THE ROLE OF HEPATIC MACROPHAGES AND KUPFFER CELLS DYSFUNCTION IN THE PATHOGENESIS OF INTRINSIC ASTHMA

THSIS

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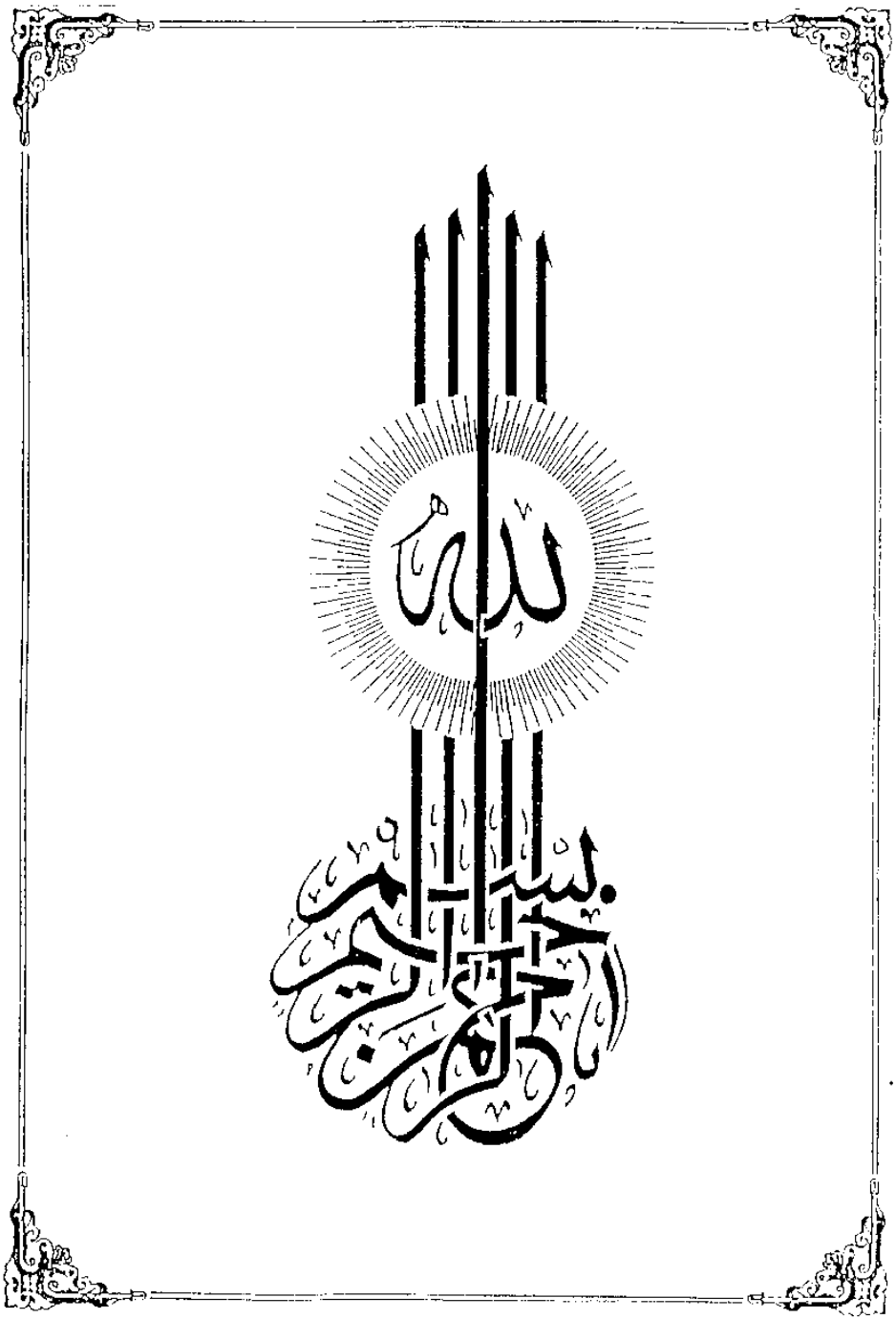
﴿ بسم الله الرحمن الرحيم ﴾

**قَالوُا سُبحَانَكَ لاَ عِلمَ لَنَا إلاَّ مَا عَلَّمتَنَا
إِنَّكَ أَنتَ العَلِيمُ الحَكِيمُ **

"صدق الله العظيم"
[البقرة : آية ٣٢]



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Researches in the pathogenesis of immunologically mediated diseases are increasingly aware of the potential effect of depravation from an immunologically protective liver function. The liver through its strategic position between the portal and systemic circulations, and its large mass of macrophages and kupffer cells is now known to perform two main functions. The first, is that the kupffer cells handle any absorbed antigens by a process of deletion through digestion of the antigenic determinant instead of advertising them to lymphocytes. The deletion process results in a minimal antigen load and low dose tolerance to important antigens as foods. Secondly, the macrophages and kupffer cells clear the gamma α-complexes against all intestinal antigens through an enterohepatic circulation thus preventing their potential noxious effect from reaching the systemic circulation.

Possible defects in these two mechanisms are now under intensive medical research as a possible pathogenic mechanism for many immunologically mediated diseases. Such researches are currently conducted through studying either morphologically or functionally abnormalities.

Intrinsic asthma still belongs to immune mediated diseases of uncertain pathogenesis. Morphological studies on kupffer cell changes by electron microscope among these patients have already revealed exciting changes which can be a reflection of disordered function ***(Mabrouk et al., 1990).***

A logical step is to attempt studying this function in terms of clearing power using the acknowledged and reproducible method ^{99m}Tc-sulpher colloid clearance. This will be the aim of the present studies.

REVIEW OF LITERATURE

BRONCHIAL ASTHMA

Definition :

Clarke and Scott (1977) defined asthma as a disease characterised by wide variations over a short time of resistance to flow in intrapulmonary airways. ***Warwick (1978)*** stated that asthma is a state of airway hyper-reactivity with reversible attacks of airway obstruction with episodic wheezing, dyspnea and cough. It provoked by many factors as allergens (in hailers, ingestants and injectants), exercise, infection, drug (as aspirin) and emotional factors.

Asthma is manifested by paroxysms of cough, dyspnea and wheezing, physiologically the whole mark is widespread narrowing of airways that can change in severity spontaneously or as a result of therapy ***(Meffaden, 1980)***.

Ellis (1983) defined asthma as an obstructive disease of the pulmonary airways, resulting from spasm of airway muscles, increased mucous secretion and inflammation.

Scadding (1983) defined bronchial asthma as a disease characterised by wide variation over short period of time in resistance to flow in intrapulmonary airways.

Druce (1985) stated that bronchial asthma is a chronic disease that is episodic in nature with acute exacerbation and symptoms free period of variable duration.

Classification of asthma :

1- Extrinsic :

Its onset is usually in childhood (5 years) or early adult life (before 30 year). There is a known external allergen as dust, pollen and danders; positive immediate skin test to specific antigen. IgE is raised in 50%-60% of cases and gives positive response tests involving the inhalation of specific antigen ***(Warwick, 1978)***.

It is intermittent in attacks and in 50% there is family history of multiple allergens (atopy) as asthma, hay fever and eczyma. It is subdivided into atopic and non atopic by ***Pepys and Frankland (1970).***

2- Intrinsic :

Previously, this type of asthma was known as intrinsic asthma but since it represents a heterogeneous group of asthmatic patients in whom different mechanisms, many of which are unknown may play a role in triggering attacks, it is more appropriate to be classified as cryptogenic asthma ***(Bonini, 1980)***. It gives negative skin test, IgE level is normal or even low. Onset is usually in older adults after 30

years and course is usually continuous, family history is less common than extrinsic 20% ***(Lopez and Salvaggio, 1987).***

Parker (1980) found that in both groups of asthma, there is blood and sputum esinophilia. Airway hypersensitivity in intrinsic groups may be due to release of triggering substances from mast cells or due to abnormal neurogenic or both as a result of non specific stimuli as infection, pollution, exercise, cold or psychogenic ***(Nadel et al., 1984).***

It was found that in asthmatic patients, there is lowered threshold for stimulation of irritant receptors of vagus afferent nerves and viral infection has the capacity to lower the threshold for stimulation of irritant receptors ***(Kaliner, 1985).***

Pathophysiology of intrinsic asthma :

In intrinsic asthma, reversible air ways obstruction is caused by a variety of stimuli that are non antigenic and seemingly unrelated.

The common denominator for intrinsic asthma may be an imbalance in the effector cell response to the sympathetic and parasympathetic activities, this may be in the form :

1- Excessive cholinergic response, since cholinergic stimulation cause smooth muscle contraction and

increased mucous gland secretion mediated directly or indirectly by CGMP.

2- Inadequate beta adrenergic response, since beta adrenergic stimulation relaxes smooth muscle, the suboptimal beta adrenergic response is mediated through a relative deficiency of CAMP.

3- Interaction between cholinergic and adrenergic systems this was suggested by clinical observation.

4- Increased alpha adrenergic receptor effect: since alpha stimulation causes bronchial smooth muscle contraction.

5- Reduced function of non-adrenergic inhibitory system in the lung.

There are two types of vagal afferent nerves, rapidly adapting irritant receptor and non myelinated C-fibers. The neural control of airway is far more complex than previously recognized ***(Barnes, 1986).***

Many recent neuropeptides have now been identified in human airways which have potent effects on airway function and it is possible that these neuropeptides might be implicated in asthma ***(Barnes, 1987).***

Vasoactive Intestinal Peptide (VIP) :

VIP, 28 amino acid peptide, is the neuropeptide found in highest concentration in human lung and is localised to efferent nerves (***Uddman and Sundler, 1987***).VIO

immuoreactive nerve fibers are associated with airway smooth muscle (particularly large airway) mucous glands, airway blood flow and parasympathetic ganglia. VIP relaxes human bronchi in vitro, and is almost 100 fold more potent than isoproterenol, making it the most potent endogenous brochodilator so far discovered ***(Palmer et al., 1986).***

In asthmatic patients nebulized VIP is rather disappointing since it has no bronchodilator effect and provides only weak protection against histamine induced bronchospasm, probably because little of nebulized peptide can reach receptors in airway smooth muscle ***(Barnes and Dixon, 1984).*** Similarly it has no bronchodilator effect when infused in normal subjects probably because the profound effects on C.V.S of the peptide limit the dose that can be given ***(Palmer et al., 1986).***

In asthmatic patients, a small bronchodilator response to intravenously administered VIP has been reported although this could be due to a reflex reduction in vagal tone resulting from histochemical studies show that VIP immuno-reactive nerves diminish in smaller airways and are absent in bronchioles. Autoradiographic mapping of VIP receptors has demonstrated on smooth muscle of large airways and are absent for smooth muscle of peripheral airways ***(Barnes and Dixon, 1986).*** VIP is a very potent vasodilator and in the

bronchial circulation might play an important role in the regulation of perfusion of the airway ***(Laitinen et al., 1987).***

Autodiographic mapping of VIP receptors in human lungs has confirmed the presence of receptors on airway glands, epithelium and vascular smooth muscle have the highest density of VIP receptors, so VIP is very potent vasodilator ***(Carstairs and Barnes, 1986).*** By electron microscopic studies, VIP may be present in the cholinergic nerves in the airway and therefore may function as a cotransmitter with acetylcholine and modulate its release, in vitro studies, it decreases the contractile effect of acetylcholine. So, it may act as a breaking mechanism to cholinergic bronchoconstriction ***(Barnes, 1991).***

If cholinergic nerve activity causes bronchoconstriction, release of VIP from activated cholinergic nerve may have an effect on nearby bronchial vessel (which are highly sensitive to VIP), so that bronchial blood flow increases as smooth muscle contracts thus supplying more nutrient to active smooth muscle cells ***(Barnes 1987).***

Peptide histidine methionine : is present in the same nerves as VIP and has similar effect on airway smooth muscle but less potent as a vasodilator than VIP suggesting that it might act on different receptors. In asthma as a result of inflammation, inflammatory cells identified in the