أعوذ بالله من الشيطان الرجيم

بسم ا لله الرحمن الرحيم

رب اشرح لى صدرى ويسر لى أمرى واحلل عقدة من لسانى يفقهوا قولى.

صدق الله العظيم

BRONCHIAL ASTHMA AND GONADOTROPINS: CAUSAL RELATIONSHIP

THESIS

SUBMITTED FOR PARTIAL FULFILMENT FOR MASTER DEGREE IN INTERNAL MEDICINE

BY

SALIM ABDUL RAZAK OLABI

SUPERVISED BY

PROF. Dr. MOHAMED DIA EL DIN SULIMAN

PROF. OF INTERNAL MEDICINE

AIN SHAMS UNIVERSITY

Dr. MAGED MUHAMED RIF'AT

LECTURER OF INTERNAL MEDICINE

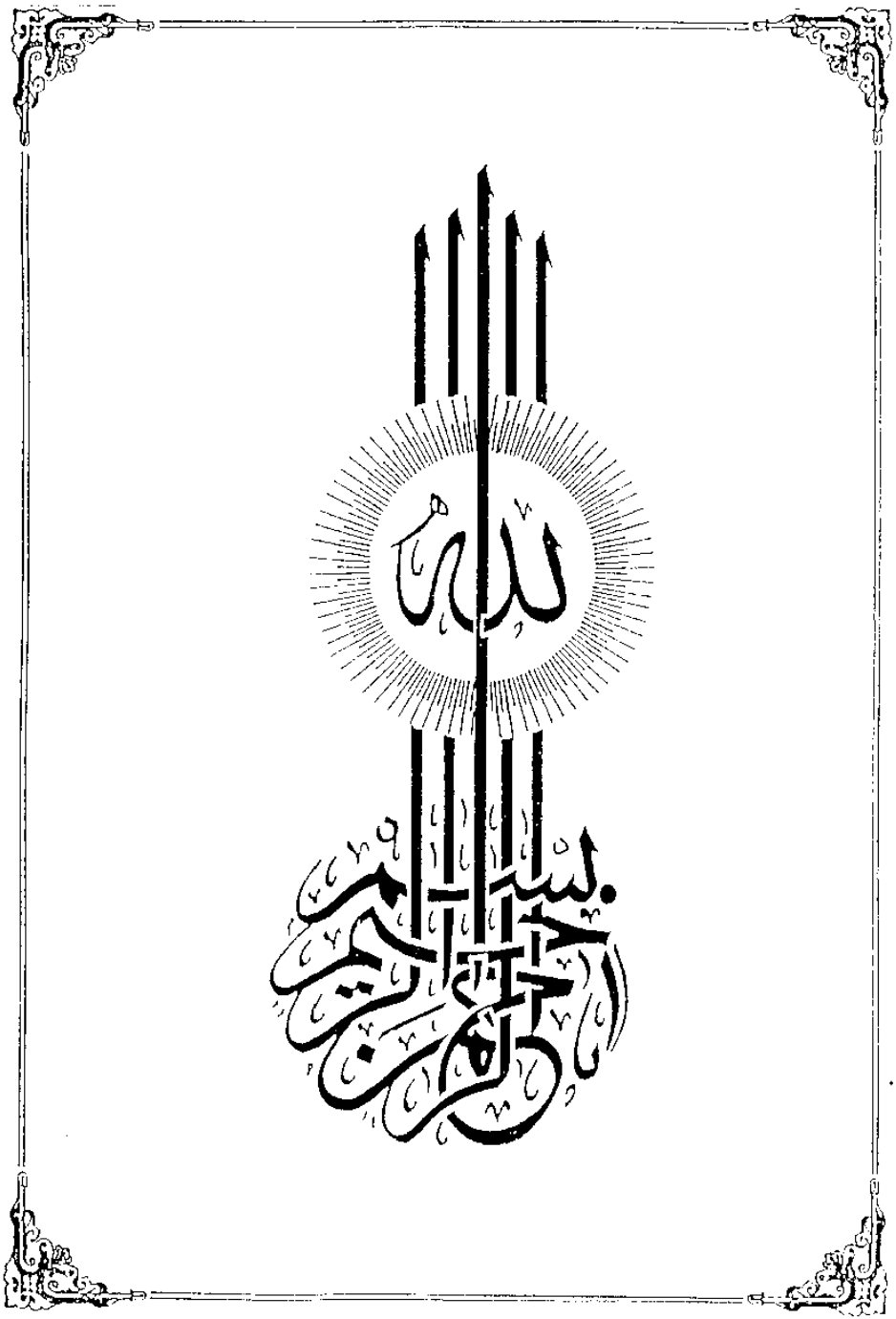
AIN SHAMS UNIVERSITY

Dr. SALWA ABDUL ZAHER MABROUK

LECTURER OF INTERNAL MEDICINE

AIN SHAMS UNIVERSITY

1994



Acknowledgement

I wish to express my sincere gratitude and deep appreciation to professor ***Dr. MOHAMED DIA EL DIN SULEIMAN,*** Professor of internal medicine, Ain Shams University, for giving me the opportunity to perform this study, his guidance, invaluable help, kind directions, supervision, generous support and continuous encouragement.

I would like to express my deep thanks to ***Dr. MAGED MOHAMED RIF'AT,*** lecturer of internal medicine, Ain Shams University for his continuous help, advice and guidance which was of great value for this study.

Also, I would like to send my deep thanks and respect to ***Dr. SALWA ABDUL ZAHER MABROUK,*** lecturer of internal medicine, Ain Shams University, for her close supervision and continuous advice and help which were of great value for this study to come to light.

Salim Olabi

List of Tables

List of Figures

List of Abbreviation

ACTH:	Adreno Cortico Trophin Hormone.
CSF:	Colony Stimulating Factor.
ECG:	Electro Cardio Graphy.
EIA:	Exercise - Induced Asthma.
EPDIF:	Epithelial - derived Inhibitory Factor.
EPDRF:	Epithelial - derived Relaxant Factor.
ESR:	Erythrocyte Sedimentation Rate.
FSH:	Follicle Stimulating Hormone.
GnRH:	Gonadotropin - Releasing Hormone.
HLA:	Human Lymphocyte Antigen.
^{125}L:	Radioiodine.
IgE:	Immunoglobuline E.
LH:	Luteinizing Hormone.
LT:	Leukotriene.
MB:	Maximum Binding.
MBP:	Major Basic Protein.
MCF:	Monocyte Chemotactic Factor.
NCNA:	Non-Cholingergic Non-Adrenergic
NEP:	Neutral Endopeptides.
NSB-CPM:	Non specific Binding - Counter per minute.
PAF:	Platelet Activating Factor.
PG:	Prostaglandin.
RIA:	Radioimmnoassay.
RSV:	Respiratory Syncytial Virus.
TC:	Total Count.
VIP:	Vasoactive Intestinal Peptide.
17-Keto:	17-Ketosteiords.

Introduction and Aim of the Work

Asthma is an inflammatory lung disease involving "reversible airway obstruction. **(Goldie, 1990)**

The characteristic features of asthma include; eosinophilia, non-specific bronchial hyperreactivity to inhaled spasmogens, airway epithelial damage, mucosal oedema and mucosal gland hyper- secretion. **(Goldie, 1990)**

Three types of asthma can be recognised:
Extrinsic, intrinsic and mixed.

In the extrinsic type there is a history of extrinsic factors provoking the attack, whereas in the intrinsic type no provoking agents can be identified. **(Warwick, 1978)**

The most important factor in the obscure aetiology of intrinsic asthma is the infection of the bronchial tree. **(Virchow, 1986)**

In the mixed type, the allergic reactivity is combined with infectious factors in the production of asthma. **(Rose and Macker, 1971)**

Many agents like; infections (especially viral), exercise, drugs (as aspirin), psychological disturbances and hormonal factors can be associated with the intrinsic type of asthma. **(Warwick, 1978)**

Fluctuations in hormonal level may enhance or suppress the expression of allergic reactions through an effect on effector cells of the immune system of 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 subset. Androgens alter the development of certain T and B subpopulation, T- cells have been shown to have androgens receptors. Progesterone increases suppressor activity and inhibits lymphocyte transformation. **(Schatz et al., 1985)**

Ovarian and testicular function is under the control of gonadotropins,, follicle stimulating hormone and luteinizing hormone secreted by the anterior pituitary gland, acting as intermediary messengers in the neuroendocrine system which transmits environmental and central nervous system information to the reproductive system. **(Bremner, 1990)**

Before, there have been many clinical observations which indicate the presence of a link between asthma (especially the intrinsic) and endocrinal system such as: many asthmatic children are spontaneously cured as they reach the age of puberty; **(Takino, 1976)**; severe premenstrual asthma can be completely prevented by injection of progesterone at the appropriate time. **(Benyon, 1988)**

Now, after the new methods and techniques of measurement of hormonal levels, we can measure these hormones in asthmatic patients trying to find any change from the normal that may prove this link.

And, this is the aim of this work; to clarify the relationship between the serum level of gonadotropins and urinary 17-Keto-steroids in the pathogenesis of intrinsic asthma for a possible link and causal relationship for a better understanding of this disease.

Chapter I
Aetiology of bronchial asthma

Chapter I
Aetiology of Bronchial Asthma

Asthma is a disease commonly encountered in the clinical practice of medicine, with prevalence in the general population of approximately 3% **(Weiss et al., 1985)**. It usually begins in childhood or early adult life. Up to 85% of asthmatic individuals experience their first symptoms before the age of 40. **(Border et al., 1962)**

In a complex disease as bronchial asthma, some aetiological factors are known, while others remain unknown, contributing triggering and aetiological factors regarding asthma will be mentioned here such as:

1. Autonomic factors.
2. Allergic factors.
3. Infections (especially viral).
4. Genetic factors.
5. Exercise - induced asthma (EIA).
6. Pharmacological factors.
7. Endocrinal factors.
8. Psychological factors.

The above mentioned factors are involved in the aetiology of asthma in varying degree in different individuals. **(Hucknaf and Madia, 1987)**

1. Autonomic factors:

Neural control of human airways is complex; in addition to the cholinergic and adrenergic mechanisms, non adrenergic non cholinergic (NANC) pathways are now recognised. **(Barnes, 1986)**

Cholinergic stimulation causes smooth muscle contraction and increased mucous gland secretion, while beta-adrenergic stimulation relaxes smooth muscles of the bronchial tree and alpha adrenergic stimulation causes their contraction **(Reed, 1974)**. In the late 1960s Szentivanyi elaborated "the beta-adrenergic blockade theory" of asthma i.e. diminished responsiveness to beta adrenergic stimulation might potentially increase impulse transmission or receptor stimulation along alpha - adrenergic or cholinergic pathways **(Szentivanyi, 1968)**. In asthmatic patients, beta-adrenergic hyporesponsiveness and alpha adrenergic and cholinergic hyperresponsiveness can be frequently demonstrated. These observations have provided support for the beta-blockade theory of asthma elaborated by Szentivanyi. **(Lemanske et al., 1990)**

Therefore, this autonomic nervous system abnormality consists of: (a) beta-adrenrgic hyporesponsiveness (b) alpha-adrenergic and cholinergic hyperresponsiveness and (c) non adrenergic-non cholinergic inhibitory system hypofunction. **(Lemanske et al., 1990)**

Lemanske, 1990 stated that three levels of response critical in asthma may be influenced:

1. Bronchial smooth muscle and response to beta-adrenergic stimulation would be reduced, whereas cholinergically and even alpha-adrenergically mediated constriction would be augmented.

2. Mast cell mediator release ordinarily suppressed by beta-adrenergic stimulation would be resistant to beta - adrenergic agonists, whereas both cholinergic and alpha-adrenergic enhancement would be exaggerated.

3. Increased mucus secretion in response to alpha-adrenergic and cholinergic stimulation would be increased whereas sodium and water fluxes into tracheo bronchial secretion in response to beta-adrenergic stimulation would be reduced.

Experiments in vitro have demonstrated the existence of a NANC inhibitory system in human airways smooth muscle **(Davis et al., 1982)**. Vasoactive intestinal peptide (VIP) is favoured as the likely inhibitory neurotransmitter. It is possible that defective NANC inhibitory nerve function in asthma could lead to elevated bronchial tone. **(Barnes, 1984)**

Viral upper respiratory infections are associated with alteration in airway autonomic responsiveness. **(Boushey, 1980)**

Epithelial desquamation resulting from airway in inflammation is also clearly a major factor influencing airway function in asthma since this expose sensory afferent nerves perhaps resulting in both neurogenic inflammation with bronchial obstruction and loss of a protective Epithelial derived inhibitory factor (EPDIF). The later is generated in response to some spasmogens. **(Goldie, 1985)**

There is increasing evidence that neuropeptides may be the neurotransmitter of the autonomic nerves such as, tachykinin, substance P, neurokinin A and calcitonin gene related peptide. All these are sensory neuropeptide that may be released from sensory nerves via an axon reflex. **(Barnes, 1986)**

Release of these peptides, triggered perhaps by the inflammatory peptide bradykinin, would thus exaggerate and spread inflammatory response in the airways, particularly since the enzymes that would normally control this response may be absent. **(Barnes, 1990)**

Autonomic nervous system abnormalities are not specific for asthma, since they have also been observed in other conditions that share many clinical features with asthma as: cystic fibrosis **(Davis, 1983)**, allergic rhinitis **(Smith et al., 1980)**, chronic obstructive lung disease **(Lemanske, 1980)**, atopic dermatitis **(Grewe et al., 1982)** and endogenous depression and psychomotor agitans. **(Mann, 1985)**