Serum ACTH and Immunoglobulin Changes in Asthmatic Patients

Thesis

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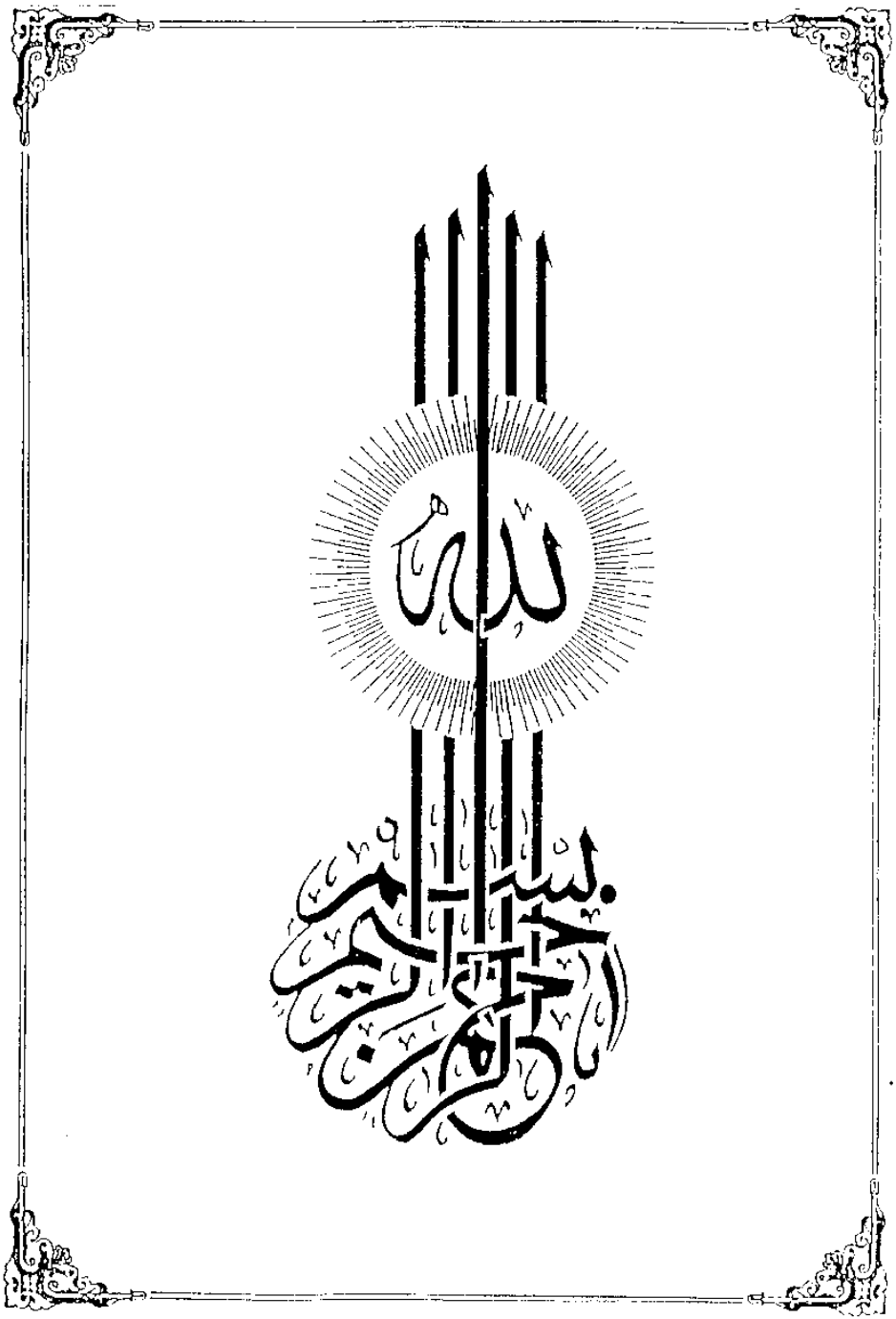
To My Parents & My Fiancée



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LIST OF ABBREVIATIONS

%	:	Per cent
ACTH	:	Corticotropic hormone
A/G ratio	:	Albumin/globulin ratio
ATP	:	Adenosine triphosphate
B	:	Bound radioactivity
B_0	:	Binding determined at the zero standard point
BAL	:	Broncho-alveolar lavage
BHR	:	Bronchial hyperactivity
BL	:	Bronchial lavage
B-LPH	:	B-lipotropin hormone
cAMP	:	Cyclic adenosine monophosphate
cGMP	:	Cyclic guanidine monophosphate
CIC	:	Circulating immune complex
cpm	:	Count per minute
D.S.C.G.	:	Disodium cromoglycate
ECF-A	:	Eosinophil chemotactic factor of anaphylaxis
EDTA	:	Ethylenediamine tetraacetic acid
ELISA	:	Enzyme linked immuno sorbent assay
FEV_1	:	First second forced expiratory volume
FVC	:	Forced vital capacity
g	:	Gram
GTP	:	Guanidine triphosphate
HPA	:	Hypothalamic-pituitary-adrenal
HR	:	High resolution
HRF	:	Histamine releasing factor
I	:	Iodine

IgD	:	Immunoglobulin D
IgE	:	Immunoglobulin E
IgG	:	Immunoglobulin G
IgM	:	Immunoglobulin M
IgND	:	Immunoglobulin ND
IU/ml	:	International unit per milliliter
K^+	:	Potassium
KIU	:	Kallikrein inactivator units
L	:	Liter
μCi	:	Microcurie
μg/day	:	Microgram per day
μl	:	Microliter
max.	:	Maximum
mg	:	Milligram
ml	:	Milliliter
mm	:	Millimeter
mmol	:	Millimole
N	:	Normality
nm	:	Nanometer
No	:	Number
PC_{20}	:	Provocation concentration of histamine required to induce a 20% fall in FEV_1
Pg	:	Picogram
POD	:	O-Phenylenediamine dihydrochloride
RAST	:	Radioallergosorbent test
r.p.m.	:	Revolution per minute
sBPT	:	Specific bronchial provocation test
SD	:	Standard deviation

Sp HRF	:	Spontaneous histamine-releasing factor.
SRS-A	:	Slow reactive substance of analphylaxis
TMA	:	Trimellitic anhydride
TM-HSA	:	Trimellityl-human serum albumin
U/ml	:	Unit per milliliter
X^2	:	Chi-square

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PART I
INTRODUCTION

INTRODUCTION

The first detailed discussions of asthma did not occur until the second century of the Christian era, when Aretaeus recognized that the disease was chronic with an episodic nature, that it affected adults and children, and that it occurred in both sexes *(Adams, 1856).*

The term asthma is derived from a Greek (asema) word that means panting (i.e., breathing quickly) or grasping for breath of severe nature (Alexander, 1928). The *Ciba Guest Symposium (1958)* defined asthma as the condition of subject with widespread narrowing of the bronchial airways which changes in severity over a short period of time, either spontaneously or under treatment and is not due to cardiovascular disease.

The term bronchial asthma, often used unqualified as asthma is employed to describe recurrent, generalized airways obstructions which, at least in the early stages, is paroxysmal and reversible. The most important clinical manifestations are dyspnoea and wheeze, although in severe asthma the obstruction may be so great that there is no audible wheeze *(Miller et al., 1960).* Recently, *Rees (1984a)* defined asthma as a disease characterized by wide variations over short period of time in resistance to airflow in intrapulmonary airways.

The great majority of surveys have found a male excess of asthma in childhood, often about 1.5:1.0, and tending to decrease as adolescence is approached. This may perhaps be due to a greater susceptibility to viral infection in boys. In adults there is little difference between the sexes, though in some series an onset after the age of 35 was much more common in women *(Editorial, 1971).*

Four main factors probably contribute to the bronchial obstruction which characterizes asthma:

1. Contraction of bronchial muscle or true bronchospasm: contraction of the bronchial muscle in response to a specific allergen has been shown experimentally in human lungs resected from patients with allergic asthma *(Schild et al., 1951)*. The bronchial muscle is found to be hypertrophied in patients dying from status asthmaticus *(Spencer, 1977)*.
2. Swelling of the mucous membrane: the importance of this is uncertain. At autopsy much of the bronchial epithelium is shed, though the basement membrane is thickened *(Spencer, 1977)*.
3. Plugging with viscous mucus: in patients dying in status asthmaticus the characteristic findings at autopsy are an increase in mucous glands and goblet cells with plugging of the peripheral bronchi by viscid mucus. It may be, of course, that the plugging occurs because the bronchial muscle is unable to relax and the bronchi cannot be cleared. Local dehydration may also play a part. Replacement of ciliated cells by goblet cells, and perhaps less effective ciliary movements may also interfere with the clearing mechanism *(Wanner et al., 1975)*.
4. Invagination of the posterior mucous membrane between the tips of the semicircular cartilages of the intrathoracic trachea and the larger bronchi on expiration owing to high transmural pressure. Although in the past, less attention has been paid to this factor, it may play a part *(Groen, 1976)*.

There are two clinical types of bronchial asthma, intrinsic and extrinsic asthma, the differentiation between them is controversial. The

criteria considered most acceptable are the presence or absence of skin sensitivity to antigens and bronchial provocation tests *(Ende et al., 1982)*.

Extrinsic Asthma

Asthma developing during childhood usually shows considerable spontaneous variability. In young people with asthma there are identifiable factors which provoke wheezing, although patients rarely have a single identifiable extrinsic cause for all their attacks. This extrinsic asthma is often associated with other features of atopy such as rhinitis and eczema *(Rees, 1984a)*.

A family history of asthma and the presence of other allergies, such as hay fever and eczema, appear to be more prevalent in patients with extrinsic asthma *(Daniele, 1980)*.

Intrinsic Asthma

When asthma begins in adult life the airflow obstruction is often more persistent and most exacerbations have no obvious stimuli other than respiratory tract infections. This pattern is often labelled intrinsic asthma *(Rees, 1984a)*.

Autoantibodies have been reported in asthmatics *(Turner, 1974)*, but these are believed to be more commonly associated with intrinsic, skin test negative asthma and are directed against non-organ specific antigens.

Recently, while testing the sera from asthmatic patients for the presence of cytotoxic lung antibodies, a distinct difference was found between patients considered to be intrinsic asthmatics as opposed to those classified as extrinsic asthmatics. These cytotoxic lung antibodies are organ

specific and present in almost all atopic asthmatics tested *(Ende et al., 1982)*. Levels of IgE are one of the criteria used to differentiate intrinsic from extrinsic asthma. IgE levels tended to be higher in extrinsic as compared to intrinsic asthmatics *(Cuevas et al., 1977)*.

Grove and associates (1975) have noted high IgG levels in asthmatics with a family history of asthma and high IgE levels in asthmatics with a past history of atopic eczema; IgE levels, however, could not be used to differentiate intrinsic and extrinsic asthma.

A variety of compounds that are used in industry have caused asthma in some individuals. Also asthma can be induced or aggravated by physical exercise and by emotional upsets *(Fishman, 1980)*.

Occupational Asthma

The importance of occupational asthma has been increasingly recognized over the past few years. Some estimates suggest that over 5% of cases of adult asthma have an occupational origin *(Ress, 1984b)*. Asthmatic patients choosing a career should avoid occupations where they are likely to be exposed to large quantities of non specific stimuli such as dust and cold air. Occupational asthma is now officially recognized as an industrial disease and is subjected to compensation. It is defined as asthma which develops after a variable period of symptomless exposure to a sensitizing agent at work *(Rees, 1984b)*. Occupational asthma can occur in any one without any special predisposition to the disease and resolve after removal from the offending environment *(Godfrey, 1985)*.

Avilla (1983) suggested that occupational asthma was not always a true asthma but sometimes was extrinsic pulmonary granulomatosis presented with asthma like symptoms.

Among the agents known to cause occupational asthma are platinum salt, isocyanates, epoxy resins, colophony fumes, proteolytic enzymes, laboratory animals, insects and grain or flower dust *(Rees, 1984b).*

A case of a nonatopic patient in whom exposure to *Voacanga africana* dust precipitated asthma has been reported. Studies revealed the presence of immediate skin test reactivity to *Voacanga africana* dust, and specific anti-*Voacanga africana* antibodies were detected in the patient's serum by the reverse enzyme immunoassay technique. Bronchial challenge with a *Voacanga africana* extract also resulted in an immediate asthmatic response without late reaction. These findings suggested a type I IgE, mediated immunologic mechanism as being responsible for the patient's respiratory symptoms. Unexposed persons did not exhibit reactivity to this seed with any of the tests referred to above. This is the first reported case of occupational asthma caused by *Voacanga africana* seeds *(Hinojosa et al., 1987).*

Allergic reactions to rat urinary proteins are an important cause of occupational asthma and rhinitis among laboratory workers *(Platts-Mills et al., 1987a).*

Exercise Induced Asthma

It is claimed that virtually all asthmatics respond to exercise with an increase in airways obstruction, though, for obvious reasons, most studies have been carried out on children and young people. In normal subjects and in patients with other respiratory diseases there is usually bronchodilation of

up to 10 per cent during exercise; minor bronchoconstriction (less than 5 per cent) may be detected after exercise *(Fitch and Godfrey, 1976).*

The exercise effect is greater after running, less after cycling and substantially less after swimming; the reason for this is uncertain. The mechanism of the exercise effect is not yet clarified but seems likely to be associated with the release of some form of bronchoconstrictor mediator, as the effect is depressed or prevented by preliminary cromoglycate (cromolyn) but not by atropine. After exercise there is a latent period during which further exercise has much less effect, suggesting that the mediator has not yet had time to reform *(Sly, 1976).*

It has been reported that the phenomenon is almost completely prevented by nasal breathing throughout the exercise *(Shturman et al., 1978).*

It is possible that the exercise effect is due to bronchial irritation by dry cold air *(Strauss et al., 1977).*

Latent Asthma

It has been shown that some individuals without asthma, but who have a family history of it, nevertheless, have hypersensitive bronchi; the bronchoconstrictor response to histamine or exercise is greater than that in normal subjects. Some of these will never develop asthma; it is possible that others will do so later in life, depending on the intensity of allergen or other exposure. Conversely children who have 'grown out of asthma' can usually still be shown to have more reactive bronchi than normals. As it is unlikely that external factors have altered, the loss of asthma must be either due to some degree of loss of bronchial hypersensitivity, to the development of