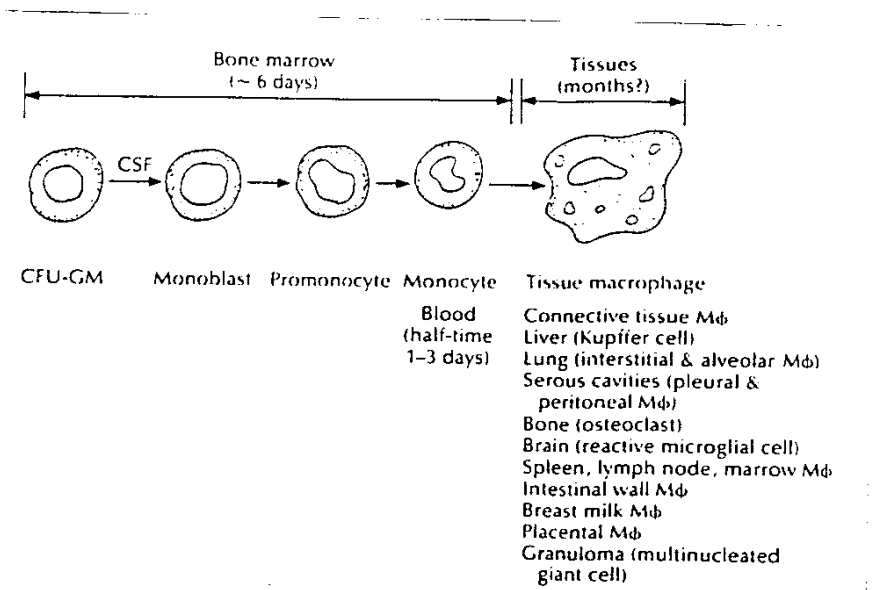


Fig.1: Sequence of the development of cells that comprise the mononuclear phagocyte system. CFU-GM, colony forming unit, granulocyte-monocyte; CSF, colony-stimulating factors; and Mo, macrophage (Johnston, 1988).

General Aspects and Development (Fig.1)

The macrophage and its precursors within the same cell lineage, as distributed throughout the body, are conceptualized as making up a physiological system. The cells comprising this 'mononuclear phagocyte system' include promonocytes and their precursors in the bone marrow, monocytes in the circulation, and macrophages in tissue **(van Furth et al., 1979)**. That these cells do, in fact, comprise a legitimate 'system' depends on their common origin, their morphology, and their common functions, including phagocytosis at a fast rate and through receptors for IgG and major fragments of the third component of complement, C3. The term mononuclear phagocyte system has generally replaced 'reticuloendothelial system', which is believed to be inadequate in the light of present knowledge. However, preference for the former term should not exclude a possible role in host defence for reticular cells, which have been postulated to give structure to the lobules of the splenic filtration beds and to control the blood flow through these beds **(Weiss, 1989)**.

The cell line originates in the bone marrow as a common committed progenitor cell for the granulocyte and monocyte-macrophage pathways - the colony-forming unit, granulocyte-monocyte (CFU-GM) **(Groopman and Golde, 1981)**. Glycoprotein hormones termed colony-stimulating factors (CSF), particularly granulocyte-macrophage-CSF

(GM-CSF), macrophage-CSF (M-CSF) and interleukin (IL-3) **(Metcalf, 1991)**, induce differentiation of this cell into a monoblast, which differentiates into a promonocyte, the earliest morphologically identifiable cell in the series. The promonocyte is capable of endocytosis and some adherence to glass but is poorly phagocytic **(Groopman and Golde, 1981)**. The monocyte is slightly smaller than its precursors but fully phagocytic and microbicidal.

The earliest monocytic precursor in the marrow is believed to undergo two or three generations before the mature circulating monocyte is produced **(Groopman and Golde, 1981)**. This results in a bone marrow transit time of about 6 days. Newly formed monocytes may remain in the marrow for up to a day, but there is no marrow reserve comparable to that for granulocytes.

The terminal stage of development in the mononuclear phagocyte line is the multinucleated giant cell, which characterizes granulomatous inflammatory diseases such as tuberculosis, leprosy or sacroidosis **(Groopman and Gold, 1981)**.

Fig.2: Shows 2 large monocytes with kidney shaped large nucleus and a basophil **(Atlas of Haematology, 1988)**.

Fig.3: Shows two large monocytes and a small lucocyte **(Atlas of Haematology, 1988)**.

Macrophage Activation

The most important step in macrophage maturation, from the standpoint of function, is the cytokine-driven conversion of the normal resting, or resident, cell to the 'activated macrophage'. Activated macrophages are bigger and display pronounced ruffling of the plasma membrane, an increased capacity for adherence and spreading on surfaces, increased pseudopodium formation, and increased numbers of pinocytic vesicles. Used in its most widely accepted sense, 'activation' indicates that the cell has an enhanced capacity to kill facultative intracellular micro-organisms or tumour cells.

Macrophage activation is accomplished during infection through release of macrophage-activating lymphokines from T lymphocytes specifically sensitized to antigens from the organism in question **(Cohn and Kaplan, 1991)**. This interaction constitutes the basis of cell-mediated immunity. Interferon-γ appears to be especially important as a macrophage-activating lymphokine **(Torrico et al., 1991)**. Granulocyte/ macrophage colony-stimulating factor is a second lymphokine with such activity **(Weiser et al., 1987)**. Activation, and accompanying enhanced resistance to infection, have been achieved in animals by injection of interferon-γ **(Brummer et al., 1988)**, the adjuvant muramyl dipeptide, a small peptide-sugar derived from the cell wall of bacteria **(Edwards et al., 1986)**, somatotropin **(Edwards et al., 1988)**, IL-2, which can effect

increased release of interferon-γ **(Kohl et al., 1989)**, and M-CSF **(Munn et al., 1990)**. These and similar studies have supported the possibility that macrophage activation might be induced as a means of treating patients with intracellular infections or cancer. Interferon-γ has been evaluated for this purpose in clinical trials, and some success has been achieved.

Macrophages exposed to endotoxin release a hormone, tumour necrosis factor alpha (TNF-alpha)/cachectin. Tumour necrosis factor alpha-cachectin can itself activate macrophages under certain conditions in vitro. It has also been shown to increase greatly the macrophage-activating capacity of interferon-γ **(Munn et al., 1990)**.

In addition to the morphological changes that take place during activation of macrophages, some plasma membrane constituents are modified, including surface enzymes that bind substrate in the extracellular medium (ectoenzymes). Certain monoclonal antibodies can identify surface antigens, some of which are specific for the macrophage; many of these antigens also are modulated by the process of activation, including F4/80, which is decreased, and lymphocyte function-associated antigen 1 (LFA-1), which is increased **(Douglas et al., 1989)**.

Some macrophage plasma membrane receptors are modified during activation **(Toossi et al., 1990)**. Activation decreases the number

of receptors for mannose-terminated sugar conjugates, prominent constituents of the surface of fungi, and increases certain IgG Fc receptors (for IgG-1 in the human) **(Johnston and Zucker-Franklin, 1988)**. These changes could influence phagocytosis of fungi **(Marodi et al., 1991)** or of particles coated with IgG, but the actual effect of these changes in vivo is not known.

Functional Activities

The macrophage-monocytes linear cell has important immunological regulatory role in immunological responses and inflammatory reaction. This function of monocytes had been demonstrated by **Dinarello in 1984** to be mediated chiefly by two products of monocytes which are interleukin-1 and prostaglandin E_2 **(Dinarello et al., 1984)**.

The major functions of mononuclear phagocytes as they participate in host defence and the changes that take place in these functions when macrophages are activated are summarized in table (1). Obviously important is the macrophages ability to ingest and kill intracellular parasites such as Mycobacterium tuberculosis, Listeria, Leishmania, Toxoplasma and some fungi **(Johnston and Zucker-Franklin, 1988)**, as well as their ability to clear from the bloodstream and eliminate extracellular pathogens such as pneumococci. Macrophages probably also suppress viral infection, including that by human immunodeficiency virus-1 **(Bernstein et al., 1991)**.