INTERRELATIONSHIP OF ADOLESCENCE AND BRONCHIAL ASTHMA

THESIS

Submitted for Partial Fullfilment of
M.D. Degree in **Pediatrics**

By

Laila Mahmoud Abdel Ghaffar Hegazy

M.B.,B.Ch., M.Sc.

Supervised By

Prof. Dr. Abdel Khalek Abdel Aziz Khattab

Professor of Pediatrics
Ain Shams University

Prof. Dr. Karima Ahmed Abdel Khalek

Professor of Pediatrics
Ain Shams University

Prof. Dr. Ali Khalifa Ali

Professor of Biochemistry
Ain Shams University

Dr. Iman Mahmoud El Salahy

Lecturer of Biochemistry
Ain Shams University

Faculty of Medicine
Ain Shams University
1993

Acknowledgement

I am greatly indebted to Professor 'Abdel Khalek Khattab' Professor of Pediatrics, Ain Shams University for giving me this precious opportunity of working under his supervision, his vast knowledge, wise experience and guidance added much to this work.

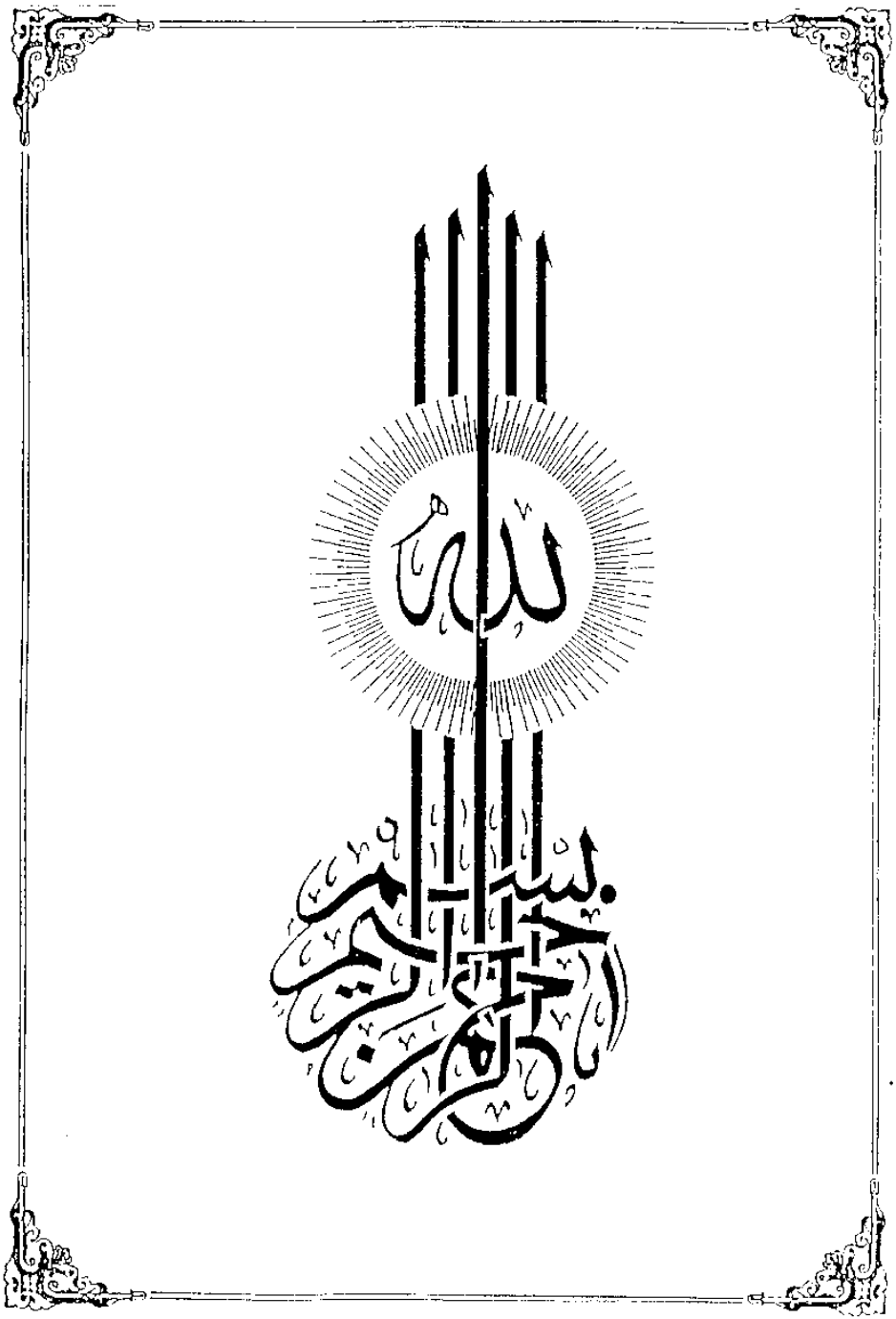
I am also indebted to Professor Dr. 'Karima Abdel Khalek', Professor of Pediatrics, Ain Shams University, I will always remember her kind help, meticulous supervision and constructive criticism throughout this work.

I would like to thank Professor Dr. 'Ali Khalifa Ali' Professor of Biochemistry, Ain Shams University for his kind assistance and continuous support.

I am also very grateful to Dr. 'Iman El Salahy' Lecturer of Biochemistry, Ain Shams University, her guidance and meticulous supervision assisted the practical part of this work.

Last but not least, my deep appreciation is expressed to all staff members and patients of the Pediatric Chest Clinic of Ain Shams University.

Laila Nagy



List of contents

List of Tables

List of Figures

List of Abbreviations

BHR	Bronchial hyperresponsiveness
BTPS	Body temperature pressure saturated with water vapour
cAMP	Cyclic adenosine monophosphate
CPM	Count per minute
EAR	Early allergic response
ECP	Eosinophil cationic protein
EIA	Exercise induced asthma
EOS	Eosinophils
EPO	Eosinophil peroxidase
FEV_1	Forced expiratory volume in 1^{st} second
FVC	Forced vital capacity
HMD	House mite dust
IL	Interleukin
LAT	Late allergic response
LT	Leukotriene
MB	Maximum binding
MBP	Major basic protein
MEFV	Maximal expiratory flow volume
MMEF	Maximal mid expiratory flow
NANC	Non adrenergic non cholinergic
NSB	Non specific binding
PAF	Platelet activating factor
PD20	Provocative dose of histamine that causes a 20% decrease in pulmonary function
PEFR	Peak expiratory flow rate
PG	Prostaglandin
RIA	Radioimmunoassay
SMR	Sex maturity rating
S(P)	Substance P
VIP	Vasoactive intestinal peptide

INTRODUCTION

Asthma is an inflammatory disease of the airway that is chronic and persistent **(Lee, 1992)**. Asthma is defined by the American Thoracic Society in (1987) as the presence of intermittent symptoms that include wheezing, dyspnea and cough resulting from airway hyperreactivity and reversible airflow obstruction. Asthma is often associated with atopy, like other inflammatory diseases, asthma is characterized by the recruitment of inflammatory cells, vascular congestion, increased vascular permeability, increased tissue volume and the presence of an exudate **(Lee, 1992)**.

Asthmatic inflammation in an atopic subject may be distinguished from other inflammatory diseases by a characteristic pattern of early mast cell activation eosinophil infiltration, fibroblast proliferation and collagen deposition, selective T-cell activation, epithelial damage and mucus hypersecretion **(Gleich et al., 1988)**.

Although asthma is a continuous and persistent process, yet it gives rise to symptoms from time to time. There are possible factors contributing to the development of symptoms these include the level of airway involvement, the relative increase in tissue volume, the expression of a latent viral infection and changes in the phenotypic characteristics of the resident cells **(Platts-Mills, 1992)**.

Recently, overreliance on beta-agonists is claimed to mask the underlying disease process and thus contributes to the rising prevalence of asthma, so a stepwise approach to the treatment of asthma is advocated by the use of a safe anti-inflammatory agent such as Nedocromil-Na or low dose inhaled corticosteroids **(Stempel and Szefler, 1992).**

Cyclic and maturational fluctuations in hormonal levels may enhance or suppress the expression of allergic reactions (atopy) through an effect on effector cells of the immune system or target tissues **(Grossman, 1984).** Estrogen receptors have been demonstrated on thymic epithelial cells and possibly on T-cells as well. Estrogens are inhibitory and depress T-cell subsets. Androgens alter the development of certain T and B-cell subpopulations, T-cells have been shown to possess androgen receptors. Testosterone treatment decreases antibody level and modulates thymic hormones. Progesterone increases suppresser activity and inhibits lymphocyte transformation **(Schatz et al., 1985).**

Aim of the work

The aim of the work was to study the gonadotropin level, sex hormones level in asthmatic adolescents compared to normal adolescents. Another objective was to study pulmonary functions in adolescent asthmatics, to study the effect of asthma severity on sex hormonal level and pulmonary functions and to correlate pulmonary functions to hormonal levels.

Chapter I

Physiology of airway receptors

Cell receptors relevant to airway function may be grouped into autonomic receptors and mediator receptors.

I- Autonomic receptors of the airways:

In addition to the classical cholinergic pathways which cause bronchoconstriction and adrenergic mechanisms which are usually bronchodilators, there is a more recently recognized component of the autonomic control which is neither cholinergic nor adrenergic **(Barnes, 1984)**. The nervous pathways influence airway caliber by activating specific receptors on target cells in the airways. Mediators for cholinergic pathways is acetylcholine, adrenergic nerves release norepinephrine and circulating epinephrine released from adrenal medulla, both act as mediators to the adrenergic pathway.

The neurotransmittor of non adrenergic, non cholinergic (NANC) nerves in airways is not certain but the most likely candidate for the non adrenergic inhibitory nerves is vasoactive intestinal peptide (VIP). VIP is the most potent endogenous bronchodilator of human airways so far described but has no bronchodilator effect when given to asthmatic subjects by inhalation **(Barnes, 1986)**.

More recently nitrous oxide has been identified as a potential (NANC) inhibitory neurotransmittor in human airways **(Belvisi et al., 1992).** This may be clinically relevant because the (NANC) inhibitory system is the only bronchodilating system with direct neural control of airways in humans **(Stempel and Szefler, 1992).**

The non cholinergic excitatory nerves is probably substance-P (SP) or related peptide. Local release of substance-P may activate neural reflex mechanisms resulting in increased microvascular leakage with mucosal oedema and increase mediator release from mast cells **(Barnes, 1986).**

*** Beta adrenoreceptors:** activation of adenylate cyclase leads to increased intracellular concentration of CAMP which activates specific protein kinase that brings about the characteristic cellular response (smooth muscle relaxation, decrease release of mediators from mast cells, decrease microvascular leak) **(Holgate et al., 1984).**

Beta agonists therefore have several beneficial actions on airways. In addition to relaxing smooth muscle, they also reduce release of mediators from mast cells, reduce cholinergic tone and possibly reduce mucosal oedema and increase clearance of the airway mucus **(Barnes, 1984).** The newer long acting B_2 agonists (formoterol and salmeterol) have shown to block the late asthmatic response to allergen exposure **(Twentyman et al., 1990).**

* **Muscarinic receptors:** in human 3 muscarinic receptors are identified, those are:

M_1: mediate vagal tone and its antagonism produce broncho-dilatation.

M_2: antagonism of M_2 receptors increase acetyl choline.

M_3: antagonism of M_3 receptors results in broncho-dilatation.

Therefore a M_1M_3 antagonist may have a more desirable effect than the currently available non specific antagonist ipratroprim or atropine derivatives **(Barnes, 1989)**.

Autonomic Abnormalities in Asthma:

An exaggeration at the excitatory mechanisms (cholinergic, alpha-adrenergic or non cholinergic excitatory) or deficiency in the inhibitory, may cause exaggerated response to a wide variety of stimuli **(Armour et al., 1984)**

II- Mediator Receptors In The Airways:

Several inflammatory mediators have now been implicated in asthma. These mediators have several effects on the airways which contribute to bronchial obstruction including contraction of the smooth muscle, mucus hypersecretion and chemotaxis of inflammatory cells which themselves then release further mediators. The cellular origin of various

Table (1)

Autonomic Receptors in the Airways:

Target cell	B-adrenergic	α-adrenergic	Muscarinic	VIP	Substance P
Smooth muscle	relax +++ (B_2)	contract + α_2	contract +++ M_2	relax +++	contract +
Submucosal gland	↑secretion + B_1B_2	↑secretion + α_1	↑secretion ++ M_1	↑secretion ++	↑secretion ++
Airway epithelium	↑secretion + B_2	↑secretion + α_1	↑secretion ++	↑secretion ++	↑secretion +
Mast cell	↓secretion +++ B_2	↑secretion ?	↑secretion ?	↓secretion ++	↑secretion
Micro-vascular	↓ leak +B_2	↓ leak +?	?	?	↑ leak ++

Barnes, 1989

Table (2)

Mediator receptors in the airways

Receptor		Chemotaxis	Smooth M	Mucous secretion	Permeability
Histamine	H_1 H_2	—	contract + ——	↑ secretion	↑leak ++?
Leukotriene	B_4, C_4, D_4	+++	– Contract +++	— ↑ secretion +++	— ↑ leak +++
Prostaglandin	$F_{2\alpha}$, D_2, E_2		Contract ++ Relax +	↑ secretion +++ ↑ secretion ++	↑ leak ++ ↑ leak ++
Thromboxane	I_2		Contract +	?	?
Adenosine	A_1 A_2		Contract + —	?	↑ leak
Platelet activating factor		++	Contract ++		↑ Leak +++
Bradykinin			Contract ++	↑ secretion ++	↑ Leak +++

(Barnes, 1989)