# NEOPTERIN ASSAY IN INTERACTABLE ASTHMA AS APARAMETER FOR CELL MEDIATED IMMUNE INJURY

Thesis

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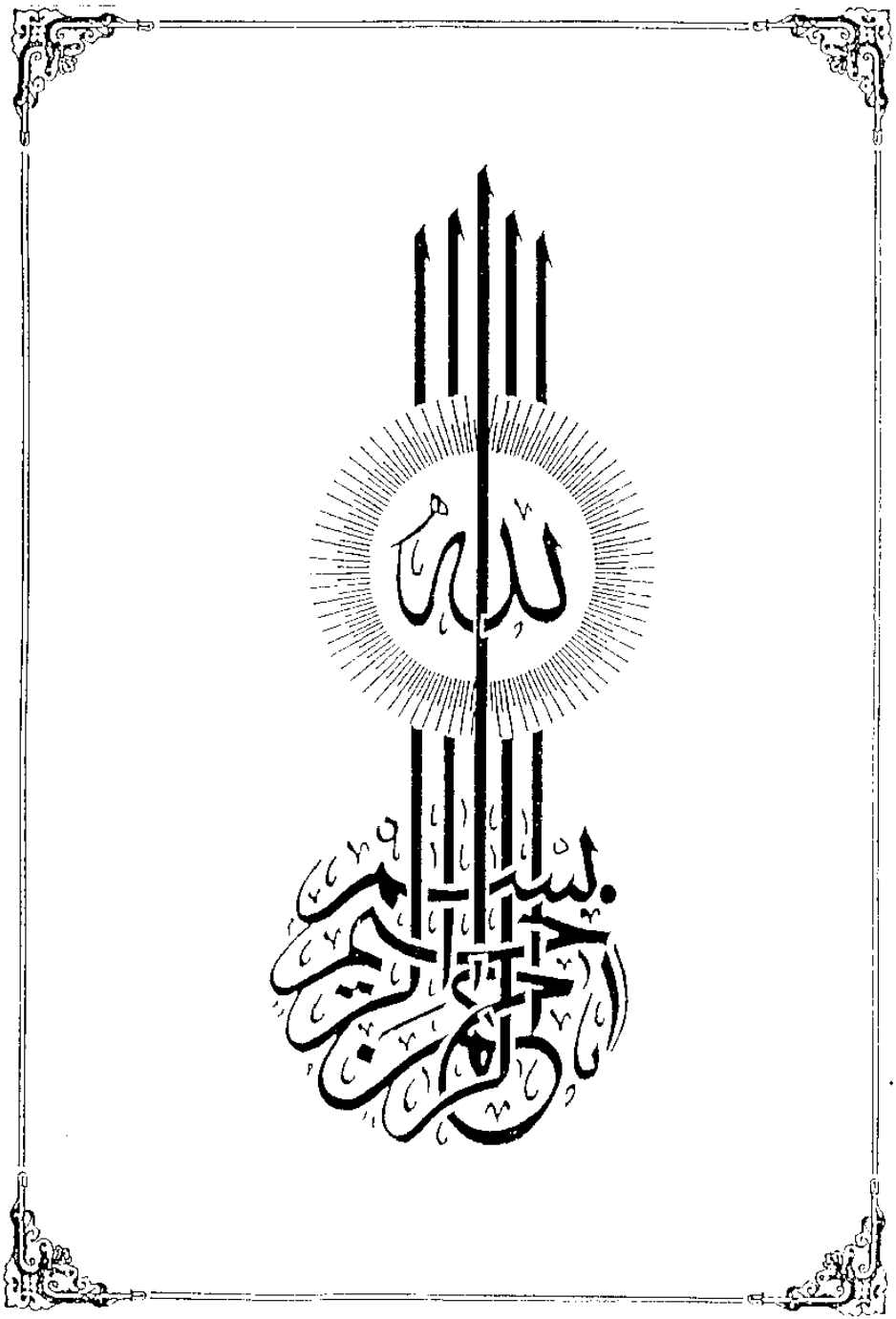

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***Thanks to ALLAH***

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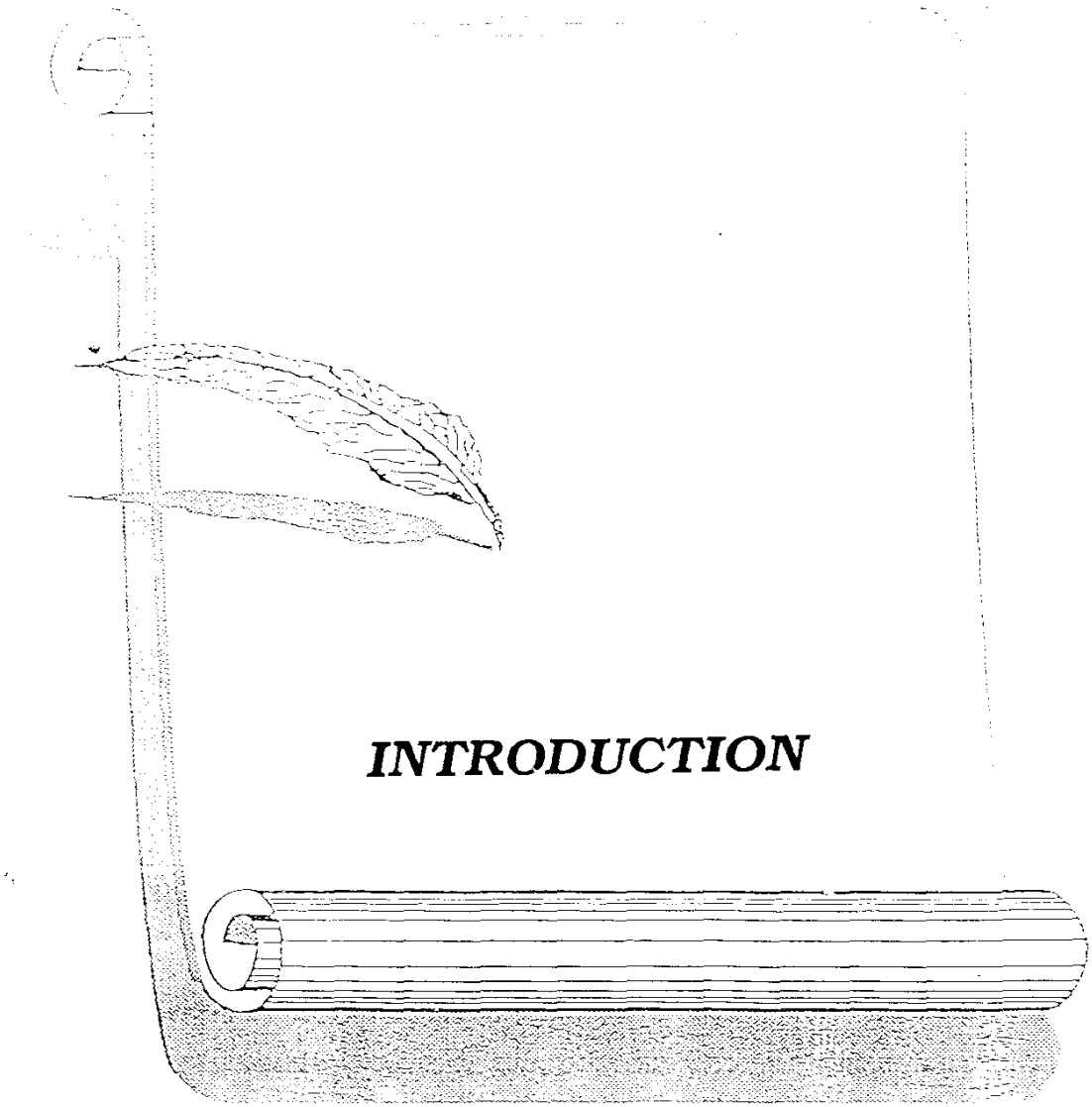

# INTRODUCTION

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Asthma results from a complex interplay of many cells and mediators, it is difficult to sort out the priorities in this field, perhaps, the single cell hypothesis of asthma is almost as unlikey to be valid as the single mediator hypothesis of the disease.

Although the integral involvement of immediate hypersensitivity in atopic asthma is unchallenged, debate continues over the precise roles for basophils, platelets, macrophages, eosinophils, lymphocytes and a host of early and late phase reactants (Busse and Reed 1988).

An area of considerable current interest is the role of theT-lymphocytes in the regulation and expression of the inflammation associated with allergy and asthma. The T-cell derived lymphokines, IL-4, IL-5 and IFN-γ, are intimately involved in the regulation of IgE production (Kay, 1991).

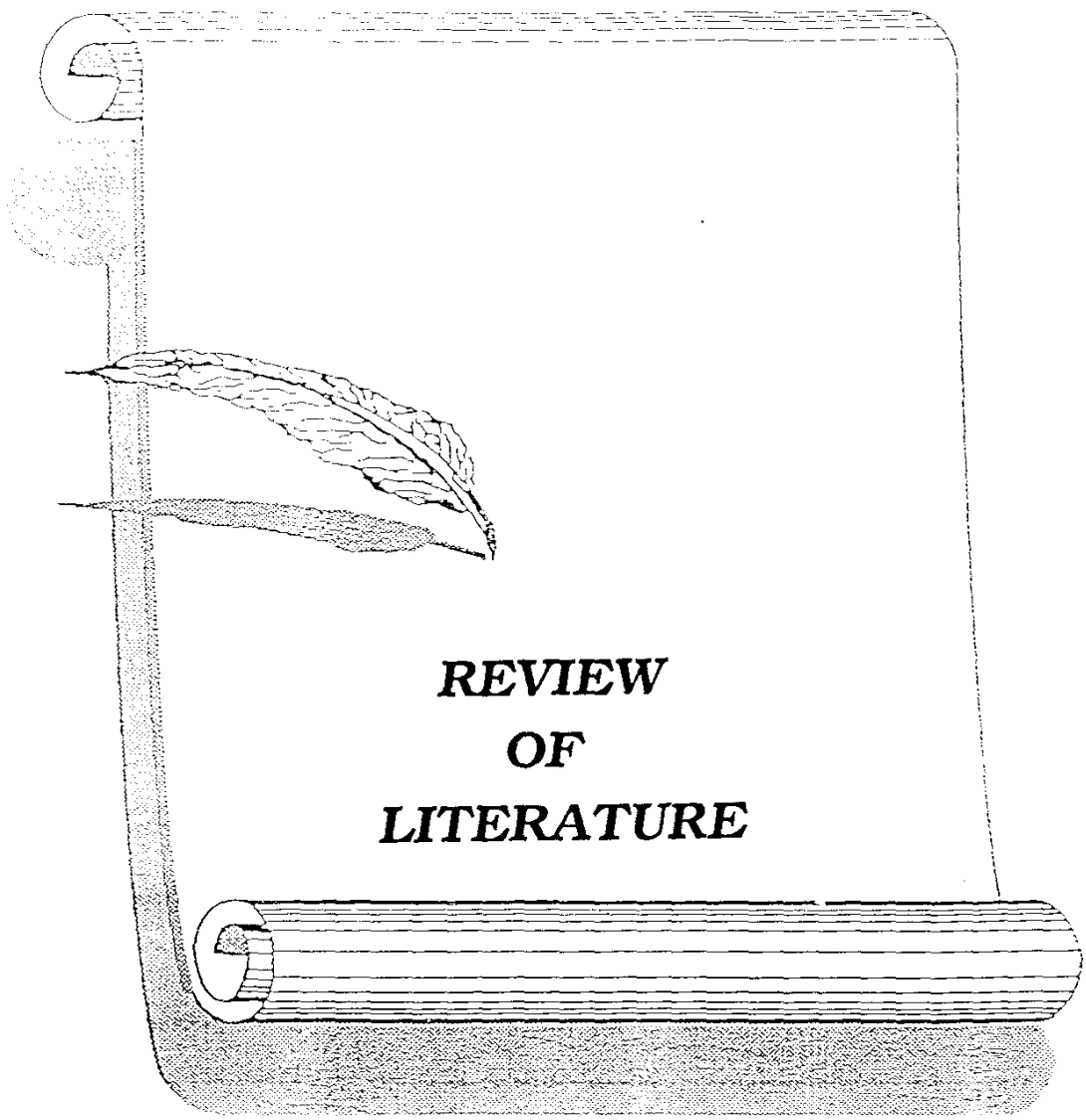
In addition, the serum concentrations of IFN-γ and soluble IL-2R were significantly elevated in patients with acute severe asthma as compared with all the control groups (Kay, 1991).

Recently, evidence is thus of a cellular immune respose with eosinophil activation as a final common pathway in atopic and non-atopic asthma (Robinson, 1993).

The research to date, demonstrates that measurements of neopterin concentration provide an immediate, sensitive and reliable means to monitor activation of T-cells and macrophages, increase in neopterin concentration supplies information on the activation state of cell mediated immunity that is not otherwise readily obtainable (Huber et al., 1984).

Uptill now, numerous investigations performed in vitro and in vivo supported the view that neopterin biosynthesis is closely associated with activation of cellular immune system (Wachter et al., 1989).

Abnormal neopterin levels have been observed in numerous disease states involving autoimmune, viral and Neoplastic processes.



# REVIEW OF LITERATURE

## BRONCHIAL ASTHMA

***DEFINITION***

(1) According to the international consensus report on diagnosis and management of asthma; the first notable feature of The report is an operational definition of asthma incorporating pathological, clinical and physiological elements. Asthma is regarded as a disease of chronic, persistant inflammation rather than one of episodic, occasional symptoms.

"Asthma is a chronic inflammatory disorder of the airways in which many cells play a role including mast cells and eosinophils. In susceptible individuals this inflammation causes symptoms which are usually associated with widespread but variable airflow obstruction that is often reversibe either spontaneously or with treatment, and causes an associated increase in airway responsiveness to a variety of stimuli" (The International Consensus Report on Diagnosis and Management of Asthma, 1992).

(2) A committee of the American Thoracic society (1993) defined asthma as "a disease characterized by an increased responsiveness of the trachea, bronchi to various stimuli and manifested by wide spread narrowing of the airways that changes in severity either spontaneously or as a result of treatment. Essentially asthma is a reversible airway obstruction".

## Etiology

From an etiologic point of view, asthma is a heterogeneous disease.

Asthma can be described under two broad groups, allergic and idiosyncratic.

***A- Allergic asthma :***

It is often associated with a personal and/ or family history of allergic diseases such as, rhinitis, urticaria and eczema, positive wheal and flare skin reaction to intradermal injection of extracts of airborne antigens increased levels of IgE in the serum and/or +ve response to provocation tests involving the inhalation of specific antigen (Kaliner et al., 1988).

***B- Idiosyncratic asthma :***

A significant segment of the asthmatic population will present with negative family or personal histories of allergy, negative skin tests, and normal serum levels of IgE and therefore cannot be classified on the basis of defined immunologic mechanisms. These we term idiosycratic asthma (McFadden, 1994).

## Classification and clinical types

It has been long recognized that asthmatic population could be separated into two main categories namely extrinsic in which a recognizable external allergen in the environment

initiates the attack, and intrinsic, in which no external allergens are recognized (Rackemann, 1947).

Rackemann, 1947 suggested that this classification (extrinsic and intrinsic) is not absolute because both types may be present in the same patients. Frequently they may start as extrinsic and becomes intrinsic and occasionally the reverse. Extrinsic asthma can be subdivided according to whether the subject is atopic (i.e manifesting type I skin reaction to a standard range of common allergens) or not.

***Extrinsic atopic asthma :***

This represents the largest group of asthmatics patients belonging to this group usually develop symptoms early in life. In many of them the advent of asthma is frequently preceeded by allergic rhinitis or eczema. The majority give a positive family history of allergy and the immediate wheal and Flare response to skin tests is predominant and of diagnostic significance (Herbert et al., 1982). Such asthma occur in persons with an inborn liability to develop reagenic (IgE) antibodies in response to the start of exposure to relevant antigens that occur in every day life (Farzan, 1978).

Between attacks the patients may be syptom free and enjoy long intervals of freedom. Generally, there is little cough during paroxysms although the attack may terminate with expectoration.

***Extrinsic non atopic asthma :***

Bryant et al., 1975 have described a form of type I asthma mediated by IgG in the absence of IgE antibody this reaction is not atopic by definition and can be described as extrinsic non atopic asthma.

Patients usually develop their symptoms 4-6 hours after exposure to environmental antigens often during the course of their job (Pepys, 1974).

Skin testing causes no wheal and Flare but a late inflammatory skin reaction "Arthus reaction" ( Nagy et al., 1982).

***Intrinsic or cryptogenic asthma :***

This is very important subgroup which is recognizable on combination to clinical, functional, sometimes histological criteria and absence of Immunological finding characterizing extrinsic asthma (Scadding, 1983).

This group of patients shows no evidence of extrinsic allergy or atopy wheather from the history taking or from skin tests against a standard variety of common allergens (British Tuberculosis and thoracic Association, 1975).

Typically cryptogenic asthma starts in middle or later adult life and is thus sometimes referred to as "adult onset asthma"

About 70% of patients with cryptogenic asthma begin their symptoms over the age of 30 years.

It has been postulated that the airway hyperreactivity to nonspecific stimuli in cryptogenic asthma results either from the release of trigger substances from mast cells or from abnormal neurogenic reflexes or both. The most important non specific irritant is infection particularly viral infectin, viral agents are thought to lower the threshold to stimulation of irritant receptors located beneath the respiratory epithelium, thereby initating bronchial hyperresponsiveness via a neural reflex involving afferent and efferent vagal fibers (Empey et al., 1976)

The fact that eosinophilia is usually present and that patients who die in a persistant episode of asthma show the same morbid anatomical and histopathological changes as do patents dying with extrinsic atopic, besides the response to corticosteroid suggest that immunological factors of some sort are concerned in its pathogenesis (Pepys, 1974).

**According to severity :- (International Consensus Report on Diagnosis and Managment of asthma 1992) .**

***Mild :-***

- Intermittent, brief symptoms < 1-2 attacks per week.
- Nocturnal asthma symptoms < 1-2 attacks per month.

- Asymptomatic between exacerbations.
- PEF or FEV1 > 80% predicted, variability < 20%

***Moderate :-***

- Exacerbations > 1-2 per week.
- Exacerbations may affect activity and sleep.
- Nocturnal asthma symptoms > 2 per month.
- Chronic symptoms requiring short-acting $\beta_2$-agonist almost daily.

***Sever :-***

- Frequent exacerbations .
- Continuous symptoms.
- Frequent nocturnal asthma symptoms.
- Physical activities limited by asthma.
- PEF or $FEV_1$ < 60% predicted , variability >30%.

**Asthma triggers:**

The stimuli that interact with airway responsiveness and incite acute episodes of asthma can be grouped into :-

***A- Allergic allergens (stimuli) :***

Allergic asthma is dependent on a IgE response controlled by T and B lymphocytes and activated by the interaction of antigen with mast - cell bound IgE molecules. Most of the allergens that provoke asthma are airborne and in order to