ELECTRON MICROSCOPIC AND FUNCTIONAL STUDIES OF VON KUPFFER CELLS IN PATIENTS WITH INTRINSIC AND FOOD ASTHMA

THESIS

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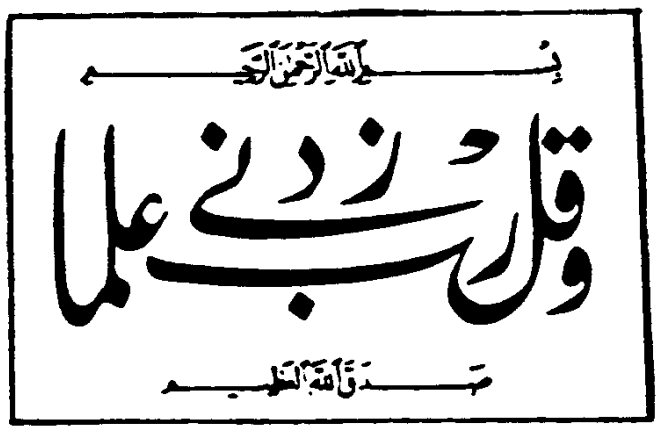

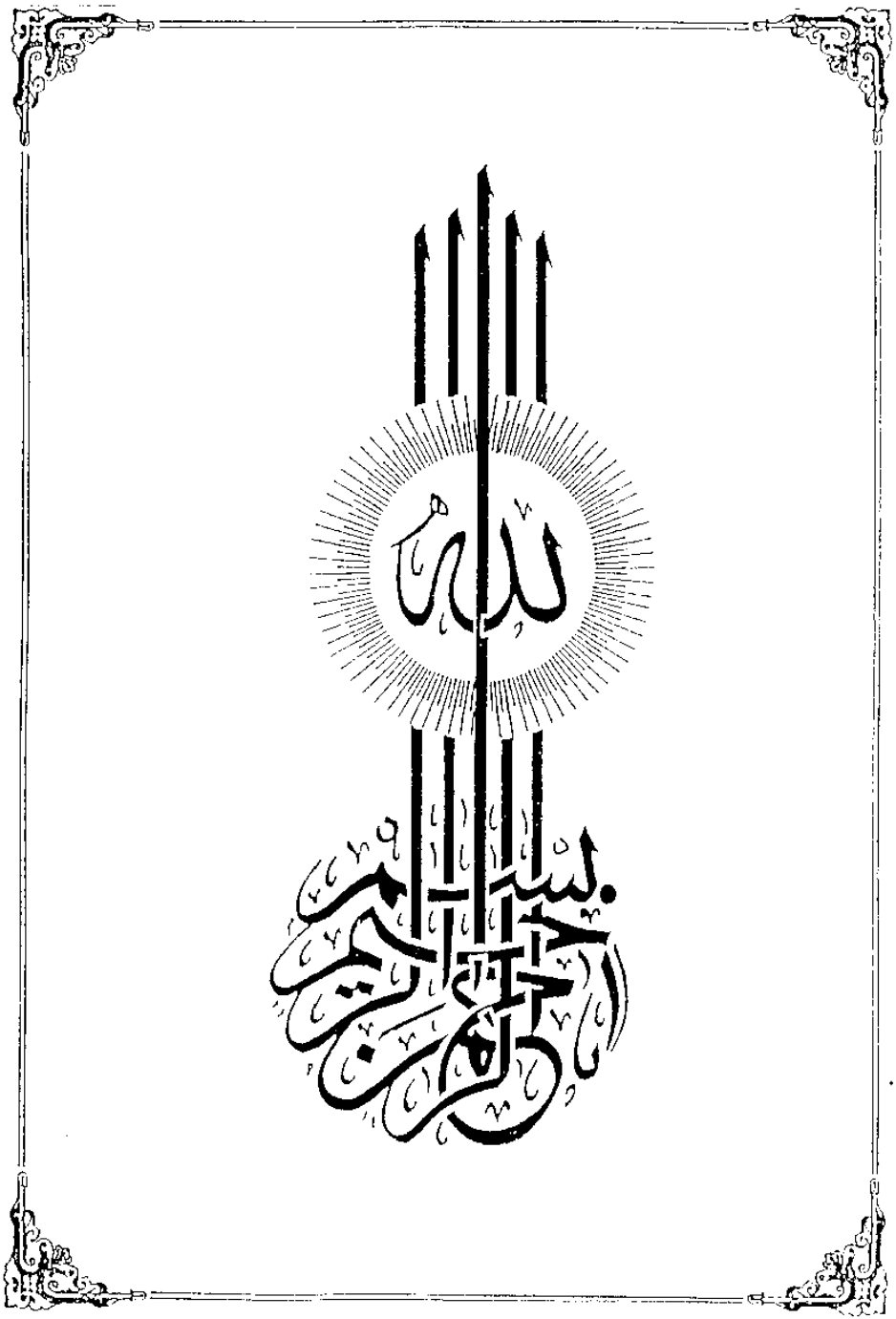

TO
MY GRACIOUS MOTHER,
MY KINDLY MOTHER IN LAW
AND
MY HELPFUL HUSBAND

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INTRODUCTION AND AIM OF WORK

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There is now ample evidence indicating that Kupffer cells play a distinct role in controlling antigenic invasion through the portal system **(Cantor and Dumont, 1967; Inchely, 1969; and Franzl, 1972).**

Kupffer cells have been found to be able to digest completely the intestinally-absorbed potentially-antigenic proteins instead of processing them like other macrophages and through this ability they save unnecessary stimulation of the central immune system **(Socken et al., 1979).**

This has been confirmed by finding that the deviation of the blood away from Kupffer cells in cirrhosis and portal shunts results in hyperglobulinaemia, secondary to loss of this characteristic and particular function of these cells **(Thomas et al., 1973; Bradfield, 1974; Thomas, 1977).**

In addition, the same cells as well as the hepatocytes are known to clear polymeric IgA complexes from the circulation into the bile, therefore guarding against their possible deleterious effect **(Hall and Andrew,1980).**

Based on these functions which indicate a unique role of Kupffer cells in antigen deletion or low-dose tolerance to portal system foreign proteins, as well as on previous studies done on

the pathogenesis of food and intrinsic asthma, which revealed only minor changes in the gastro-intestinal mucosal immune system **(Sabri et al., 1984; Moursi et al., 1988)** and which are not sufficient to explain the pathogenic role of food and/or intestinal flora in these disease entities, we are tempting to theorize a possible Kupffer cell deficiency among these patients. But, this requires studies for confirmation or negation and therefore this research work is planned accordingly through studying electron microscopic morphological integrities of Von-Kupffer cells in liver biopsies taken from these patients as well as by detecting the antibody titres against enteric versus nonenteric flora based on the fact that antibodies titres to the "O" antigen of the non-enteropathogenic E. coli is used as a parameter for natural tolerance in these patients **(Soliman et al., 1987)** and finally, both results of the two groups will be compared with normal controls to be evaluated and discussed.

BRONCHIAL ASTHMA

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Definition:

CIBA Foundation Guest Symposium "1959" suggested the following definition: "Asthma is a disorder of function characterised by widespread partial obstruction of the airways which varies in severity, is reversible either spontaneously or as a result of treatment and is not due to cardiovascular disease.

Clarke and Scott (1977) defined asthma as a disease characterised by wide variations over a short time of resistance to flow in intrapulmonary airways.

(Warwich, 1978) defined asthma in terms of function as an increase in airway resistance which is completely reversible either spontaneously or by treatment.

The word asthma is defined from the Greek "vou" and signifies panting. originally it was used to describe the respiratory illness and breathlessness. Clinically the disease 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.

Classification of Asthma:

(1) Extrinsic:

In which there is a history of extrinsic factors provoking the attack, it is further subdivided to:

"A": Atopic type:

It is associated with immediate skin test, stimulated by specific type of allergen, inherited allergen, IgE release specific mediators and blocked by intal not by corticosteroids **(Warwich, 1978).**

"B": Non atopic type:

It is not associated with history of allergy to particular specific antigen, associated positive skin test, inhalation test causes asthma to appear late i.e. 4-5 hours with fever and leucocytosis. Age of onset is late, and specific IgG can be demonstrated **(Pepys, 1969; Howell, 1976; Peyps et al., 1979 and Lopez and Salvaggio, 1987).**

(2) Intrinsic "cryptogenic" asthma:

In which no provoking agents can be identified, it is described as cryptogenic because agents are quite unknown at the present time. Many agents like exercise, infection specially viral, drugs.... etc, can be associated with this type of asthma. Typically it starts in the middle or late adult life **(Warwick, 1978).**

It is possible to suggest that intrinsic asthmatic are indeed sensitive, but to allergens which have not yet been defined **(Lichtenstein, 1978).**

(Fishman, 1980) defined intrinsic asthma as reversible airway obstruction by a variety of stimuli which are non antigenic and seemingly unrelated.

The non antigenic "non specific" stimuli in intrinsic asthma are:

(1) Infection.

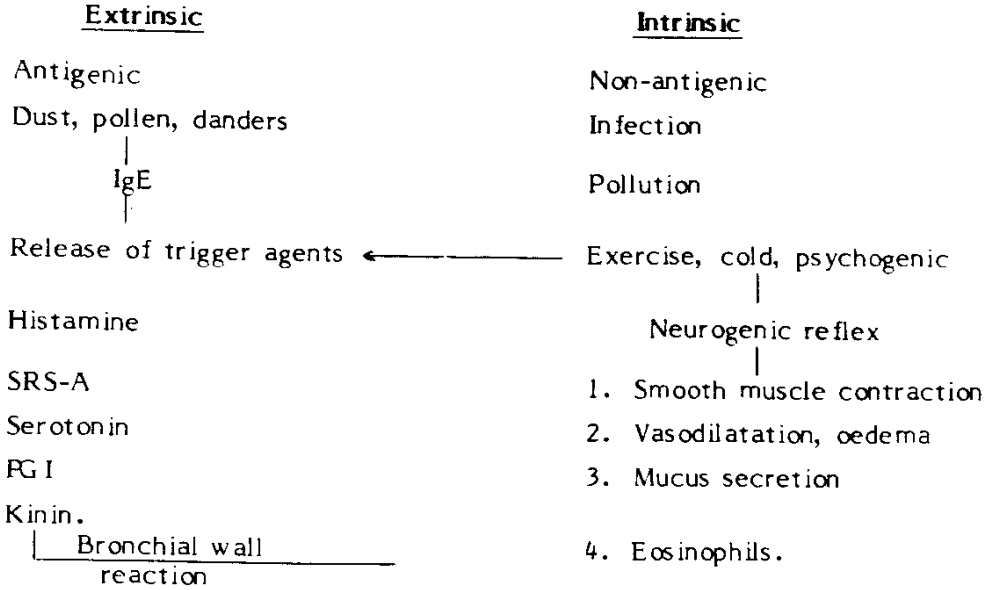
(2) Pollution.

(3) Exercise.

(4) Cold.

(5) Psychogenic.

These stimuli produce bronchoconstriction either directly by the release of trigger agents e.g. histamine, SRS-A, Serotonin, PG E, Kinin or reflexly through the vagus.



(Daniel, 1980) stated that intrinsic asthma is a form of the disease in which there is no inciting cause. It generally has its primary onset before the age of 5 or after the age of 35. The most important factor in its obscure aetiology is the infection of the bronchial tree. Attacks are usually but not necessary precipitated by or coincide with bronchial or paranasal sinuses infection and these patients often produce sputum with pathogenic organism as neisseria catarhalis or haemophilus influenzae.

These patients may have anintolerance to aspirin and other non-steroidal anti-inflammatory drugs **(Virchow , 1986)**. They may have no family or personal history of allergy but often they have a previous history of repeated attacks of bronchitis. Atopic background is absent and skin tests to common inhalants and food allergens are usually negative. It is a constant asthma which may be difficult to control with the usual modalities of therapy. IgE is normal or low and oesinophilia is common **(Lopez and Salvaggio, 1987)**.

(3) Mixed asthma:

The termis applied to patients in whom the allergic reactivity is combined with infectious factors in the production of their asthma and either the allergic or infectious factor will usually predominate.

It is a chronic or intermittent asthma starting at child or adulthood, the immediate skin test responses and the atopic background are usually present **(Rose and Macker, 1971)**.

Pathophysiology of asthma:

Asthma is a disease characterised by muscle spasm, inflammation and mucous plugging of the airways, but the relative importance of these abnormalities varies with the state of the disease. For example when an asthmatic attack is easily and completely reversible by drugs that relax smooth muscle, it seems likely that smooth muscle spasmis themajor cause of the airway obstruction. Similarly when patients die of asthma and their airways are solidly plugged, it seems reasonable to conclude that the plugs are the cause of death **(Hogg, 1982).**

Two separate, pathogenetic theories have been formulated to describe human asthma; direct and indirect. According to the direct theory, bronchoconstriction results from the direct stimulation of the airway smooth muscle by mediators secreted from respiratory mast cells. In the indirect theory, direct stimulation of smooth muscles is considered minimal, but the bronchoconstriction occurs through an indirect factors including vagal reflex effect.

Histamine and other non-specific irritant "stimuli" stimulate an afferent vagal (rapidly adapting) receptors, and bronchoconstriction results from efferent vagal output after amplification of the afferent stimulus in the central nervous system **(Leef, 1980).**

(1) Smooth muscle spasm:

In the guinea pig, the smooth muscle spasm is not associated with airway oedema or mucous plugging of the airways, so that