A FAMILY STUDY APPROACH TO THE GENETIC BASIS OF ASTHMA

BY

BONNIE SUZANNE SIBBALD

A thesis submitted to the University of London in conformity with the requirements for the degree of Doctor of Philosophy

Department of Medicine
Cardiothoracic Institute,
Brompton Hospital.

A FAMILY STUDY APPROACH TO THE GENETIC BASIS OF ASTHMA

By Bonnie Sibbald

The hereditary basis of asthma was investigated by family studies of patients with 'extrinsic', 'intrinsic', childhood and adult forms of the disease. Asthma probands were selected, according to defined criteria, from hospital outpatient clinics and general practices. Non-asthmatic controls, selected from the general practices, were matched for age and sex with certain of the asthma probands. Information on relatives was obtained from medical records and by personal interviews and questionnaires. The atopic status of probands and their relatives was assessed by skin prick testing.

Extrinsic, intrinsic, childhood and adult groups of asthma probands resembled each other both in the proportion of probands with at least one asthmatic relative and in distribution of asthma among relatives. In all groups, the prevalence of asthma in the siblings of probands was higher when one or both parents were asthmatic than when neither parent was affected. In addition, asthma was more prevalent in the relatives of child and adult asthma probands than in the relatives of controls.

On the other hand, when atopic and non-atopic probands were examined separately, it was found that the prevalence of asthma was higher in the relatives of atopic than non-atopic asthma probands. However, its prevalence did not differ between the relatives of atopic and non-atopic controls. The prevalence of atopic asthma in the relatives was higher for atopic than non-atopic asthma probands; whereas the prevalence of non-atopic asthma did not vary with the probands' atopic status.

In adult probands and their relatives, age of onset of asthma had no demonstrable genetic basis apart from its relation to atopy, nor was it associated with severity. Although a correlation was found between severity in probands and severity in relatives, it was unclear whether this was genetic or environmental. No evidence of a direct genetic sex-influence was found in either atopic or non-atopic asthma.

It was concluded that extrinsic, intrinsic, childhood and adult forms of asthma shared a common genetic defect which had a polygenic mode of inheritance. Although asthma was inherited independently of atopy, the presence of atopy increased the likelihood of a genetic predisposition to asthma being expressed.

TABLES OF CONTENTS

	Page
Abstract	i
Table of Contents	ii
List of Tables	v
List of Figures	ix
Preface	x
Acknowledgements	xi
CHAPTER ONE	
Heredity in Asthma - A Review of our Current Understanding	
Introduction	1
Family and Twin Studies	4
Asthma Genes	8
Mode of Inheritance of Asthma	13
Environmental Influences	16
Present Study	18
CHAPTER TWO	
Extrinsic and Intrinsic Asthma	
Introduction	21
Patients and Methods	24
Results	29
Discussion	50
Conclusion	56

Page

CHAPTER THREE

Asthma in Children and its Association with Wheezy Bronchitis

Introduction 57

Patients and Methods 61

Results 64

Discussion 78

CHAPTER FOUR

Asthma in Adults

Introduction 87

Patients and Methods 88

Results 96

Discussion 105

CHAPTER FIVE

Age of Onset, Severity and Sex Distribution of Asthma

Introduction 110

Patients and Methods 111

Results 112

Discussion 127

Page

CHAPTER SIX

Heredity in Asthma - Its Theoretical and Practical Importance

Synopsis of Findings 137

Mode of Inheritance 147

Genetic Counselling 154

Relationship of Findings to Immunopharmacological Investigations 158

Conclusion 163

APPENDICES

A. Separate Analyses of the Data from the Brompton Hospital and the Doncaster Royal Infirmary 165

B. Sample Asthma Questionnaire 171

C. Pilot Study of Asthma Questionnaire 175

D. Sample Letters to Patients 185

E. Sample Calculations for Tables 187

REFERENCES 189

CIRCULA VITAE 202

ADDITIONAL READING MATERIAL inside back cover

LIST OF TABLES

Table No.		Page
1	Comparison of Brompton and Doncaster Asthmatics	
	A. Polar Extrinsic Asthmatics	33
	B. Polar Intrinsic Asthmatics	34
2	Clinical Characteristics of Probands: Brompton and Doncaster Pooled	35
3	Prevalence of Asthma, Hay Fever and Eczema Among First Degree Relatives of Polar Extrinsic Asthmatics: Brompton and Doncaster Pooled	36
4	Prevalence of Asthma, Hay Fever and Eczema Among First Degree Relatives of Polar Intrinsic Asthmatics: Brompton and Doncaster Pooled	37
5	Prevalence of Asthma Among Siblings of Polar Asthmatics When Neither, One or Both Parents Have Asthma: Brompton and Doncaster Pooled	38
6	Prevalence of Hay Fever Among Siblings of Polar Asthmatics When Neither, One or Both Parents Have Hay Fever: Brompton and Doncaster Pooled	39
7	Prevalence of Eczema Among Siblings of Polar Asthmatics When Neither, One or Both Parents Have Eczema: Brompton and Doncaster Pooled	40
8	The Clinical Characteristics of the Probands	44
9	Prevalence of Asthma, Hay Fever and Eczema Among First Degree Relatives of Asthmatics	45
10	Significance Tables	
	A. Influence of Atopy, Hay Fever/ Eczema (HES) and Allergic Provoking Factors (PA) in Asthmatics on the Prevalence of Asthma, Hay Fever and Eczema Among Their First Degree Relatives	46

Table No.		Page
10	B. Influence of Atopy on the Prevalence of Asthma, Hay Fever and Eczema Among First Degree Relatives of Asthmatics Grouped According to Skin Test Sensitivity	46
11	Prevalence of Asthma in Parents, Siblings and Offspring of Asthmatics	47
12	Prevalence of Hay Fever in Parents, Siblings and Offspring of Asthmatics	48
13	Prevalence of Eczema in Parents, Siblings and Offspring of Asthmatics	49
14	Characterization of Probands	70
15	Clinical Characteristics of Probands in Skin Test Group	71
16	Prevalence of Asthma, Atopy, Hay Fever and Eczema in First Degree Relatives	72
17	Significance of the Differences in the Prevalence of Asthma, Hay Fever, Eczema, and Atopy Between Parents and Siblings of Probands, and Between Relatives of Atopic and Non-Atopic Probands	73
18	Prevalence of Asthma in Siblings of Asthmatics when Neither, One or Both Parents are Asthmatic	74
19	Distribution of Asthma and Atopy in Relatives of Probands	75
20	Prevalence of Atopic and Non-Atopic Asthma Among First Degree Relatives of Probands	76
21	Prevalences of Asthma and Wheezy Bronchitis in the First Degree Relatives of the Probands	77
22	Response Rates Among Asthmatic and Control Probands	99
23	Characterization of Probands	100
24	Distribution and Prevalence of Asthma Among Relatives of Probands	101
25	Distribution of Atopic and Non-Atopic Asthma Within Families	102

Table No.		Page
26	Risk of Asthma in Siblings of Asthma Probands	103
27	Influence of Breast Feeding on Incidence of Asthma	104
28	A. Association Between Age of Onset and Atopic Status of Probands and Their Affected First Degree Relatives	114
	B. Association of Age of Onset with Frequency of Attacks and Frequency of Remission for Five or More Years	116
29	Association Between Age of Onset of Asthma in Probands and the Prevalence of Asthma in Their First Degree Relatives	118
30	Probands' Responses to Questionnaire Section C	121
31	Prevalence of Asthma in Siblings of Probands With One Affected Parent	125
32	Prevalence of Asthma Among Male and Female Relatives of Male and Female Asthmatics	
	A. Probands with Three or More Positive Prick Tests	126
	B. Probands with No Positive Prick Tests	126
33	Prevalence of Asthma in the First Degree Relatives of Asthmatic and Control Patients	144
34	Prevalence of Asthma in the Siblings of Asthma Patients with Neither, One or Both Parents Asthmatic	145
35	Distribution of Asthma Among First Degree Relatives of Asthma Patients	146
36	Expected Proportion of Asthmatic Offspring from Various Mating Types	151
37	Comparison of Observed with Expected Risks of Asthma in Offspring	
	A. Risk of Asthma in Offspring of Atopic Patients: Gene Frequency of 15% (A_2) and Penetrance of 30% (P_1)	152
	B. Risk of Asthma in Offspring of Non-Atopic Patients: Gene Frequency of 15% (A_2) and Penetrance of 10% (P_2)	152

Table No.		Page
37	C. Combined Risk of Asthma in Offspring: Gene Frequency of 10% (A_1) and Penetrance of 30% (P_1)	153
38	Expected Mating Frequencies	157
39	Prevalence of Asthma, Hay Fever and Eczema Among First Degree Relatives of Polar Extrinsic Asthmatics	165
40	Prevalence of Asthma, Hay Fever and Eczema Among First Degree Relatives of Polar Intrinsic Asthmatics	166
41	Prevalence of Asthma Among Siblings of Polar Asthmatics When Neither, One or Both Parents Have Asthma	167
42	Prevalence of Hay Fever Among Siblings of Polar Asthmatics When Neither, One or Both Parents Have Hay Fever	168
43	Prevalence of Eczema Among Siblings of Polar Asthmatics When Neither, One or Both Parents Have Eczema	169
44	Significance Table: Comparison of the Prevalence of Asthma, Hay Fever and Eczema Among First Degree Relatives of Polar Extrinsic and Polar Intrinsic Asthmatics	170
45	Response Rate Among Probands to Questionnaire Survey	180
46	Questionnaire Section A: Patients Responses	181
47	Questionnaire Section B: Patients Responses	182
48	Questionnaire Section C: Patients Responses	183

LIST OF FIGURES

Figure No.		Page
1	Classification of Probands	28
2	The Canbury Medical Centre (Kingston-upon-Thames)	90
3	Correlation Between Age of Onset and Severity in Patients	115
4	Correlation Between Age of Onset in Atopic Patients and Age of Onset in First Degree Relatives	117
5	Correlation Between Severity in Patients and Prevalence of Asthma in Relatives	122
6	Correlation in Severity of Asthma Between Patients and First Degree Relatives	123
7	Description of Probands	179
8	Distribution of Severity Scores	184

PREFACE

The role of heredity in asthma is of both practical and scientific interest. A clear understanding of the genetic basis of asthma would lead, not only to advances in our theoretical knowledge of the causes of asthma, but also to improvements in the identification and counselling of high risk patients.

Unfortunately, our understanding of the genetics of asthma is limited. Although previous studies have done much to clarify the role of heredity in asthma, a number of important issues have yet to be investigated. Foremost among these are the problems of whether asthma is genetically homogeneous and whether asthma has an hereditary component independent of that which underlies atopy. Also of interest is the role heredity may play in governing the age of onset, severity and sex distribution of asthma.

In this thesis, I have attempted to resolve some of these important questions. My background and training have meant that the approach to this task was that of a geneticist, the medical aspects having been learned over the course of the investigation. Nonetheless, I have endeavoured to present the findings in a form which is comprehensible and meaningfull to physicians and scientists alike.

ACKNOWLEDGEMENTS

I have been helped by many people to all of whom I should like to express my thanks. In particular, I am indebited to my supervisor, Professor Margaret Turner-Warwick, whose valuable advice during all phases of this research was a tremendous aid. Special thanks must also be given to Dr. Joan Slack for her counselling on the genetic aspects and to Dr. Ian Gregg for his criticism of the text and our many stimulating discussions. I am also indebited to Dr. Hugh Smyllie, Dr. Mary Horn and the doctors of the Canbury Medical Centre (Kingston-upon-Thames) for making their patients and medical files available for study. Finally, I should like to thank the many patients without whose patience and cooperation this work would not have been possible.

The study was supported by a Commonwealth Scholarship from the British Council and the Association of Commonwealth Universities, to whom I wish to express my gratitude.

CHAPTER ONE

HEREDITY IN ASTHMA - A REVIEW OF OUR CURRENT UNDERSTANDING

There is no universally recognized definition of bronchial asthma. Although it is accepted that episodic breathlessness is the cardinal symptom of asthma, patients vary so widely in their clinical presentation that it is difficult to find a set of diagnostic criteria which is both comprehensive and exclusive. The diagnostic criterion most frequently encountered is that of an increase in airflow resistance which is reversible either spontaneously or with treatment (Ciba Sympsium, 1971). The problem is one of degree of reversibility since, at one extreme, obstruction to airflow may become fixed when previously it was reversible. While at the other extreme, a small degree of reversible airflow obstruction may be found in such disorders as chronic bronchitis, whose etiology appears fundamentally different from that of asthma.

Hyperreactivity of the bronchi is the abnormality most commonly ascribed to asthma. The bronchi of asthmatic subjects are thought to have both a decreased stimulus threshold and an increased response for bronchoconstriction, as compared with those of normal subjects. Airflow obstruction arises from the increase in muscle bulk associated with bronchoconstriction together with mucous hypersecretion and oedema of the respiratory mucosa. Bronchial hyperreactivity, as assessed by methacholine or histamine challenge, is not related to sex, age, type of asthma, allergic background

or initial level of airways obstruction (Cade and Pain, 1971). However, the wide variability in the clinical presentation of asthma has led many to suppose that the mechanism underlying bronchial hyperractivity may differ between patients.

As early as 1928, Rackemann recognized that some forms of asthma appeared to be allergic in nature, whereas other forms did not (Rackemann and Edwards, 1952). His division of asthma into an allergic or 'extrinsic' type and a non-allergic or 'intrinsic' type has survived to the present with little modification. Extrinsic asthma may now be used to describe those patients whose asthma is provoked by known external agents associated with specific antibody; whereas intrinsic asthma may be used to describe those patients whose asthma appears unrelated to any demonstrable immunological stimulus. In addition, there are a large number of patients, forming an intermediate group, who fail to satisfy the variously stated criteria for either extrinsic or intrinsic asthma.

Relatively little is known of the mechanism of bronchial hyperreactivity in either extrinsic or intrinsic asthma. Investigation of extrinsic patients has shown that there are two main patterns of response to antigenic challenge: (1) the immediate asthmatic reaction, thought to be mediated by a type I inflammatory process, and (2) the late asthmatic reaction, which was thought to arise from a combination of types

I and III inflammatory processes (Pepys, 1973), although this has now been disputed. These inflammatory mechanisms well describe asthmatic attacks provoked by specific antigens, but cannot account for the susceptibility of many patients to attacks provoked by non-allergic stimulii, such as exercise and emotion.

Although our understanding of extrinsic asthma is limited, even less is known of intrinsic asthma. Indeed it is not certain whether the factors provoking intrinsic asthma are externally or internally derived, or whether patients have similar or different etiologies. The presence of eosinophilia in some patients and their responsiveness to corticosteroid therapy shows there is an inflammatory component. However, its origin has yet to be determined.

Whatever the mechanisms underlying bronchial hyperreactivity, it is certain that genetic factors are involved. The existence of an hereditary basis to asthma has long been known, although its nature and magnitude have yet to be fully described. The main obstacle to research has been and continues to be, the absence of an unambiguous definition of asthma. Investigators cannot be certain of selecting homogeneous groups of patients for study, and the findings of one investigation cannot readily be compared with those of another. Despite these drawbacks, genetic studies have contributed much to our understanding of asthma and their potential in increasing this knowledge has not yet been exhausted.

FAMILY AND TWIN STUDIES

The occurrence of multiple cases of asthma in individual families was noted as early as the 17th century. However, the significance of this familial aggregation was not recognized until the late 1800's when Mendel's work was rediscovered by Correns and DeVries. There followed the publication of numerous pedigrees reaffirming the tendency of asthma to cluster in families and suggesting that this disorder may have an hereditary basis.

One of the most important of the early family studies was that of Schwartz (1952). His study group consisted of 191 asthmatic patients (referred to by him as 'allergic') and 59 patients with Baker's asthma (referred to by him as 'non-allergic'). Schwartz compared the prevalences of asthma and other allergic diseases in the relatives of these patients with those in the relatives of 200 non-asthmatic controls, matched for age. Results showed that the family history of asthma did not differ between his 'allergic' and 'non-allergic' asthmatic patients. However, the prevalence of asthma and other allergic diseases was significantly higher in the relatives of both groups of asthmatics than in the relatives of controls. On this evidence, he concluded that asthma was genetically based.

Leigh and Marley (1967) later confirmed these findings. From a general practice population, they

selected 55 asthmatic patients and 55 non-asthmatic controls, matched for age and sex. The prevalence of asthma, hay fever and eczema in the first and second degree relatives of these patients were obtained by personal interview, and where possible verified by reference to the patients' medical records. Results showed that the prevalence of all three disorders was higher in the relatives of asthmatic patients than in the relatives of controls. Thus Leigh and Marley (1967) agreed with Schwartz (1952) in concluding that asthma was hereditary.

Additional evidence for an hereditary component in asthma was provided by family studies which showed that the prevalence of asthma in offspring was higher when one or both parents were asthmatic than when neither parent was affected (as summarized by Charpin and Arnaud, 1971). A recent study by Gerrard et al, (1976) supported these observations, but showed also that hay fever or eczema in offspring were all higher when parents suffered from one or more of these disorders. However, Gerrard et al (1976) showed that children were more likely to develop the same allergic disorder as their parents, than to manifest some other allergy. Therefore, it was concluded that the predisposition to a specific allergic disease, such as asthma, may be inherited in addition to a general susceptibility to allergy.

The studies of Schwartz (1952), Leigh and Marley

(1967) and Gerrard et al (1976) clearly show that asthma aggregates in families. However, such family studies were unable to show how much of this aggregation was caused by a common heredity and how much was attributable to a common environment. This issue was resolved by twin studies.

Twin studies can be used to assess the relative affects of heredity and the environment on the development of a disorder. The technique involves determining the percentage of monozygotic (MZ) twins which are concordant for the disease under investigation, and comparing this percentage with the percentage of dizygotic (DZ) twins concordant for the disease. The assumption is made that environmental variation is the same for DZ twins as it is for MZ twins. Since MZ twins are genetically identical, whereas DZ twins share only half their genes, it follows that any increase in the concordance among MZ twins as compared with that among DZ twins indicates the disorder must have a genetic component.

Early studies based on small numbers of twins suggested that the concordance for asthma was higher in MZ than in DZ twins (Spaich and Ostertag, 1936; Charpin and Arnaud, 1971). These findings were later confirmed by Edfors-Lubs (1971) who examined the concordance of asthma and other allergic diseases in 2434 pairs of MZ twins and 4302 pairs of DZ twins. Results showed that the concordance in MZ twins

was significantly higher than that in DZ twins for both the number and the specificity of their allergic symptoms. From this she concluded that the severity of allergy, as measured by the number of allergic symptoms, as well as the predisposition to a specific allergy were hereditary. However, since the concordance for asthma was low (ie., 19% in 2434 pairs of MZ twins and 4.8% in 4302 pairs of twins) she also suggested that environmental factors must play a prominant role in the development of this disorder. Subsequent twin studies have supported these findings (Townley et al, 1976).

When they are considered together, these family and twin studies strongly suggest that asthma has a genetic basis. Family studies have shown that asthma clusters in the families of asthmatics, while twin studies have shown that part of this familial aggregation is genetically determined. Researchers have therefore turned their attention to the problem of indentifying the 'asthma gene'.

ASTHMA GENES

The search for an asthma gene initially centred on associations between asthma and the major histocompatibility antigens. The production of these antigens is genetically controlled by the HL-A locus which consists of three subloci, each with many different alleles. As the subloci lie adjacent to each other on the chromosome, the alleles on the same DNA strand are inherited as a single unit known as a haplotype.

Early family studies had shown that sensitivity to ragweed pollen extract was closely associated with HL-A haplotype (Levine et al, 1972; Marsh et al, 1973). Subsequent investigations then showed that the specificity of this allergy might be determined by an immune response gene (Ir) linked to the HL-A locus (Blumental et al, 1974). Although these findings have since been disputed (Black et al, 1976), the possibility remained that Ir genes might exist, one of which might confer a specific susceptibility to asthma.

Although literally hundreds of investigators have looked into the question of linkage between HL-A and asthma, the findings have been singularly inconclusive. In some studies, associations between asthma and HL-A have been reported (Wagatsuma et al, 1976; Turner et al, 1977; Brostoff et al, 1976; Thorsby et al, 1971). However, in many other studies, no such associations have been found

(Flaherty et al, 1977; Bruce et al, 1976; Rachelefsky et al, 1976 and 1977).

At least part of this confusion has been the result of poor technique. Often such large numbers of HL-A specificities were examined that, by chance alone, some significant associations would have been expected. In addition, case selection has sometimes been poor, including patients whose asthma was complicated by other kinds of chronic obstructive lung disease.

In a recent study by Turton et al (1979), care was taken to avoid these common pitfalls. Only patients with carefully defined extrinsic atopic or intrinsic asthma were accepted, while those who satisfied the MRC criteria for chronic bronchitis were excluded. Correction was made for the number of HL-A specificities examined.

The association between asthma and HL-A was assessed using both population and family study methods. In the population study, the frequency of HL-A antigens was examined in 41 intrinsic and 40 extrinsic asthmatic patients, and the distributions compared with that in 167 normal individuals. There were no significant differences between groups.

In the family study, the haplotype of the index case was compared with that of his asthmatic and non-asthmatic siblings. In the ten families which were suitable for study, no significant

associations were found between HL-A haplotype and asthma. Turton et al (1979) therefore concluded that 'no association of overall biological importance between HL-A and asthma had been found'.

While these findings cannot be considered definitive proof that asthma is never linked to HL-A, they do show that in many patients, genes associated with the HL-A complex do not influence the development of asthma. Thus HL-A is unlikely to be an important factor in the causation of asthma.

Another promising avenue in the search for an asthma gene concerned the association of asthma with $alpha_1$-antitrypsin (ANT). ANT is the most common protease inhibitor in serum, accounting for nearly 90% of all trypsin inhibiting capacity. Production of this enzyme is regulated by a gene (Pi), with nine alleles. The 'M' allele is the most common giving normal levels of ANT, whereas alleles 'P,S,W and Z' are associated with reduced levels. (Fagerhol and Hauge, 1969).

It has been shown that the severe deficiency of ANT accompanying the SS and ZZ genotypes is associated with an increased risk of developing emphysema and possibly other forms of chronic obstructive lung disease (COLD) (Lieberman, 1969; Townley et al, 1970). Therefore, it seemed possible

that moderate deficiences of ANT accompanying the MS and MZ genotypes might also lead to COLD, including asthma.

Two approaches to this problem were adopted. To begin, the prevalences of ANT deficient phenotypes in patients with COLD, including asthma, were compared with those in a group of asymptomatic controls, matched for age and sex. Many studies showed that the prevalences of MS and MZ genotypes were higher in the patients with asthma, than in controls (Fagerhol and Hauge, 1969; Mano et al, 1975; Arnaud et al, 1976). It was also suggested that deficient ANT phenotypes might lead to an earlier age of onset and an increased severity of asthma (Arnaud et al, 1976), although this has been disputed (Katz et al, 1976). These findings support the hypothesis that the moderate deficiency of ANT associated with the MS and MZ genotypes may lead to an increased risk of developing asthma as well as other forms of COLD.

In a second approach to the problem, the distribution of Pi genotypes in large, unselected populations was determined. The prevalences of COLD in patients with Pi deficient genotypes were then compared with those in patients with normal (MM) genotypes. In such studies, no significant association was found between Pi genotype and COLD, including asthma (Morse et al, 1975 and 1977;

Lebowitz et al, 1978).

When they are considered together, the findings of these studies suggest that moderate deficiencies of ANT do not alone cause asthma. However, when they occur, such deficiencies may act in conjunction with other factors to increase the risk of asthma. Thus studies dealing with unselected populations of patients will detect many people with deficient phenotypes but without asthma; while studies dealing with patients, selected because they have asthma, are likely to find a higher than normal prevalence of deficient phenotypes. It follows that Pi cannot be used as a marker gene for asthma since there is no strict association between Pi and asthma, and deficiency of ANT does not necessarily cause asthma.

Other investigations have suggested that asthma is associated with MN, haptoglobin (2-2) blood type (Ksenofontov, 1974; Ksenofontov and Rumyantzev, 1976) or with blood type A (de la Vega and Cortes, 1976). However, no associations of these kind were found in the more detailed study of Mano et al (1975).

In summary, the search for an asthma gene has, so far, proved fruitless. The most promising links between asthma and HL-A, and between asthma and Pi have failed to reveal any causal associations. Although future research may result in the discovery of an asthma gene, the evidence for an hereditary basis to asthma must rest for now on the family and twin studies already described.

MODE OF INHERITANCE

The knowledge that asthma has a genetic component is of limited use to physicians. Although it can be said that children of asthmatic parents have a higher risk of developing asthma, physicians are unable to counsel patients about the magnitude of their risk or to advise prospective parents of the chance their child might be affected. Such information depends on knowledge of how asthma is inherited.

Early studies designed to establish the mode of inheritance of asthma were based on the analysis of isolated pedigrees or small numbers of families. Standarized methods of case finding were not generally used and the statistical techniques available for analysis were poor. In consequence, many different modes of inheritance were initially proposed.

Cooke and Vander Veer (1916) investigated the families of 504 allergic patients, most of whom had asthma. They suggested that the predisposition to asthma, but not the disorder itself, was inherited as a Mendelian dominant gene. By suggesting that only the tendency to asthma could be inherited, they were able to explain why asthma might skip a generation in some families, a finding which would otherwise have conflicted with dominant inheritance.

In 1936, Weiner et al used published data to propose a new hypothesis. They agreed with Cooke

and Vander Veer in suggesting that asthma was caused by a dominant gene, but suggested that dominance was incomplete. Under this hypothesis, the hh homozygote would be normal, while the HH homozygote would develop early onset asthma. Since H could not completely mask the influence of h, Hh heterozygotes would also develop asthma, but the onset would occur later in life.

Schwartz (1952) agreed with earlier investigations in suggesting that asthma was inherited as a dominant trait. However, he rejected Weiner's hypothesis of incomplete dominance and substituted that of incomplete penetrance. By this he meant that the asthma gene required a particular genetic background in order to be expressed.

Tips (1954) advanced yet another theory. In a study of 99 families, he proposed that asthma and other allergies were caused by Mendelian reccessive genes, one for each disorder.

These early studies were followed by more sophisticated investigations. The best known of the more recent studies is that of Leigh and Marley (1967) who examined the distribution of asthma in the first and second degree relatives of 55 asthmatic patients. Analysis showed that the distribution was best explained by a dominant gene with incomplete penetrance, as proposed by Schwartz. However, Leigh and Marley noted that this mode of inheritance is,

in practice, indistinguishable from polygenic inheritance. Indeed, they preferred the polygenic to the dominant hypothesis, since polygenic inheritance could better describe the variability observed in the clinical presentation of asthma.

The twin study by Edfors-Lubs (1971) supported this conclusion. Edfors-Lubs used the concordance for asthma in MZ and DZ twins to generate the expected frequency of affected offspring in families where neither, one or both parents had asthma. This distribution was then tested for goodness-of-fit to distributions expected under various genetic hypothesis. Results showed that a good fit was obtained with both polygenic inheritance and dominant inheritance with incomplete penetrance. However, Edfors-Lubs preferred the polygenic hypothesis for the same reasons as Leigh and Marley (1967) had preferred it. Thus recent investigations agree that asthma is most likely a polygenic trait whose development is dependent on several genetic factors.

ENVIRONMENTAL INFLUENCE

While it seems certain that asthma has an hereditary basis its development may also be influenced by environmental factors. The extent to which the environment may influence heredity is revealed when changes in the prevalence of asthma are examined in time and space.

The highest known prevalence of asthma is found on the island of Tristan da Cunha, where a 1949 survey showed that some 49% of the 200 inhabitants suffered from asthma (Mantle and Pepys, 1974). Since this community was established by only 15 immigrants, some of whom were known to have had asthma, it seems certain that the unusually high prevalence of asthma is caused by genetic factors which have spread throughout the population as a result of inbreeding.

However, hereditary cannot be the sole factor accounting for this high prevalence. In 1974, a second survey showed that the prevalence of asthma had declined from 49% to 22% a drop too sudden to have resulted from genetic processes (Mantle and Pepys, 1974). Instead, the decline has been attributed to improved medical care, illustrating the importance of the environment in the development of this disease.

Many geographical differences in the prevalence of asthma have been noted (Gregg, 1977). For example, in Tucson, Arizona, Lebowitz and Burrows

(1975) have shown that the prevalence of asthma among indigenous people was 5.6%, significantly higher than the national rate of 3.0%. In Papua, New Guinea, Anderson (1974) found only three cases of asthma in a population of 2000, a prevalence far lower than in Australian or European communities. While these marked differences in prevalence may have arisen from differences between populations in the frequency of the asthma genes, immigration studies suggest this may not be the case.

Although very few such studies have been conducted, those which have been done show that children of immigrant parents have the same prevalence of asthma as indigenous children; whereas children born abroad have prevalences similar to their country of origin (Gregg, 1977). Morrison-Smith (1976) has noted that children born in England of West Indian and Asian parents have a high prevalence of asthma, while those born abroad have a low prevalence. Similarly, Waite et al (1980) showed that Tokelau islanders who have migrated to New Zealand have a higher prevalence of asthma than islanders who did not migrate. Thus environmental factors seem able to override or at least modify the effects of heredity.

PRESENT STUDY

It is clear that our understanding of the hereditary basis of asthma is limited. Although previous studies have done much to clarify the genetics of asthma, a multitude of important questions have been left unanswered: Is asthma a homogeneous or a heterogeneous disorder? Can asthma be inherited independently of atopy or is it simply an atopic manifestation? Are sex differences in the prevalence of asthma genetically based? Does hereditary influence the severity of the disease and its age of onset? What is the genetic relationship, if any, between asthma and other forms of wheezy illness?

The possibility that asthma may have more than one genetic form is most apparent when the relationship of extrinsic to intrinsic asthma is examined. The many clinical differences between typical groups of these patients strongly suggest their etiologies may differ. Nonetheless, as there are a number of intermediate patients who fail to satisfy the full criteria for either extrinsic or intrinsic asthma, the possibility cannot be ruled out that these two forms of asthma may share a common defect.

The role of atopy in asthma is intimately associated with the problem of heterogeneity. Atopy, which may be defined as the capacity to readily

produce IgE in response to environmental stimulation (Pepys, 1973), is known to have an hereditary basis (Marsh, Bias and Ishizaka, 1974). Since extrinsic and intrinsic asthmatic patients differ in their association with atopy, they must also differ genetically in at least one respect. However, the extent to which atopy may account for their many clinical and epidemiological differences is unknown.

Furthermore, the relationship of asthma to atopy in clearly atopic, extrinsic asthmatic patients is but poorly understood. Although family and twin studies have suggested that asthma may have an hereditary component separate from that which underlies atopy, it has remained unclear whether this asthmatic component can be manifested independently of atopy or whether it is dependent on atopy for its expression.

Also of interest is the possible influence of hereditary on the age of onset and severity of asthma, and its role in determining sex differences in the prevalence of asthma. The genetic basis, if any, of age of onset and severity has not yet been investigated. Similarly the role of heredity in determining sex differences in the prevalence of asthma has not been examined.

In this thesis are reported the findings of a series of family studies which help to resolve these

problems. The studies seek to (1) assess the hereditary similarities and differences between extrinsic and intrinsic asthma, (2) to examine the genetic basis of the relationship between asthma and atopy in children and in adults, and (3) to assess the role of heredity in the age of onset, severity and sex distribution of asthma.

CHAPTER TWO

EXTRINSIC AND INTRINSIC ASTHMA

Asthma may be classified into an extrinsic and an intrinsic form. Those patients whose asthma is provoked by known external agents associated with specific antibody may be said to have extrinsic asthma; whereas those patients whose asthma appears unrelated to any demonstrable immunological stimulus may be said to have intrinsic asthma. In addition, there is an intermediate group of patients who fail to satisfy the variously stated criteria for either extrinsic or intrinsic asthma.

When defined groups of extrinsic and intrinsic asthmatic patients are compared, a number of important clinical differences between them are revealed. The majority of extrinsic patients are atopic, giving a positive immediate response on skin prick testing to common environmental allergens (Turner-Warwick, 1971). They frequently have associated allergic diseases such as hay fever or eczema, and there is often a family history of asthma and allergic disease (Pepys, 1973; Williams and McNicol, 1969). Extrinsic asthma usually has its onset in childhood or adolescence and, in many studies, boys are more frequently affected than girls (Gregg, 1977). Wheezy attacks tend to be intermittent and remission rates are high with the majority of children recovering by early adulthood (Wilken-Jensen, 1978).

By definition, intrinsic patients are non-atopic, giving no response on skin prick testing (Turner-Warwick, 1971). Associated allergic disease is rare and a family history of allergy and asthma is found less frequently than in extrinsic patients (Molina et al, 1977; Pepys, 1973). Intrinsic asthma usually begins late in life (over 30 years of age) and women are equally, if not more often, affected than men (Molina et al, 1977). Attacks tend to occur more continuously and the remission rate is low (Ogilvie, 1962).

The relationship of extrinsic to intrinsic asthma is not well understood. On the one hand, the many clinical differences which exist between them suggest they may differ genetically. On the other hand, the existence of an intermediate group of patients and the fact that bronchial hyperreactivity is not related to allergic background or type of asthma suggest that extrinsic and intrinsic asthma may have similar etiologies. Thus the possibility exists that both forms of asthma share a common hereditary defect, although the ways in which it is manifested may differ between patients.

Genetic investigations have not explored, let alone resolved, this issue. Since, in the majority of studies, no attempt was made to separate patients

whose asthma was clearly immunological in nature from those whose asthma was not, it is uncertain that both forms of the disease are hereditary or, if they are, that they share a common genetic defect.

In this investigation, family studies were used to establish how and to what extent extrinsic and intrinsic asthma may resemble each other genetically. Since different physicians use different criteria in defining these types of asthma, the influence of the system of classification on the family history of asthma was also investigated.

PATIENTS AND METHODS

Probands were selected from outpatients attending the asthma clinics of the Brompton Hospital in London and the Doncaster Royal Infirmary in Doncaster, within the period of 1973-77. All patients had a history of episodic wheeziness or breathlessness and the majority demonstrated reversible airways obstruction either between successive visits or upon treatment with a bronchodilator. Ascertainment of probands was assumed to be single and incomplete (McKusick, 1969).

Both hospitals employed a standard protocol in the investigation of patients referred to their asthma clinics. All data arising from the routine investigation of these patients was recorded in their medical files and the information extracted by the author for the purposes of the present study.

Skin prick tests to 21 common allergens were performed on all patients. The allergens used included moulds, animal danders, house dust, pollens and foods. A positive reaction was defined as a weal with a diameter greater than that in the control test. Individuals were said to be atopic when one or more tests were positive. Non-atopic individuals had no positive tests.

The maximum peak expiratory flow rate (PEFR) was recorded on each visit to the clinic. Reversibility

of airways obstruction was defined as a change of 15% or more in PEFR between any two visits.

When possible, eosinophil counts were done on blood samples from all patients over the age of 15 years. Eosinophilia was said to be present when the count exceeded $400x10^9$ per litre.

Patients were asked if they had ever had hay fever or flexural eczema, and if they believed that their asthmatic attacks were precipitated by pollens, dust or animals.

Inquiries were also made about the patients' history of cough and sputum production. Patients who reported a cough lasting 3 or more months of the year for at least 2 years were diagnosed as suffering from chronic bronchitis (MRC criteria, 1965).

The smoking history was also recorded. Individuals who were smokers at the time of the first interview and those who had smoked in the past were all classified as smokers.

Information on the first degree relatives of asthmatics was taken from an asthma questionnaire completed by a physician on the patients' first visit to the clinic. For each patient, the following data were available: number and sex of siblings and offspring, number and sex of siblings and offspring with asthma, hay fever or eczema, number and sex of parents with asthma, hay fever or eczema.

Part One

For the preliminary study, markedly atopic patients were selected as extrinsic probands and clearly non-atopic patients were selected as intrinsic probands in order to maximise the probability of detecting differences between these two groups. These probands were designated 'polar' as they represented the extremities of the asthma spectrum.

Polar extrinsic asthmatics had 3 or more positive skin prick tests and either a positive history of hay fever and/or eczema, or asthma provoked by pollens, dust or animals. Only patients whose age of onset was under 20 years of age were accepted.

In contrast, polar intrinsic asthmatics had no positive skin prick tests, no history of hay fever or eczema, and their attacks of wheeziness were not provoked by pollens, dust or animals. Only patients whose age of onset was over 30 years were accepted.

The Chi-square test was used to assess differences between groups in the prevalences of asthma, hay fever and eczema in first degree relatives.

Part Two

In this study, the strict criteria adopted for polar extrinsic and polar intrinsic asthma were relaxed to assess the influence of the system of classification on the family history of asthma. Probands were selected from outpatients attending the asthma clinic of the Brompton Hospital.

Probands were classified in groups according to (1) their atopic status as assessed by skin prick testing, (2) their history of hay fever/eczema and, (3) their history of asthma provoked by pollens, dust or animals. The groups are described in figure one.

The influence of each of the three clinical characteristics of the probands on the prevalence of asthma in their first degree relatives was assessed by examining the variation in the prevalence of asthma between groups of patients who resembled each other in two of the characters (dependent variables), but differed with respect to the third (independent variable). A Chi-square value was calculated for each such comparison and the sum of these values used to determine the significance of the effect of the independent variable on the prevalence of asthma. The influence of each of the three clinical characters on the prevalence of hay fever and eczema was assessed in like manner.

Figure 1

Classification of Probands

Proband's Allergic History	Proband's Skin Test Result: Negative Group No.	N	1 or 2 Positive Group No.	N	3 or More Positive Group No.	N
PA-Negative HES-Negative	1	82	5	51	9	62
PA-Negative HES-Positive	2	10	6	10	10	60
PA-Positive HES-Negative	3	8	7	8	11	56
PA-Positive HES-Positive	4	7	8	8	12	154
SUM		107		77		332

PA - History of asthma provoked by pollens, dust or animals

HES - History of hay fever and/or eczema

RESULTS

Part One

The object of this study was to establish how and to what extrinsic and intrinsic asthma may resemble each other genetically. In order to maximise the possibility of detecting differences between these two forms of asthma, comparison was made of the family histories of asthma and allergy in markedly atopic patients (polar extrinsic asthmatics) with that in clearly non-atopic patients (polar intrinsic asthmatics).

The data were analysed separately for the Brompton and Doncaster clinics in order to ascertain whether there were any important differences between the two populations in the factors influencing the family history of asthma. The findings have been detailed in appendix A and summarized in Table one.

The clinical characteristics of the polar intrinsic asthmatics and their family history of asthma, eczema and hay fever did not differ between Brompton and Doncaster. However, among polar extrinsic asthmatics, there were reduced prevalences of both chronic bronchitis and reversibility in PEFR and an increased prevalence of eczema in Brompton patients as compared with Doncaster patients. In addition, the prevalence of asthma, hay fever and eczema were higher in the relatives of Brompton extrinsic asthmatics than

in the relatives of Doncaster extrinsic asthmatics. (table one).

Despite these differences, the distribution of asthma, hay fever and eczema in the relatives of both extrinsic and intrinsic asthmatics were similar in Brompton and Doncaster. The two populations did not differ in the distribution of asthma, hay fever or eczema among the parents, siblings and offspring of asthmatics (appendix A: tables 39-40). Nor did they differ in the distribution of these diseases in the siblings of asthmatics when neither, one or both parents were affected (appendix A: tables 41-43). In addition, the differences between the relatives of extrinsic and intrinsic asthmatics in the prevalences of asthma, hay fever and eczema were the same in the Brompton as in the Doncaster patients.

This high degree of similarity suggested that the factors influencing the prevalence of asthma were most likely common to both populations. Therefore, the populations were combined and the conclusions drawn from the pooled data.

The clinical characteristics of the probands are summarized in Table 2. Polar extrinsic asthmatics formed a larger percentage of the total population than did polar intrinsic asthmatics. By definition, there were no polar intrinsic probands with hay fever or eczema, whereas in polar extrinsic asthmatics, the prevalences of these traits were high. There was a

slight excess of males among polar extrinsic asthmatics and a slight excess of females among polar intrinsic asthmatics, but these differences did not reach significance. In addition, there were no differences between extrinsic and intrinsic probands in the prevalences of chronic bronchitis and reversibility in PEFR. However, there was an increased prevalence of eosinophilia and a reduced prevalence of smoking in polar extrinsic asthmatics compared with polar intrinsic asthmatics.

The family history of asthma, hay fever and eczema differed between polar extrinsic and polar intrinsic asthmatics (Table 2). Although the proportion of patients with at least one affected relative was similar in the two groups, the prevalence of asthma was significantly higher in relatives of extrinsic probands. In addition, there were marked increases in the prevalences of hay fever and eczema in the relatives of extrinsic asthmatics as compared with the relatives of intrinsic asthmatics.

The distribution of asthma, hay fever and eczema among the parents, siblings and offspring of asthmatics was similar in polar extrinsic and polar intrinsic asthmatics (Tables 3-4). Where sample sizes were sufficiently large, analysis showed that the prevalences of hay fever and eczema were evenly distributed over the parents, siblings and offspring. In contrast, the prevalence of asthma was higher in the parents of probands than in their siblings or offspring.

The prevalence of asthma, hay fever and eczema were examined in the siblings of probands, when neither, one or both of their parents were affected. In polar extrinsic asthmatics, the prevalence of asthma in the siblings of probands was higher when one or both parents were asthmatic than when neither parent was affected (Table 5). Similarly, the prevalence of hay fever increased when one or both parents had hay fever (Table 6). Eczema also tended to increase with the number of affected parents, but sample sizes were too small to permit statistical analysis of the trend (Table 7).

In polar intrinsic asthmatics, small sample sizes prevented statistical evaluation of the distributuons of asthma, hay fever and eczema among the siblings of probands when neither, one or both of their parents were affected. However, the distributions appeared similar to those for the polar extrinsic asthmatics (Tables 5-7).

Table 1 a

Comparison of Brompton and Doncaster Asthmatics

A. Polar Extrinsic Asthmatics

Character	Doncaster		Brompton		Significance (d.f. =1)
Probands					
Proportion in Pop.	119/379	(31%)	208/787	(26%)	N.S.
Sex-Ratio	0.83		1.12		N.S.
Hay Fever	38	(32%)	61	(29%)	N.S.
Eczema	16	(13%)	50	(24%)	$X^2=4.19$, $p < 0.05$
Chronic Bronchitis	39	(33%)	21	(10%)	$X^2=20.70$, $p<0.01$
Smoking	35	(29%)	55	(26%)	N.S.
Reversibility:PEFR	89	(75%)	98	(47%)	$X^2=10.18$, $p< 0.05$
Eosinophilia	40/101	(40%)	70/140	(50%)	N.S.
Relatives					
No.Relatives/Proband	5.4		4.1		N.S.
Pos.Fam.Hist.Asthma	46	(39%)	89	(44%)	N.S.
Prevalence of Asthma	67/639	(10%)	132/858	(15%)	$X^2=6.65$, $p < 0.05$
" Hay Fever	44/639	(7%)	134/858	(16%)	$X^2=23.51$, $p < 0.01$
" Eczema	28/639	(4%)	69/858	(8%)	$X^2=7.13$, $p < 0.01$

Table 1 b

B. Polar Intrinsic Asthmatics

Character	Doncaster		Brompton		Significance (d.f. =1)
Probands					
Proportion in Pop.	26/379	(7%)	63/787	(8%)	N.S.
Sex-Ratio	0.73		0.66		N.S.
Chronic Bronchitis	8	(31%)	11	(17%)	N.S.
Smoking	16	(61%)	34	(54%)	N.S.
Reversibility:PEFR	20	(77%)	35	(55%)	N.S.
Eosinophilia	5/17	(29%)	13/56	(23%)	N.S.
Relatives					
No.Relatives/Probands	7.2		7.0		N.S.
Pos.Fam.Hist.Asthma	8	(31%)	18	(28%)	N.S.
Prevalence of Asthma	9/187	(5%)	19/439	(4%)	N.S.
" Hay Fever	1/187	(1%)	9/439	(2%)	N.S.
" Eczema	2/187	(1%)	5/439	(1%)	N.S.

Table 2

Clinical Characteristics of Probands: Brompton and Doncaster Pooled

Character	Polar Intrinsic		Polar Extrinsic		Comparison of Extrinsic and Intrinsic Asthmatics Significance (d.f. =1)
Probands					
Proportion in Pop.	89/1166	(8%)	327/1166	(28%)	X^2=136.20, $p < 0.01$
Sex-Ratio	0.68		1.01		N.S.
Hay Fever	0	(0%)	99	(30%)	-
Eczema	0	(0%)	66	(20%)	-
Chronic Bronchitis	19	(21%)	60	(18%)	N.S.
Smoking	50	(56%)	90	(27%)	X^2=16.97, $p < 0.01$
Reversibility:PEFR	55	(62%)	187	(57%)	N.S.
Eosinophilia	18/73	(25%)	110/241	(46%)	X^2=6.30, $p < 0.05$
Relatives					
No.Relatives/Probands	7.0		4.6		N.S.
Pos.Fam.Hist.Asthma	26	(29%)	135	(41%)	N.S.
Prevalence of Asthma	28/626	(4%)	199/1497	(13%)	X^2=32.20, $p < 0.01$
" Hay Fever	10/626	(2%)	178/1497	(12%)	X^2=52.04, $p < 0.01$
" Eczema	7/626	(1%)	97/1497	(6%)	X^2=26.47, $p < 0.01$

Table 3

Prevalence of Asthma, Hay Fever and Eczema Among First Degree Relatives of Polar Extrinsic Asthmatics: Brompton and Doncaster Pooled

Trait	Prevalence (%) Parents	Siblings	Offspring	All Relatives	Comparison of Prevalence Among Parents, Siblings & Offspring Significance
Asthma	104/654 (15.9)	70/666 (10.5)	25/177 (14.1)	199/1497(13.3)	$X^2_2=7.55$, $p < 0.05$
Hay Fever	91/654 (13.9)	69/666 (10.4)	18/177 (10.2)	178/1497(11.9)	$X^2_2=3.47$, $p > 0.05$
Eczema	38/654 (5.8)	45/666 (6.8)	14/177 (7.9)	97/1497(6.5)	$X^2_2=1.11$, $p > 0.05$

Table 4

Prevalence of Asthma, Hay Fever and Eczema Among First Degree Relatives of Polar Intrinsic Asthmatics: Brompton and Doncaster Pooled

Trait	Prevalence (%) Parents	Siblings	Offspring	All Relatives	Comparison of Prevalence Among Parents, Siblings & Offspring Significance
Asthma	14/178 (7.9)	7/290 (2.4)	7/158 (4.4)	28/626 (4.5)	$X_2^2=7.27$, $p < 0.05$
Hay Fever	0/178 (0)	4/290 (1.4)	6/158 (3.8)	10/626 (1.6)	-
Eczema	1/178 (0)	3/290 (1.0)	3/158 (1.9)	7/626 (1.1)	-

Table 5

Prevalence of Asthma Among Siblings of Polar Asthmatics When Neither, One or Both Parents Have Asthma: Brompton and Doncaster Pooled

Number of Parents with Asthma	Polar Intrinsic N	Prevalence	(%)	Polar Extrinsic N	Prevalence	(%)
Neither	75	4/258	(1.6)	229	38/475	(8.0)
One	14	3/32	(9.4)	92	28/177	(15.8)
Both	0	-		6	4/14	(28.6)
Significance		-		X_2^2=10.08, $p < 0.01$		

Table 6

Prevalence of Hay Fever Among Siblings of Polar Asthmatics When Neither, One or Both Parents Have Hay Fever: Brompton and Doncaster Pooled

Number of Parents with Hay Fever	Polar Intrinsic N	Prevalence (%)	Polar Extrinsic N	Prevalence (%)
Neither	89	4/290 (1.4)	244	46/533 (8.6)
One	0	-	73	16/121 (14.0)
Both	0	-	10	6/12 (50.0)
Significance		-		$X_2^2=52.76$, $p < 0.01$

Table 7

Prevalence of Eczema Among Siblings of Polar Asthmatics When Neither, One or Both Parents Have Eczema: Brompton and Doncaster Pooled

Number of Parents with Eczema	Polar Intrinsic N	Prevalence (%)	Polar Extrinsic N	Prevalence (%)
Neither	88	3/286 (1.0)	291	35/603 (5.8)
One	1	0/4 (0)	36	10/63 (15.9)
Both	0	-	0	-
Significance		-		-

RESULTS

Part Two

In this study, the strict criteria adopted for 'polar' extrinsic and intrinsic asthma were relaxed to assess the influence of the system of classification on the family history of asthma. Probands were grouped according to (1) their atopic status as assessed by skin testing, (2) their history of hay fever/eczema and (3) their history of asthma provoked by pollens, dust and animals. (figure one).

The clinical characteristics of the probands are summarised in Table 8. When the patients were grouped according to their number of positive skin tests, there were no significant differences between groups in the prevalences of reversibility in PEFR, eosinophilia and positive family history of asthma. However, the prevalences of chronic bronchitis and smoking were higher in skin test negative probands than in probands with positive skin tests. In addition, the sex-ratio (males/females) was high in probands with three or more positive skin tests and low in probands with no positive skin tests.

The prevalence of asthma in the first degree relatives of the probands is shown in Table 9. When the probands' history of hay fever/eczema (HES) and allergic provocation (PA) were held constant, there was no significant association between the prevalence

of asthma in relatives and the number of positive skin tests in the probands (Table 10). However, when probands were grouped according to number of positive skin tests, irrespective of their histories of HES or PA, the prevalence of asthma did increase with the number of positive skin tests in the probands ($X^2=34.5$, $p<0.001$). The prevalence of asthma also rose when the probands had a positive history of hay fever/eczema, but was not influenced by the probands' history of asthma provoked by pollens, dust or animals. (Table 10).

The prevalence of hay fever in the relatives of the probands is shown in Table 9. Atopy and a positive history of hay fever/eczema in the probands were both associated with an increased prevalence of hay fever in the first degree relatives. However, allergic provoking factors in the probands again had no influence on the prevalence (Table10).

The prevalence of eczema in first degree relatives of probands is shown in Table 9. When the probands' history of HES and PA were held constant, the prevalence of eczema was not influenced by the number of positive skin tests in the probands. However, when probands were grouped according to their skin test sensitivity, irrespective of their histories of HES or PA, the prevalence of eczema in relatives increased with the number of positive skin tests in the probands,

(X^2=13.75, $p<0.01$). The prevalence of eczema also rose when the proband had a history of hay fever/eczema, but was not influenced by the probands' history of asthma provoked by pollens, dust or animals. (Table 10).

The distribution of asthma, hay fever and eczema among the parents, siblings and offspring of probands in each of the 12 groups are shown in Tables 11-13. In most groups, the sample sizes were too small to make a statistical assessment of the distribution. However, in those groups which were sufficiently large to test, the prevalence of asthma tended to be higher in the parents than in the offspring and siblings of asthmatics although the trend only reached significance in one group. In contrast, the prevalence of hay fever was highest in parents, intermediate in siblings and least in offspring. Eczema tended to be equally distributed over the parents, siblings and offspring of patients.

Table 8

The Clinical Characteristics of the Probands

Atopic Group	Sex-Ratio (male/female)	Chronic Bronchitis		Smoker		Reversibility		Eosinophilia		Positive Family History Asthma	
		N	%	N	%	N	%	N	%	N	%
Negative	0.58	21/94	(22)	53/94	(56)	58/94	(62)	24/80	(30)	30/107	(28)
1 or 2 Positive	0.83	12/77	(16)	33/77	(43)	41/77	(53)	34/66	(51)	31/77	(40)
3 or More Positive	1.35	31/298	(10)	95/298	(32)	148/298	(50)	95/197	(48)	142/332	(43)
Significance (d.f.=2)	$X^2=5.81$, $p>0.05$	$X^2=7.76$, $p<0.05$		$X^2=11.81$, $p<0.01$		$X^2=2.30$, $p>0.05$		$X^2=5.42$, $p>0.05$		$X^2=4.54$, $p>0.05$	

NOTE: As complete information was not available for all patients, the numbers are expressed as a percentage of the total number of individuals tested in each category.

Table 9: Prevalence of Asthma, Hay Fever and Eczema Among First Degree Relatives of Asthmatics

Proband Group*	Prevalence of Asthma		Hay Fever		Eczema	
	N	(%)	N	(%)	N	(%)
Negative						
1	20/529	(3.8)	11/529	(2.1)	10/529	(1.9)
2	8/53	(15.1)	2/53	(3.8)	2/53	(3.8)
3	3/50	(6.0)	0/50	(0)	0/50	(0)
4	5/37	(13.5)	1/37	(2.7)	0/37	(0)
TOTAL	36/669	(5.4)	14/669	(2.1)	12/669	(1.8)
1 or 2 Positive						
5	24/313	(7.7)	5/313	(1.6)	8/313	(2.5)
6	4/49	(8.2)	3/49	(6.1)	4/49	(8.2)
7	4/43	(9.3)	2/43	(4.6)	2/43	(4.6)
8	6/61	(8.2)	1/61	(1.6)	2/61	(3.3)
TOTAL	38/466	(8.1)	11/466	(2.4)	16/466	(3.4)
3 or More Positive						
9	26/305	(8.5)	23/305	(7.5)	8/305	(2.6)
10	39/246	(15.8)	36/246	(14.6)	14/246	(5.7)
11	20/258	(7.7)	17/258	(6.6)	13/258	(5.0)
12	108/667	(16.2)	109/667	(16.3)	52/667	(7.8)
TOTAL	193/1476	(13.1)	185/1476	(12.5)	87/1476	(5.9)

*See figure one for decription of groups

Table 10

Significance Tables

A. Influence of Atopy, Hay Fever/Eczema (HES) and Allergic Provoking Factors (PA) in Asthmatics on the Prevalence of Asthma, Hay Fever and Eczema Among Their First Degree Relatives

Factor in Proband	Influence on Prevalence of Asthma	Hay Fever	Eczema
Atopy	$X^2_7=12.11$, $p > 0.05$	$X^2_7=42.98$, $p < 0.001$	$X^2_4=4.71$, $p > 0.10$
HES	$X^2_2=16.11$, $p < 0.01$	$X^2_2=19.70$, $p < 0.001$	$X^2_2=4.85$, $p < 0.10$
PA	$X^2_3= 0.12$, $p > 0.10$	$X^2_2= 0.41$, $p > 0.10$	$X^2_2=3.55$, $p > 0.10$

B. Influence of Atopy on the Prevalence of Asthma, Hay Fever and Eczema Among First Degree Relatives of Asthmatics Grouped According to Skin Test Sensitivity

Influence on the Prevalence of	Significance
Asthma	$X^2_2=29.91$, $p < 0.001$
Hay Fever	$X^2_2=99.04$, $p < 0.001$
Eczema	$X^2_2=13.75$, $p < 0.01$

Table 11: Prevalence of Asthma in Parents, Siblings and Offspring of Asthmatics

Proband Group*	Prevalence of Asthma						Significance
	Parents		Siblings		Offspring		
	N	(%)	N	(%)	N	(%)	
Negative							
1	9/164	(5)	6/247	(2)	5/118	(4)	$X_2^2=2.5$, $p > 0.05$
2	4/18	(22)	3/21	(14)	1/14	(7)	-
3	0/16	(0)	2/24	(8)	1/10	(10)	-
4	3/14	(21)	1/21	(5)	1/2	(50)	-
Total	16/212	(7)	12/313	(4)	8/144	(5)	$X_2^2=3.7$, $p > 0.05$
1 or 2 Positive							
5	13/102	(13)	7/154	(4)	4/57	(7)	-
6	3/20	(15)	1/25	(4)	0/4	(0)	-
7	2/16	(12)	1/22	(4)	1/5	(20)	-
8	2/16	(12)	3/31	(10)	1/14	(7)	-
Total	20/154	(13)	12/232	(5)	6/80	(7)	$X_2^2=7.1$, $p < 0.05$
3 or More Positive							
9	17/124	(14)	7/139	(5)	2/42	(5)	-
10	17/120	(14)	20/106	(19)	2/20	(10)	-
11	14/112	(12)	5/123	(4)	1/23	(4)	-
12	50/308	(16)	42/288	(14)	16/71	(22)	$X_2^2=2.8$, $p > 0.05$
Total	98/664	(15)	74/656	(11)	21/156	(13)	$X_2^2=3.12$, $p > 0.05$
TOTAL	134/1030	(13)	98/1201	(8)	35/380	(9)	$X_2^2=53.1$, $p < 0.001$

* See figure one for description of groups

Table 12: Prevalence of Hay Fever in Parents, Siblings and Offspring of Asthmatics

Proband Group*	Prevalence of Hay Fever						Significance
	Parents		Siblings		Offspring		
	N	(%)	N	(%)	N	(%)	
Negative							
1	0/164	(0)	5/247	(2)	6/118	(5)	-
2	2/18	(11)	0/21	(0)	0/14	(0)	-
3	0/16	(0)	0/24	(0)	0/10	(0)	-
4	0/14	(0)	1/21	(5)	0/2	(0)	-
Total	2/212	(1)	6/313	(2)	6/144	(4)	-
1 or 2 Positive							
5	1/102	(1)	2/154	(1)	2/57	(3)	-
6	2/20	(1)	0/25	(0)	1/4	(25)	-
7	0/16	(0)	1/22	(4)	1/5	(20)	-
8	0/16	(0)	1/31	(3)	0/14	(0)	-
Total	3/154	(2)	4/232	(2)	4/80	(5)	-
3 or More Positive							
9	12/124	(10)	9/139	(6)	2/42	(5)	-
10	22/120	(18)	11/106	(10)	3/20	(15)	-
11	6/112	(5)	8/123	(6)	3/23	(13)	-
12	63/308	(20)	42/288	(14)	4/71	(6)	$X_2^2=8.7$, $p < 0.05$
Total	103/664	(16)	70/656	(11)	12/156	(8)	$X_2^2=9.8$, $p < 0.01$
TOTAL	108/1030	(10)	80/1201	(7)	22/380	(6)	$X_2^2=13.0$, $p<0.01$

* See figure one for description of groups

Table 13: Prevalence of Eczema in Parents, Siblings and Offspring of Asthmatics

Proband Group*	Prevalence of Eczema						Significance
	Parents		Siblings		Offspring		
	N	(%)	N	(%)	N	(%)	
Negative							
1	3/164	(2)	4/247	(2)	3/118	(2)	-
2	1/18	(5)	1/21	(5)	0/14	(0)	-
3	0/16	(0)	0/24	(0)	0/10	(0)	-
4	0/14	(0)	0/21	(0)	0/2	(0)	-
Total	4/212	(2)	5/313	(1)	3/144	(2)	-
1 or 2 Positive							
5	4/102	(4)	4/154	(2)	0/57	(0)	-
6	3/20	(15)	0/25	(0)	1/4	(25)	-
7	1/16	(6)	0/22	(0)	1/5	(20)	-
8	1/16	(6)	1/31	(3)	0/14	(0)	-
Total	9/154	(6)	5/232	(2)	2/80	(2)	-
3 or More Positive							
9	2/124	(2)	6/139	(4)	0/42	(0)	-
10	6/120	(5)	7/106	(7)	1/20	(5)	-
11	3/112	(3)	8/123	(6)	2/23	(9)	-
12	19/308	(6)	25/288	(9)	8/71	(11)	$X^2_2=2.5$, $p > 0.05$
Total	30/664	(4)	46/656	(7)	11/156	(7)	$X^2_2=3.8$, $p > 0.05$
TOTAL	43/1030	(4)	56/1201	(5)	16/380	(4)	$X^2_2=0.3$, $p > 0.05$

* See figure one for description of groups

DISCUSSION

The clinical differences between the Brompton and Doncaster asthmatics (Table 1) showed that patients in these two hospitals were not drawn from an homogeneous population. Nonetheless, the similarities between the populations in the distribution of asthma, hay fever and eczema among the relatives of asthmatics suggested that the factors influencing the prevalence of asthma were common to both. The populations were therefore combined and the conclusions drawn from the pooled data.

There were few clinical differences between the polar extrinsic and intrinsic asthmatic probands. The sex-ratio was not significantly different from 1.00 in either group and the proportion with reversibility in PEFR was similar.

However, smoking was more prevalent in intrinsic probands than in extrinsic probands and this difference would seem to have arisen from differences in their ages of onset. Since all the intrinsic asthmatics had a late age of onset (over 30 years), they were more likely to have established a smoking habit in their youth than were extrinsic asthmatics, whose early age of onset (under 20 years) might have acted as a deterrent.

Intrinsic asthmatics also differed from extrinsic asthmatics in the prevalence of eosinophilia. The

decreased prevalence of eosinophilia found in intrinsic probands may reflect either the non-immunological nature of their asthma or, more likely, an increased use of steroids in their treatment.

In the absence of control groups, it is difficult to show that both extrinsic and intrinsic asthma have a genetic basis. However, the finding that the prevalences of asthma in the siblings of both extrinsic and intrinsic probands increased when one or both of their parents were asthmatic suggests that both forms of asthma have an hereditary component. The similarity between extrinsic and intrinsic probands in the distribution of asthma among their parents, siblings and offspring further suggests that, if both forms are hereditary, their modes of inheritance may be similar. Thus, the findings support the hypothesis that extrinsic and intrinsic asthma share a common genetic defect.

Despite these similarities, the prevalence of asthma was higher in the relatives of extrinsic probands than in the relatives of intrinsic probands. This difference appears to have arisen from a difference in the number of asthmatic relatives per family, since the proportion of probands with at least one affected relative did not differ significantly between extrinsic and intrinsic asthmatics.

Therefore, if they are to share a common genetic defect, the penetrance of asthma genes must be greater in the relatives of the extrinsic asthmatics than in the relatives of the intrinsic asthmatics.

The clinical differences between skin test negative probands and probands with three or more positive skin tests (Table 8), resembled those between extrinsic and intrinsic patients. Smoking was most common among non-atopic probands, whose typically later age of onset might have led to their establishing the habit in their youth. The high prevalence of smoking may have led, in turn, to their increased prevalence of chronic bronchitis. Eosinophilia tended to be more prevalent in atopic than in non-atopic probands, reflecting either the immunological nature of atopic asthma or a reduced use of steroids in its treatment.

Although the sex distribution of asthma did not differ significantly among groups, there was an obvious tendency for the sex-ratio to decline with decreases in the probands' number of positive skin tests. This association has been observed in other populations and will be discussed in greater detail elsewhere (Chapter five).

The distribution of asthma among the relatives of probands was similar to that observed in the preliminary study. In the majority of probands, asthma tended to be more prevalent in the parents

than in the siblings and offspring of asthmatics. This difference may have resulted from their differences in age; since the siblings and offspring of probands were younger than the parents, they would have had less time in which to express a liability to asthma. If this is true, then the prevalences of asthma in the parents, siblings and offspring of probands would be similar should all first degree relatives be examined at the same age. The similarity between different groups of probands in the distribution of asthma among their first degree relatives supports the hypothesis that there is a genetic defect common to all forms of the disease.

Atopy was found to exert a strong influence on the family history of asthma, the risk of asthma being far greater for relatives of atopic probands than for relatives of non-atopic probands. Although the proportion of probands with at least one affected first degree relative did not vary with the probands' atopic status, the prevalence of asthma in the relatives increased with the probands' number of positive skin tests. Thus the number of asthmatic relatives per family was positively correlated with the degree of atopy in the probands. This finding is consistant with that of the preliminary study and suggests that atopy may enhance the likelihood of a genetic predisposition to asthma being expressed.

The findings further suggest that the expression of asthma is less strongly dependent on atopy than is the expression of hay fever. In this study, (Table 10) as in previous investigations (Pepys, 1973), the prevalence of hay fever in relatives was shown to be more closely associated with the atopic status of probands than was the prevalence of asthma. Thus the development of asthma may involve factors other than those which underly clearly atopic disease.

Since only a portion of all atopic individuals actually suffer from allergic disease, other factors must exist which act in conjunction with atopy to produce allergic disease. That these factors could be hereditary and may also enhance the likelihood of asthma being expressed, was indicated by the association between hay fever/eczema in the probands and the prevalence of asthma in the first degree relatives.

Allergic provocation of asthma in probands was not associated with differences in the prevalence of asthma, eczema or hay fever in their relatives. Therefore, this factor appears to have little or no influence on the genetics of asthma and allergic disease.

It may be concluded that, of the clinical characters investigated, atopy and a history of hay fever/eczema are the two which most influenced the

family history of asthma. The presence of either or both factors in probands was associated with an increased prevalence of asthma in their first degree relatives. However, as both the proportion of probands with at least one asthmatic relative and the distribution of asthma among relatives did not vary with the atopic or allergic status of the probands, it seems probable that there was a common genetic defect shared by all probands. Atopy and its manifestations (eg. hay fever and eczema) seemed only to enhance the risk that the genetic defect would be expressed.

CONCLUSION

The findings suggest that there was a genetic defect common to all forms of asthma. The similarity between clinically different groups of patients both in the proportion of patients with at least one affected first degree relative and in the distribution of asthma among the relatives supported this hypothesis. Atopy and allergic disease in probands were associated with an increased prevalence of asthma in their first degree relatives, indicating that atopy may enhance the likelihood of a genetic predisposition to asthma being expressed.

Since the family history data were limited to the patients' knowledge of their relatives, it is possible that the estimated prevalences of asthma and allergic disease in the relatives of probands were biased. However, this bias could not have given rise to the observed similarities or differences between groups of probands, since all groups would have been equally subject to its influence. Furthermore, the large numbers of patients interviewed minimizes any chance variations arising from patients differing in their knowledge of their families. Thus, the data provide good support for the hypothesis that asthma is genetically homogeneous, and that atopy may enhance the likelihood of a genetic predisposition to asthma being expressed.

CHAPTER III

ASTHMA IN CHILDREN AND ITS ASSOCIATION WITH WHEEZY BRONCHITIS

Among the most important problems concerning asthma in childhood are the nature of its association with atopy and its relationship to wheezy bronchitis.

It is well established that childhood asthma is closely associated with atopy and allergic disease. Pepys (1973) found that 68% of 469 patients whose asthma began under 10 years of age had three or more positive skin prick tests, while only 8% were skin test negative. In contrast, 53% of 228 patients whose asthma began over 30 years of age were skin test negative and only 21% had 3 or more positive skin tests. Apart from skin test positivity, childhood asthma has also been shown to be closely associated with elevated levels of serum IgE, blood and nasal eosinophilia and presence of other allergic diseases such as hay fever, eczema and urticaria (McNicol and Williams, 1973). Indeed McNicol and Williams (1973) have suggested that 'probably all asthmatic children if studied adequately throughout childhood would be found to develop evidence of an allergic state'.

This association of asthma with atopy is not well understood. Immunopharmacological studies suggest that, in atopic patients, bronchospasm may be caused by a type I inflammatory process (see Chapter Two). Family studies support this association of asthma with reaginic activity by showing

there is a strong correlation between the degree of skin test positivity in patients and the prevalence of asthma in their first degree relatives (Pepys, 1973). Thus the development of asthma may depend on the presence of atopy.

On the other hand, antigen-reagin based mechanisms cannot account for the susceptibility of asthmatic patients to wheezy attacks provoked by non-allergic stimulii such as exercise and emotion. In addition, the onset of asthma in atopic patients may precede the appearance of atopy and its manifestations, and children with the most pronounced allergic symptoms do not necessarily have the most severe forms of asthma (McNicol and Williams, 1973). Thus atopy may not be essential to the development of childhood asthma.

Family studies of extrinsic and intrinsic asthmatic patients (Chapter two) favour the hypothesis that asthma is inherited independently of atopy, but that atopy may enhance the likelihood that a genetic predisposition to asthma will be expressed. However, it could not be shown that asthma and atopy segregate independently, since the atopic status of asthmatic relatives of patients were not recorded. In addition, the findings of these preliminary studies may have been biased as they dealt exclusively with hospital outpatients who were likely to have had a more severe form of asthma than occurs in the general population.

Therefore, a family study of asthma in children was devised to investigate the possibility that asthma segregates independently of atopy and to verify the findings of the preliminary studies in a less highly selected group of patients.

The clinical differences between asthma and wheezy bronchitis in children are not well defined resulting in confusion over their relationship. While many children with wheezy bronchitis grow out of this tendency, some may develop frank asthma later in childhood. Moreover, wheezy bronchitis is known to precede asthma in many childhood asthmatics. Comparison of the histories of respiratory disease and the clinical features of allergy in wheezy bronchitic children with those in asthmatic and non-wheezy control children, has shown that wheezy bronchitic children bear a much closer resemblance to asthmatic children than to controls (Williams and McNicol, 1969). Therefore, it is possible that asthma and wheezy bronchitis share a common defect as suggested by Williams and McNicol.

Other findings suggest that the etiologies of the disorders may differ. Despite the viewpoint expressed by Williams and McNicol (1969), their data showed that the prevalences of hay fever, skin test positivity and nasal eosinophilia were lower in children with wheezy bronchitis than in those with asthma. Taussig and Lebowitz (1976) confirmed

these observations and showed also that wheezy bronchitic children have fewer abnormalities in pulmonary function than asthmatic children. Therefore, it is possible that the etiologies of asthma and wheezy bronchitis differ, the former depending upon factors which are not essential for the development of wheezy bronchitis.

In order to clarify this issue, data were collected on the family histories of asthma and wheezy bronchitis in asthmatic and wheezy bronchitic children, thus enabling a comparison to be made of their hereditary similarities and differences.

PATIENTS AND METHODS

The study group consisted of 242 children, aged 1-12 years, and their families attending a general practice in Roehampton, South-West London. The data were collected in the course of a survey of asthma and wheezy bronchitis which was carried out between 1967-76 by the Department of Clinical Epidemiology in General Practice of the Brompton Hospital (Horn and Gregg, 1973; Horn et al, 1975 and 1979). The data were made available to the author by Dr. M.E.C. Horn for the purposes of this investigation.

The first child from each family to be recruited in the original survey was designated the proband for the purposes of the present study. Probands were classified into groups according to their history of respiratory illness as follows:

Wheezy Bronchitis - one or more episodes of wheezing which occurred only in association with symptoms suggestive of respiratory infection. On auscultation there was high pitched wheeze over most parts of the lungs in addition to medium crepitations or rhonchi.

Asthma - recurrent episodes of wheezing which occurred in response to allergens, exercise or emotion, as well as with symptoms suggestive of respiratory infection. On auscultation there was high pitched wheeze over most parts of the lungs.

Control - no history of wheeze. Although the majority nad experienced one or more episodes of respiratory

infection, wheeze had never been detected on auscultation.

The groups were each subdivided into atopic and non-atopic groups according to the probands' reactions to skin prick tests of house dust, house dust mite, pollens, animal danders and moulds. The criterion for a positive reaction was a weal of 2mm or more in diameter in the absence of any equivalent reaction to the control solution. Patients with one or more positive reactions were designated atopic, while those with no positive reactions were designated non-atopic.

The age, sex and personal history of hay fever and eczema were recorded for each proband. The history of asthma and wheezy bronchitis in each of the probands' first degree relatives (ie., parents and siblings) was obtained through interviews with one or more members of the family and by scrutiny of medical records.

A relative was said to have a history of wheezy bronchitis if, at any time during his life, he had had one or more episodes of wheezing which occurred only in association with symptoms suggestive of respiratory infection. On the other hand, if the relative had had wheezy episodes which occurred in response to allergens, exercise or emotion as well as with symptoms suggestive of respiratory infection, then he was said to have a history of asthma.

Estimation of the prevalence of atopy, as shown by the presence of positive skin tests, was carried out in all accessible relatives of asthmatic and control children. Complete information was available for the families of 32 (41%) of the asthmatic children and 30 (34%) of the control children.

Ascertainment was assumed to be single and incomplete (McKusick, 1969). The Chi-square test was used to evaluate differences between groups.

RESULTS

Characterization of Probands

Table 14 summarises the clinical characteristics of the probands in each of the asthma, wheezy bronchitis and control groups. There were no significant differences between groups in the proportion of males or the mean age of the probands. The prevalences of atopy, hay fever and eczema were all significantly higher in asthmatic than in wheezy bronchitic or control children. The proportion of children with a positive family history of asthma was greater in both the asthma and wheezy bronchitis groups than in the control group, but the proportion with a positive family history of wheezy bronchitis did not differ significantly among groups.

Those probands, all of whose first degree relatives were skin tested, form a subset of the above population and are described in Table 15. As in the larger population, there were no differences between asthma and control probands in the sex-ratio or mean age of the probands; the prevalences of atopy and hay fever were again higher in asthmatic than control probands. However, the skin tested population did differ from the larger sample in that the prevalence of atopy and the proportion with a positive family history of asthma were not significantly higher in asthmatics than controls.

Despite these discrepancies, direct comparison of the skin tested population with the whole sample showed there were no significant differences between the two groups in the measured parameters.

Family Histories of Asthma, Atopy, Hay Fever and Eczema

The family history of asthma differed between asthmatic and control probands. The overall prevalence of asthma was higher in relatives of asthmatic probands than controls, and this difference was more pronounced for relatives of atopic probands than for relatives of non-atopic probands (Table 16). The relatives of atopic and non-atopic controls were equally affected; whereas in the asthma group, the prevalence tended to be higher in the relatives of atopic than non-atopic probands (Table 17). Parents were more often affected than siblings in the families of asthmatics; while in the control group, parents and siblings were equally affected (Table 17).

In the relatives of asthma patients, the prevalence of asthma in offspring tended to be higher when one or both parents were asthmatic than when neither parent was affected. However, the difference did not reach significance (Table 18).

The family history of atopy was similar for asthma and control probands. Although the prevalence of atopy tended to be higher in relatives of asthmatics than in relatives of controls, this difference did

not reach significance (Table 16). Similarly, atopy tended to be more common among relatives of atopic than non-atopic probands (Table 16), but again the differences were not significant (Table 17). In both groups, the parents and siblings of probands were equally affected (Table 17).

The prevalence of hay fever in relatives was closely associated with the atopic status of probands. The prevalence was significantly higher in the relatives of asthmatic than control probands (Table 16), and relatives of atopic probands were more often affected than relatives of non-atopic probands (Table 17). Hay fever was more common in the parents than the siblings of asthma probands but, although a similar trend existed in the control group, this difference did not reach significance (Table 17).

The family history of eczema differed from that of either hay fever or atopy. The overall prevalence of eczema was slightly higher in the relatives of asthmatics than controls, but there were no differences in prevalence between the relatives of atopic and non-atopic probands (Table 17). Siblings were significantly more often affected than parents in the asthma group but, although a similar trend existed in the relatives of

controls, the difference did not reach significance (Table 17).

Distribution of Asthma and Atopy in Families

Table 19 shows the distribution of asthma and atopy within the families of asthmatic and control probands.

In the asthma group, most probands (34/49, 69%) were born in families where neither parent had had asthma. Atopic probands usually had one or more atopic parents (34/40, 85%), whereas non-atopic probands were evenly distributed between families where neither parent was atopic (5/9, 56%) and families where at least one parent was atopic (4/9, 44%). In families where one parent had had asthma, the proband tended to have the same atopic status as his affected parent (11/14, 79%), but this was not true in all cases (3/14, 21%). Similarly, asthmatic siblings of probands tended to have the same atopic status as the probands (6/8, 75%), although there were some who differed (2/8, 25%).

In the control group, most probands were born to non-asthmatic parents (39/42, 93%). Atopic probands usually had one or more atopic parents (11/14, 78%), whereas non-atopic probands were evenly distributed between families where both parents were non-atopic (15/28, 54%) and families where at least one parent was atopic (13/28, 46%).

Two of the four asthmatic siblings of controls were atopic and both were born to families where neither parent had asthma but one parent was atopic. Of the remaining non-atopic asthmatic siblings, one was born to non-asthmatic parents, one of whom was atopic; and the other was born to non-atopic parents, one of whom had asthma.

The distribution of atopic and non-atopic asthma in families has been summarised in Table 20. In the relatives of asthmatic probands, the prevalence of atopic asthma exceeded the prevalence of non-atopic asthma, irrespective of the atopic status of the proband. In contrast, the prevalences of atopic and non-atopic asthma were equal in the relatives of atopic and non-atopic controls.

Comparison of the Family Histories of Asthma and Wheezy Bronchitis

The prevalences of asthma and wheezy bronchitis in the first degree relatives of probands are summarised in Table 21. The overall prevalence of asthma was higher in the relatives of controls ($X^2=16.02$; $p<0.01$). A similar trend was observed in the prevalence of wheezy bronchitis, but the differences did not reach significance ($X^2=1.94, p>0.10$).

In all groups, there were no significant differences between the relatives of atopic and non-atopic probands in the prevalences of either asthma or wheezy bronchitis. However, in the asthma and

wheezy bronchitis groups, the prevalence of asthma tended to be higher in relatives of atopic probands; whereas the prevalence of wheezy bronchitis tended to be higher in relatives of non-atopic probands. (Table 21).

Table 14

Characterization of Probands

Proband	N		Males		Hay Fever		Eczema		Family History of Asthma		Family History of Wh.Bron.		Mean Age
	(%total)		No	(%)	No	(%)	No	(%)	No	(%)	No	(%)	(years)
Asthma													
Atopic	64	(83)**	42	(66)	25	(39)*	33	(52)*	25	(39)**	17	(26)	7.5
Non-atopic	13	(17)	9	(69)	0	(0)	0	(0)	4	(31)	5	(38)	5.4
Total	77		51	(66)	25	(32)**	33	(43)**	29	(38)**	22	(28)	7.1
Wheezy Bronchitis													
Atopic	36	(46)	26	(72)	4	(11)	5	(14)	13	(36)*	8	(22)	6.2
Non-atopic	42	(54)	25	(59)	0	(0)	5	(12)	12	(29)	13	(31)	4.6
Total	78		51	(65)	4	(5)	10	(13)	25	(32)**	21	(27)	5.3
Control													
Atopic	38	(44)	25	(66)	5	(13)	8	(21)	4	(10)	4	(10)	6.0
Non-atopic	49	(56)	24	(49)	0	(0)	8	(16)	5	(10)	13	(26)	5.4
Total	87		49	(56)	5	(6)	16	(18)	9	(10)	17	(19)	5.6

Excess as compared with control value: * $p<0.05$, ** $p<0.01$

Table 15

Clinical Characteristics of Probands in Skin Test Group

Proband -	N (% total)		Males No	(%)	Hay Fever No	(%)	Eczema No	(%)	Family History of Asthma No	(%)	Mean Age (years)
Asthma											
Atopic	28	(88)**	16	(57)	11	(39)	14	(50)	10	(36)	7.7
Non-Atopic	4	(12)	2	(50)	0	(0)	0	(0)	1	(25)	5.0
Total	32		18	(56)	11	(34)*	14	(44)	11	(34)	7.4
Control											
Atopic	10	(33)	8	(80)	3	(30)	2	(20)	2	(20)	6.1
Non-Atopic	20	(67)	7	(35)	0	(0)	7	(35)	3	(15)	4.9
Total	30		15	(50)	3	(10)	9	(30)	5	(17)	5.3

Excess as compared with control: * $p < 0.05$, ** $p < 0.01$

Table 16

Prevalence of Asthma, Atopy, Hay Fever and Eczema in First Degree Relatives

Proband	Prevalence of Asthma		Atopy		Hay Fever		Eczema	
	No	(%)	No	(%)	No	(%)	No	(%)
Asthma								
Atopic	34/252	(13)	61/101	(60)	49/252	(19)	27/252	(11)
Non-Atopic	5/52	(10)	5/14	(36)	1/52	(2)	2/52	(4)
Total	39/304	(13)*	66/115	(57)	50/304	(16)**	29/304	(9)
Control								
Atopic	4/129	(3)	20/35	(57)	17/129	(13)	7/129	(5)
Non-Atopic	7/173	(4)	29/69	(42)	12/173	(7)	8/173	(5)
Total	11/302	(4)	49/104	(47)	29/302	(10)	15/302	(5)

Excess as compared with control value: * $p < 0.05$, ** $p < 0.01$.

Table 17

Significance of the Differences in the Prevalence of Asthma, Hay Fever, Eczema, and Atopy Between Parents and Siblings of Probands, and Between Relatives of Atopic and Non-Atopic Probands

Prevalence of	Parents vs. Siblings of Probands with		Atopic vs. Non-Atopic Probands with	
	Asthma	Control	Asthma	Control
Asthma	$X^2=5.03$	$X^2=0$	$X^2=0.69$	$X^2=0.37$
	$p<0.05$*	$p=1.00$	$p>0.10$	$p>0.10$
Atopy	$X^2=0$	$X^2=0.09$	$X^2=1.27$	$X^2=1.12$
	$p>0.10$	$p>0.10$	$p>0.10$	$p>0.10$
Hay Fever	$X^2=3.45$	$X^2=2.27$	$X^2=8.67$	$X^2=3.55$
	$p<0.10$*	$p>0.10$	$p<0.01$*	$p<0.10$*
Eczema	$X^2=3.45$	$X^2=2.50$	$X^2=2.17$	$X^2=0.28$
	$p<0.10$**	$p>0.10$	$p>0.10$	$p>0.10$

* Excess Among Parents
** Excess Among Siblings

*Excess Among Relatives Atopic Probands

Table 18

Prevalence of Asthma in Siblings of Asthmatics When Neither, One or Both Parents are Asthmatic

Proband	Prevalence of Asthma in Siblings (%)			Significance
	Neither Parent Affected	One Parent Affected	Both Parents Affected	
Atopic	8/87 (9)	1/32 (6)	1/3 (33)	s.s
Non-atopic	1/18 (5)	0/7 (0)	-	s.s
Total	9/105 (8)	2/42 (5)	1/3 (33)	N.S

s.s Sample size too small to test

N.S Not significant

Table 19: Distribution of Asthma and Atopy in Relatives of Probands

Parents	ATOPIC PROBAND No.	Sibs	N	AO	AA	NA	Asthmatic Parents	NON-ATOPIC PROBAND No.	Sibs	N	AO	AA	NA	
N x N	3 (1)	1		1				12 (6)	8	6	2			
N x AO	8 (6)	11	5	4	1	1	Neither	8 (6)	8	5	2	1		
AO x AO	3 (3)	3		3				5 (5)	8	4	4			CONTROL
N x NA								1 (1)	4	2	1		1	
N x AA							One	1 (1)	0					
AO x AA								1 (0)	3	3				
N x N	3 (2)	2	1			1		3 (2)	4	3		1		
N x AO	14 (11)	18	4	9	5		Neither	4 (1)	1		1			
AO x AO	10 (8)	13	5	8										
N x NA	2 (2)	0						1						ASTHMA
N x AA	5 (1)	6	1	4	1		One							
AO x AA	5 (3)	5	1	4				1 (1)	1	1				
AA x AA	1						Both							

N - normal
AO - atopy only
NA - non-atopic asthma
AA - atopic asthma
NO. - number of mating types (number where all children skin tested)

Table 20

Prevalence of Atopic and Non-Atopic Asthma Among First Degree Relatives of Probands

Proband	N	Relatives At Risk	Atopic Asthma No.	(%)	Non-Atopic Asthma No.	(%)	Row Significance
Asthma							
Atopic	28	101	10	(10)	3	(3)	$X^2=3.78$, $p < 0.10$
Non-Atopic	4	14	2	(14)	0	(0)	$X^2=2.00$, $p > 0.10$
Total	32	115	12	(10)	3	(3)	$X^2=5.78$, $p < 0.10$
Column Significance			$X^2=5.33, p<0.05$		$X^2=1.50, p>0.10$		
Control							
Atopic	10	35	1	(3)	1	(3)	$X^2=0$, $p = 1.0$
Non-Atopic	20	69	2	(3)	2	(3)	$X^2=0$, $p = 1.0$
Total	30	104	3	(3)	3	(3)	$X^2=0$, $p = 1.0$
Column Significance			$X^2=0.33, p>0.10$		$X^2=0.33, p>0.10$		

Table 21

Prevalences of Asthma and Wheezy Bronchitis in the First Degree Relatives of the Probands

Proband	Prevalence (%) in First Degree Relatives: Asthma		Wheezy Bronchitis	
Asthma				
Atopic	34/252	(13)**	17/252	(7)
Non-Atopic	5/52	(10)	6/52	(11)
Total	39/304	(13)**	23/304	(8)
Wheezy Bronchitis				
Atopic	18/127	(14)**	8/127	(6)
Non-Atopic	14/163	(9)*	17/163	(10)
Total	32/290	(11)**	25/290	(9)
Control				
Atopic	4/129	(3)	4/129	(3)
Non-Atopic	7/173	(4)	13/173	(7)
Total	11/302	(4)	17/302	(6)

Excess as compared with control value: * $p < 0.10$, ** $p < 0.01$.

The comparison of non-atopic asthmatic probands to non-atopic control probands was prohibited by small sample sizes.

DISCUSSION

The family study was designed to investigate the possibility that asthma segregates independently of atopy in children and to verify the findings of the preliminary studies in a less highly selected group of patients. Since there is confusion over the relationship of asthma to wheezy bronchitis in children, the hereditary similarities and differences between these two forms of wheezy illness were also examined.

The prevalences of atopy, hay fever and eczema, and the sex-ratio in asthma probands were similar to those found in other studies (Burrows et al, 1976; Williams and McNicol, 1969). However, the prevalences of atopy and the sex-ratio in control probands were higher than are generally found in children this age (Barbee et al, 1976; Morrison-Smith, 1973); a discrepancy which may have been caused by the high proportion of bronchitic children among control probands (see below). Nonetheless, the findings show that the prevalences of atopy, eczema and hay fever, and the proportion of children with at least one asthmatic relative were all significantly higher in asthmatic children than in a comparable group of non-wheezy controls.

Asthma was found to cluster in the relatives of asthmatics, supporting the hypothesis that this

disease is hereditary. The overall prevalence of asthma in the first degree relatives of asthmatics was 13%, while that in the relatives of controls was only 4%. These figures agree well with those of Leigh and Marley (1967) whose family data were collected by similar methods. They found a prevalence of 13.2% in the first degree relatives of asthmatics and a prevalence of only 1.5% in the relatives of controls.

When atopic and non-atopic probands were considered separately, the findings showed there was an increased prevalence of asthma in the relatives of both atopic and non-atopic asthmatics as compared with the relatives of controls. In addition, the prevalence of asthma in the siblings of probands tended to increase when one or both parents were asthmatic. Thus it seems likely that both atopic and non-atopic asthma are hereditary. Furthermore, the similarity between them in the distributions of asthma among their first degree relatives suggest that, if they are hereditary, they may share a common genetic defect.

Despite this similarity, the prevalence of asthma in relatives tended to be higher in atopic than non-atopic asthmatics. In addition, the difference in the prevalence of asthma between relatives of atopic asthmatics and atopic controls

was greater than the difference between relatives of non-atopic asthmatics and non-atopic controls. Although these trends did not reach significance, they are consistent with the findings of the preliminary studies (Chapter two) and suggest that atopic asthma may have a stronger hereditary component than non-atopic asthma. Since the proportion of children with a family history of asthma did not differ between atopic and non-atopic probands (Table 4), this increased heritability of atopic asthma may have resulted from the enhanced susceptibility to asthma of relatives inheriting both a predisposition to asthma and a predisposition to atopy.

In the control group, the prevalence of asthma in relatives did not differ between atopic and non-atopic probands (Table 16). This finding suggests that when a proband has no history of wheezy illness, his atopic status does not influence the risk of asthma in his first degree relatives. Thus it seems the development of asthma does not depend on the presence of atopy and atopy itself cannot give rise to asthma.

The prevalence and distribution of atopy in relatives showed a surprising lack of correlation with the atopic status of probands. Although the trends were all in the expected direction, there was no significant difference in the prevalence of atopy between relatives of asthmatics and

controls, nor was there a significant difference between relatives of atopic and non-atopic probands. A number of factors may have contributed to this apparent homogeneity in the prevalence: (1) the overall high prevalence of atopy in the population may have obscured differences between groups, (2) small sample sizes may have led to atypically high prevalences of atopy, and (3) the increased similarity between the skin tested asthma and control probands, as compared with the larger sample, might have enhanced the similarity in their family histories of atopy.

Nonetheless, it is clear that, while the prevalence of atopy in relatives was similar for asthmatics and controls, the prevalence of asthma in relatives was significantly higher in the asthma group. Thus there is support for the hypothesis that the manifestation of asthma may depend on genetic factors, other than those associated with the development of atopy.

Comparison of the family history of asthma with those of hay fever and eczema showed that asthma differed in small but important ways from other, atopic diseases.

The prevalence and distribution of hay fever in families resembled that of asthma, but showed a much stronger association with the atopic status of probands. The prevalence of hay fever in relatives

was significantly higher in asthmatics than controls; and the relatives of atopic probands were significantly more often affected than the relatives of non-atopic probands. In all groups, parents were more often affected than siblings; however, this difference might have vanished as siblings grew older and more cases of hay fever appeared.

In contrast, the family history of eczema was less strongly associated with the atopic status of probands than were the family histories of asthma or hay fever. Although the prevalence of eczema in relatives was slightly higher in asthmatics than controls, relatives of atopic and non-atopic probands were equally affected. In all groups, siblings were more often affected than parents; but this difference may have resulted from parents forgetting or being unaware of episodes of infantile eczema in their childhood.

These differences in family histories support the findings of other investigations in suggesting that asthma, hay fever and eczema may each have separate hereditary components, although all may be influenced by atopy (Edford-Lubs, 1971; Gerrard et al, 1976).

Examination of the distributions of atopy and asthma in relatives gives addtional information on the association of asthma with atopy. Table 19 shows

that the relationship in atopic status between probands and their parents was similar in the asthma and control groups. In both cases, atopic probands tended to have at least one atopic parent; whereas non-atopic probands were evenly distributed between families where neither parent was atopic and families where at least one parent was atopic. Thus the presence of asthma in probands did not influence their family history of atopy.

Although most of the asthmatic relatives of asthma probands had the same atopic status as the proband, there were exceptions. In five families, the atopic status of probands was found to differ from that of their asthmatic parents or siblings. Thus there was no strict correlation between asthma and atopy. Indeed, the prevalence of atopic asthma exceeded that of non-atopic asthma in the relatives of both atopic and non-atopic probands. Therefore, it seems probable that, in some families at least, atopy and asthma were segregating.

When these findings are considered together, they strongly suggest that clinically different forms of asthma share a common genetic defect, which can be inherited and manifested independently of atopy. Although atopy itself cannot give rise to asthma, it may enhance the likelihood that a genetic predisposition to asthma will be expressed. Thus the findings of this study uphold those of the preliminary investigation.

Asthma and Wheezy Bronchitis

The family study of asthma and wheezy bronchitis in children supports the hypothesis of Williams and McNicol (1969) that these diseases have a common underlying defect.

There was a strong similarity in the family history of asthma between asthmatic and wheezy bronchitic probands. The percentage of children with at least one asthmatic relative was significantly greater in the asthmatic and wheezy bronchitic probands than in the controls; and the prevalence of asthma was significantly higher in the relatives of both groups of wheezy probands than in the relatives of controls. This clustering of asthma in the relatives of wheezy children supports the hypothesis that at least some of the genetic factors underlying asthma may also be present in wheezy bronchitis.

The family history of wheezy bronchitis was similar to that of asthma. The percentage of children with at least one wheezy bronchitic relative tended to be greater in asthmatic and wheezy bronchitic probands than controls; and the prevalence of wheezy bronchitis tended to be higher in the relatives of both groups of wheezy probands than in the relatives of controls. Although these differences did not reach significance, the tendency of wheezy bronchitis to cluster in the relatives of wheezy children lends

support to the idea that wheezy bronchitis and asthma share a common genetic defect.

The composition of the control group may have contributed to the absence of a significant difference between wheezy and control probands in their family histories of wheezy bronchitis. Control children were not normal in that 62 (71%) had had one or more episodes of bronchitis. The prevalence of atopy (44%) and the sex-ratio (1.29) were higher in these probands than are generally found in children this age (Barbee et al, 1976; Morrison-Smith. 1973), suggesting that the control children may have had some genetic factors in common with the asthmatic and wheezy bronchitic children.

Since wheezy bronchitis often precedes asthma in children, some of the probands with wheezy bronchitis may have had incipient asthma. Their presence would be expected to enhance the similarity in the family histories of asthma and wheezy bronchitis between asthmatic and wheezy bronchitic probands. However, the marked differences between the two groups of probands in their histories of atopy and allergic disease (Table 14), suggest there were not many children with incipient asthma among those with wheezy bronchitis. Therefore, it is unlikely that the family histories of asthma and wheezy bronchitis were altered appreciably by this bias.

The prevalences of atopy, hay fever and eczema were lower in wheezy bronchitic than asthmatic probands. Although these differences may have arisen, in part, from the slightly lower age of the wheezy bronchitic as compared with the asthmatic children (Barbee et al, 1976), other investigations dealing with children of uniform age have also found that atopy and allergy were less prevalent in wheezy bronchitics (Taussig and Lebowitz, 1976; Williams and McNicol, 1969). These findings suggest that the reduced predisposition to asthma of many wheezy bronchitic children may result from their failure to inherit a predisposition to atopy or allergy. The finding that the prevalence of wheezy bronchitis was higher in the relatives of non-atopic than atopic probands, whereas the reverse was true of asthma, lends support to this hypothesis.

In conclusion, the similarity between asthmatic and wheezy bronchitic children in their family histories of asthma and wheezy bronchitis suggests that these diseases may share a common genetic defect. However, it should be noted that the familial clustering of the diseases does not necessarily mean a common hereditary defect is involved; a similar family environment may also lead to clustering. Therefore the magnitude of the hereditary component should be evaluated in twin studies.

CHAPTER IV

ASTHMA IN ADULT POPULATIONS

Asthma in adults may differ from that in children. Although the majority of adults with asthma may be atopic (Burr et al, 1975), there are often more non-atopic asthmatics among adults than children (Pepys, 1973). In addition, the sex-ratio in asthmatic children is often unbalanced in favour of males, whereas the sex-ratio in adults appears even (Gregg, 1977) or women are more frequently affected than men (Molina et al, 1977). The prognosis is generally better in early than late onset asthma, children having a higher remission rate (Blair, 1978; Wilken-Jensen, 1978) and a lower frequency of attacks (Ogilvie, 1962) than adults. Thus adult asthma may differ from childhood asthma in the prevalence of atopy, the sex-ratio, and the severity of asthma in patients.

To investigate the possibility that these differences may reflect age related variations in the hereditary basis of asthma, family studies of adult asthmatics were conducted and the findings compared with those obtained in the studies of children.

MATERIALS AND METHODS

Patients

The study group consisted of 101 adults, aged 20 to 60 years inclusive, and their families attending a general practice in Kingston-upon-Thames, during 1978-79. The practice is described more fully in figure 2.

All asthma probands had a history of recurrent episodic wheezing or breathlessness and all had been diagnosed as having had asthma by their doctor. Only those probands who had had at least one asthmatic episode within the previous 24 months were recruited to the study. Suitable probands were first identified using a continuous case finding system (ALISS), employed by the practice, and the information then verified by reference to the patients' medical records. Otherwise suitable probands were excluded from the study if their medical record indicated they had other, severe chronic obstructive lung disease (eg. chronic bronchitis, tuberculosis, emphysema, etc.,), cardiac asthma, severe psychiatric disturbance or they were adopted.

A control group, consisting of patients with no history of wheezy illness, was selected and matched with the group of asthma probands for age, sex, and where possible, atopic status. Suitable control patients were first identified using the

ALISS and the information then verified by reference to the patients' medical records. Otherwise suitable control patients were excluded from the study if their medical records indicated they had severe chronic obstructive lung disease, cardiac asthma, severe psychiatric disturbance or they were adopted.

Ascertainment was assumed to be single and incomplete.

Figure Two

The Canbury Medical Centre (Kingston-upon-Thames)

Number of Doctors	5	
Trainees	1	
Number of Patients *	6012	
Sex-Ratio (males: females)	2164: 3848	
Age Distribution		
75 years or more	320	(5.3%)
65-74 years	486	(8.0%)
16-64 years	4172	(69.4%)
0-15 years	1034	(17.2%)
Mean Age	35 years	
Social Class Distribution		
Classes 1-2	35.5%	
3	37.2%	
4-5	14.8%	
Not Known	12.6%	

---

* The description of the practice is based on a sample of 6012 patients attending the surgery during the months of January 1977 and July 1978. The data were supplied by Dr. M. D'Souza of the practice.

Skin Tests

Skin tests were administered to all probands and those of their first and second degree relatives who complained of having had asthma or other wheezy illness. Children under five years of age were not tested.

The following nine reagents were used: glycerol saline, 5 pollen grass mix, 5 pollen flower mix, 5 pollen tree mix, cat dander, house dust and D. pyteronyssinus, A. fumigatus and histamine.

A positive reaction was evidenced by a weal, 1mm or more in diameter in the absence of a reaction to glycerol. In those cases where a weal was produced to glycerol, a reaction was said to be positive only if it was at least twice the diameter of that caused by the glycerol. The findings of any test were discarded if histamine failed to produce a weal.

Patients with one or more positive reactions to any of the seven allergens were said to be atopic. Those with no positive reactions were said to be non-atopic.

Asthma Questionnaire

An asthma questionnaire was completed by all probands and those of their first and second degree relatives who had a history of wheezy illness. Parents of children under 15 years of age were asked to complete the questionnaire on behalf of their

child. In cases where a relative was deceased, his nearest living relative was asked to complete the questionnaire on his behalf.

The questionnaire was composed of three sections as shown in appendix B. The first section was concerned with the diagnosis of asthma and chronic bronchitis. The second section dealt with the age of onset of asthma and the patients' atopic status as assessed by skin prick tests and personal history of allergy. The third section gave an estimate of the severity of the patients' asthma as assessed by work disability, frequency and duration of attacks, exercise liability, treatment with steriods and history of hospitalisation.

The questionnaire was tested in a pilot study of 50 patients attending the asthma outpatient clinic of the Brompton Hospital. The findings of this pilot study are described in detail in appendix C and the conclusions summarised below.

A patient was said to have had asthma if (1) he said a doctor had told him he had had asthma or (2) if he had had at least three of the five asthma symptoms listed on the questionnaire and did not have heart trouble.

A patient was said to have had chronic bronchitis if he said a doctor had told him he had chronic bronchitis and he complained of the symptoms of the disease (MRC criteria, 1965).

The age of onset of asthma which was given by the patient was assumed to be correct.

A patient was said to be atopic if he had at least one positive reaction on skin prick testing. A patient was said to be non-atopic if he had had no positive reactions on skin prick testing. (These criteria only applied to those patients who were not skin prick tested by the author).

The patients' responses to each of nine questions dealing with the severity of his asthma were weighted as shown in appendix C and the values added together to produce a 'severity score'. The maximum possible score was 100, 50 points being alloted to morbidity in the past 12 months and 50 points being given to morbidity in previous years. Increasing scores represented increasing degrees of severity.

Methods

All probands were sent a letter which outlined the purpose of the study and invited their participation. A self-addressed, stamped envelope was enclosed for their response. Separate form letters were available for asthmatic and control probands (appendix D).

Patients indicating their willingness to participate were contacted by the author to arrange a suitable time and place for the interview. Patients not responding to the initial letter of invitation

were sent up to two more letters inviting their cooperation. The medical records of those patients refusing to participate were subsequently examined to see how they may have differed from those of patients who cooperated in the study.

The majority of interviews were conducted in the patients' homes at times when most other members of the family could be present. Interviews with asthma patients lasted 30-45 minutes, while those with control patients lasted 20-30 minutes.

The proband and any member of his family complaining of asthma or wheezy illness were first skin prick tested and then asked to complete an asthma questionnaire. The results of the skin test were read after the patient had completed the questionnaire. Details of the patients' family history of asthma and wheezy illness were then recorded. Patients were asked for the age (or age at death), the sex and the presence of asthma or wheezy illness in each of their first and second degree relatives.

All first and second degree relatives not present at the initial interview were sent a letter which outlined the purpose of the study and invited their participation (appendix D). Interviews were sought with accessible relatives. Asthma questionnaires were mailed to inaccessible relatives. Where possible, the information collected through inter-

views and questionnaires was verified by reference to the patients' medical records.

When one or more of the probands' relatives were unavailable for study, or the information pertaining to relatives was incomplete, the proband and his family were excluded from the investigation.

All phases of this investigation were carried out by the author.

RESULTS

The response rate was higher among asthma probands than among controls (p 0.01, Table 22). Comparison of the probands recruited to the study with those who did not participate showed that, in both the asthma and control groups, there were no significant differences in the sex distribution or mean age of the probands.

The probands who participated in the study are described in Table 23. There were no significant differences between asthma and control probands in the prevalence of atopy, prevalence of chronic bronchitis, sex-ratio or mean age of probands. However, the proportion of probands with a positive family history of asthma was significantly higher among asthmatics than controls (p 0.05).

Of the 58 asthma probands, 44 (76%) were atopic and 28 (48%) had a positive family history of asthma. Females outnumbered males by a ratio of 1.8: 1.0 (p 0.05), but this sex-ratio was not significantly different from that in the general population (X^2= 0.08, p 0.10; figure 2).

There were no significant differences between atopic and non-atopic probands in the sex-ratio, mean age, mean severity or proportion of patients with a positive family history of asthma. However, the mean age of onset of asthma was significantly lower in atopic than in non-atopic probands (p 0.01).

The prevalence and distribution of asthma in the relatives of the probands are shown in Table 24. There were no significant differences in the prevalences of asthma among the parents, siblings and offspring of either asthma probands (X^2= 0.43, $p>0.10$) or controls (X^2= 0.40, $p>0.10$). The prevalence of asthma in first degree relatives tended to be higher for atopic than for non-atopic probands, but the differences did not reach significance (asthma: X^2= 1.35, $p>0.10$; control: X^2 = 0.31, $p>0.10$). In both the asthma and control groups, the prevalence of asthma in the first degree relatives of probands was significantly higher than that in the second degree reltaives of probands (asthma: X^2= 27.57, $p<0.01$; control: X^2= 19.20, $p<0.01$). However, the prevalences of asthma in both the first and the second degree relatives of asthma probands were significantly higher than those in the relatives of controls (first degree relatives: X^2= 8.96, $p<0.01$; second degree relatives: X^2= 9.52. $p<0.01$).

The distribution of atopic and non-atopic asthma among the first degree relatives of probands is shown in Table 25. In the asthma group, the prevalence of atopic asthma was higher in the relatives of atopic probands than in the relatives of non-atopic probands; whereas the prevalence of non-atopic asthma in relatives did not vary with the atopic status of the

probands. Overall, atopic asthma was more prevalent than non-atopic asthma in the relatives of asthma probands. In contrast, the prevalences of atopic and non-atopic asthma did not differ significantly between the relatives of the atopic and non-atopic controls.

The risk of asthma in the siblings of probands with asthmatic parents is shown in Table 26. In both atopic and non-atopic probands, the prevalence of asthma in siblings tended to be higher when one parent was asthmatic than when neither parent was affected. This difference was significant when atopic and non-atopic probands were combined ($p < 0.05$).

The influence of breast feeding on the prevalence of asthma was examined. There were 10 families in which asthma probands had at least one asthmatic and one normal offspring. The distribution of breast and bottle feeding among these asthmatic and normal offspring is shown in Table 27. Although there was a tendency for asthmatic children to have been bottle fed, while their normal siblings were breast fed, the differences did not reach significance.

Table 22: Response Rates Among Asthmatic and Control Probands

	Asthma Probands				Control Probands			
Complied	Recruited	Not Interviewed	Rejected	Total	Recruited	Not Interviewed	Rejected	Total
Number	58	5	0	63	43	9	2	54
Mean Age (yrs)	35	36	-	35	39	40	34	39
Males (%)	20 (34)	2 (40)	-	22 (35)	12 (28)	1 (11)	1 (50)	14 (26)
Not Complied	No Response	Moved	Refused	Total	No Response	Moved	Refused	Total
Number	20	6	5	31	75	6	2	83
Mean Age (yrs)	37	47	44	40	38	42	59	39
Males (%)	9 (45)	4 (67)	3 (60)	16 (52)	32 (43)	4 (67)	1 (50)	37 (44)

There were no significant differences between patients who complied and those who did not comply.

Overall, the response rate was significantly higher in asthma patients than in control patients ($X^2 = 7.95$, $p < 0.01$).

Table 23: Characterization of Probands

Probands	N(%)	Males(%)	Chronic Bronchitis(%)	Mean Age	Mean Age Of Onset	Mean Severity	Positive Family History of Asthma (%)	Average Duration of Asthma (yrs)
Asthma								
Atopic	44 (76)	16 (36)	2 (4)	35±4	14±4	28 ± 4	22 (50)	21 ± 4
Non-Atopic	14 (24)	5 (36)	1 (7)	41±6	24±7	35 ± 10	6 (43)	18 ± 7
Total	58	21 (36)	3 (5)	36±10	16±11	30 ± 14	28 (48)*	20 ± 11
Control								
Atopic	25 (58)	9 (36)	0	37±4	-	-	5 (20)	-
Non-Atopic	18 (42)	3 (17)	0	41±5	-	-	4 (22)	-
Total	43	12 (28)	0	39±9	-	-	9 (21)	-

Excess as compared with control value * $p<0.05$, $X^2=5.39$.

Table 24: Distribution and Prevalence of Asthma Among Relatives of Probands

Probands		Prevalence of Asthma							
		Parents		Siblings		Offspring		1^{O}Relatives		2^{O}Relatives	
	N	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Asthma											
Atopic	44	10/88	(11)	14/92	(15)	10/57	(17)	34/237	(14)	16/415	(4)
Non-Atopic	14	3/28	(11)	3/31	(10)	1/26	(4)	7/85	(8)	3/168	(2)
Total	58	13/116	(11)	17/123	(14)	11/83	(13)	41/322	(13)	19/583	(3)
Control											
Atopic	25	4/50	(8)	1/42	(2)	3/37	(8)	8/129	(6)	1/248	(0.4)
Non-Atopic	18	2/36	(5)	2/35	(6)	1/29	(3)	5/100	(5)	1/214	(0.5)
Total	43	6/86	(7)	3/77	(4)	4/66	(6)	13/229	(6)	2/462	(0.4)

Table 25: Distribution of Atopic and Non-atopic Asthma Within Families

Probands	N	Prevalence atopic asthma (%) P	S	O	Total	Prevalence Non-atopic asthma (%) P	S	O	Total	Significance
Asthma										
Atopic	237	5 (6)	14 (15)	10 (18)	29 (12)	5 (6)	0	0	5 (2)	$X^2=16.9, p<0.01$
Non-Atopic	85	2 (7)	0	1 (4)	3 (4)	1 (4)	3 (10)	0	4 (5)	$X^2=0.1, p>0.10$
Total	322	7 (6)	14 (11)	11 (13)	32 (10)	6 (5)	3 (2)	0	9 (3)	$X^2=12.9, p<0.01$
Control										
Atopic	129	2 (4)	1 (2)	2 (5)	5 (4)	2 (4)	0	1 (3)	3 (2)	-
Non-Atopic	100	2 (5)	0	1 (3)	3 (3)	0	2 (6)	0	2 (2)	-
Total	229	4 (5)	1 (1)	3 (4)	8 (3)	2 (2)	2 (2)	1 (2)	5 (2)	$X^2=0.7, p>0.10$

Where N - Total number of first degree relatives at risk

P - parents

S - siblings

O - offspring

Significance - comparison of total prevalence of atopic asthma with that of non-atopic asthma

Table 26: Risk of Asthma in Siblings of Asthma Probands

Asthma Proband/ No. Affected Parents	N	Prevalence of Asthma In Siblings (%)		Expected Prevalence In Siblings (%)		Significance	
Atopic Proband							
Neither	34	6/65	(9)	Sample too small to test			
One	10	8/27	(30)				
Total	44	14/92	(15)				
Non-Atopic Proband							
Neither	11	2/22	(9)	Sample too small to test			
One	3	1/9	(11)				
Total	14	3/31	(10)				
All Probands							
Neither	45	8/87	(9)	12/87	(14)	$X^2=1.33$	N.S
One	13	9/36	(25)	5/36	(14)	$X^2=3.20$	N.S
Total	58	17/123	(14)	17/123	(14)	$X^2_2=4.53.$	$p<0.05$

Table 27: Influence of Breast Feeding on Incidence of Asthma

Offspring	Method of Feeding in Infancy				Total	
	Breast Fed	(%)	Bottle Fed	(%)		
Normal	11	(42)	4	(15)	15	(57)
Asthmatic	5	(19)	6	(23)	11	(12)
Total	16	(62)	10	(38)	26	

Contingency $X^2 = 2.67$, $p > 0.10$

DISCUSSION

A family study of asthma in adults was designed to investigate the possibility there may be age-related differences in the hereditary basis of asthma.

Atopic and non-atopic asthma probands resembled each other in their sex-ratio, mean age, and proportion with a family history of asthma (Table 23). However, atopic asthmatics tended to have a lower age of onset and a lower mean severity score than did non-atopic asthmatics. These findings are consistent with those of previous investigations which have shown that atopy is usually associated with a younger age of onset (Pepys, 1973) and that atopic asthma is generally less severe than non-atopic asthma(Blair 1978, Ogilvie, 1962). The factors which may govern age of onset and severity are discussed in detail in Chapter five.

Asthma was found to cluster in the relatives of asthmatics, supporting the concept this disease has an hereditary basis. The proportion of probands with a positive family history of asthma, as well as the prevalence of asthma in first degree relatives, were significantly higher among asthma probands than controls. Furthermore, when atopic and non-atopic probands were considered separately, there was an increased prevalence of asthma in the first degree relatives of both atopic and non-atopic asthma probands as compared with the relatives of controls. Thus, atopic and non-atopic asthma may both be heritable.

The finding that the risk of asthma in the siblings of both atopic and non-atopic asthma probands was greater when one parent was asthmatic than when neither parent was affected, lends support to this hypothesis.

The overall prevalence of asthma in the first degree relatives of asthmatics was 13%, which compares extremely well with previous family studies in general practice (see discussion, Chapter three). However, the prevalence of asthma in the first degree relatives of controls (6%) was higher than has previously been reported. The discrepancy might have been caused by the methods used to recruit non-wheezy subjects to the control group. It is possible that many of the control subjects who agreed to participate in the study did so because one or more of their family had had asthma. Certainly, Table 22 shows that compliance was higher among asthma probands than controls, presumably because the asthmatics had a greater interest in the disease. Thus, among the control subjects who were recruited, there may have been a disproportionate number with a positive family history of asthma.

The family history of asthma differed between atopic and non-atopic asthma probands. Although the proportion of probands with a positive family

history of asthma was similar, the prevalence of asthma tended to be higher in the relatives of atopic than non-atopic asthma probands. In addition, the difference in the prevalence of asthma between the relatives of asthmatics and controls was greater for atopic than non-atopic probands. Although these trends did not reach significance, they suggest that atopic asthma may have a greater heritability than non-atopic asthma.

Examination of the distribution of atopic and non-atopic asthma in the relatives of asthma probands showed that atopic asthma was more prevalent in the relatives of atopic probands than in the relatives of non-atopic probands. In contrast, the prevalence of non-atopic asthma in relatives did not vary with the atopic status of the probands (Table 25). Therefore, the difference in the prevalence of asthma between relatives of atopic and non-atopic asthmatics may be attributed to an increased prevalence of atopic asthma in the relatives of atopic probands.

The findings also showed that there was no strict association between asthma and atopy in the probands and their relatives. Asthma probands and their affected first degree relatives occassionally differed in their atopic status, suggesting that asthma and atopy may have been segregating in some

families. In addition, atopic and non-atopic asthma were equally prevalent in the relatives of atopic and non-atopic controls, showing that the atopic status of non-asthmatic probands does not influence the risk of asthma in their relatives. Thus asthma and atopy may be inherited independently and atopy itself cannot give rise to asthma.

When they are considered together, these findings suggest that atopy may enhance the likelihood of a genetic predisposition to asthma being expressed. Relatives of atopic asthma probands may inherit a predisposition to both asthma and atopy, and so are more likely to express asthma than are the relatives of non-atopic asthma probands, who may only inherit a predisiposition to asthma.

A comparison of these adult asthma probands (Table 23) with the child asthma probands already described (Table 14) supports previous observations that the sex-ratio and prevalence of atopy may differ between child and adult asthmatics (see introduction, Chapter four). The findings showed that the sex-ratio in adult probands was biased in favour of females, whereas that in children was biased in favour of males. In addition, the prevalence of atopy in probands tended to be lower in adults than children, although this difference did not reach significance (X^2= 0.15, N.S).

Despite these differences, child and adult asthma probands resembled each other closely in their family histories of asthma. Adult and child asthma probands did not differ significantly either in the proportion of probands with a positive family history of asthma (X^2= 1.15, N.S.) or in the prevalence of asthma in their first degree relatives (X^2=0). Most importantly, the relationship of asthma to atopy was found to be the same in adult asthma probands as in child asthma probands. Therefore, there were no demonstrable age related differences in the hereditary basis of asthma.

Recently, there has been considerable interest in the influence of breast feeding on the incidence of allergy in children. It has been shown that breast feeding is associated with a reduced incidence of eczema in children (Mathew et al,1977) and may also be associated with a reduced incidence of asthma (Blair, 1977). In the present study, there was a tendency towards a lower prevalence of asthma among the breast fed as compared with the bottle fed infants of asthmatic parents. However, the sample size was small and the differences did not reach significance (Table 27). Prospective studies of children with asthmatic parents would be a more useful method of assessing the influence of breast feeding on the incidence of asthma.

CHAPTER FIVE

AGE OF ONSET, SEVERITY AND SEX DISTRIBUTION OF ASTHMA

The age of onset, severity and sex distribution of asthma may be closely associated. Age of onset is correlated with atopic status, there being a trend towards an earlier age of onset with increasing skin test positivity (Andrews, Bayliss and Baldry, 1975; Pepys, 1973). In early onset asthma, males are more often affected than females; whereas, in late onset asthma, females are equally if not more often affected than males(Gregg, 1977). In addition, it has been suggested that asthma is more intermittent in early onset asthma than in late onset asthma (Ogilvie, 1962; Turner-Warwick, 1971) and that remission is more frequent in children than adults (Blair, 1977; Wilken-Jensen. 1977).

The family studies of adult and child asthmatics, already described (Chapters 3 and 4), support these findings by showing that there was a trend towards a higher prevalence of atopy, a greater percentage of males, and a milder form of asthma in child asthmatics as compared with adult asthmatics.

In the present study, the nature of these associations is examined in more detail. Particular attention is given to the possibility that the age of onset, severity and sex distribution of asthma may have a genetic basis.

MATERIALS AND METHODS

Age of onset and severity of asthma were investigated in 58 asthma probands and their relatives attending a general practice in Kingston-upon-Thames. The probands are described more fully elsewhere (Table 23). Information on the age of onset, atopic status and severity of asthma in each of the probands and their affected first degree relatives was ascertained by personal interviews, questionnaires and scrutiny of medical records, as described in Chapter four.

Investigation of the sex distribution of asthma was carried out in 469 outpatients attending the asthma clinic of the Brompton Hospital. The asthma probands are described more fully elsewhere (Table 8). Information on asthma probands and their first degree relatives was obtained by questionnaires and scrutiny of medical records, as described in Chapter two.

The association between pairs of continuous variables were assessed using the product moment correlation coefficient (r). The Chi-square test was used to assess differences between groups of discontinuous variables.

RESULTS

Age of Onset

The relationship of age of onset to the atopic status and severity of asthma in patients was examined in asthma probands and their affected first degree relatives. The prevalence of atopy in asthma patients was found to decline significantly with increases in their age of onset (Table 28a). However, there was no significant correlation between the probands' age of onset and the severity of their asthma (figure 3).

Since previous studies suggested there may be a relationship between age of onset and frequency of remission (see introduction), these associations were also examined. However, no correlation was found between the age of onset of asthma and the frequency of attacks in probands ($t = -1.58$, p 0.10; Table 28b). In addition, the percentage of probands who had been free of their asthma for 5 or more years did not appear to be associated with the probands' age of onset, although the number of patients was too small for analysis (Table 28b).

The relationship of age of onset of asthma in probands to the age of onset and prevalence of asthma in their first degree relatives was also examined. Since, age of onset was shown to be associated with atopic status, atopic and non-

atopic asthma probands were investigated separately. In atopic probands, no significant correlation was found between the age of onset of asthma in probands and the age of onset of asthma in their affected first degree relatives (figure 4). Nor was there an association between the probands' ages of onset and the prevalence of asthma in their first degree relatives (Table 29). In non-atopic asthma probands, there were too few patients to permit analysis of these relationships.

Table 28 a

Association Between Age of Onset and Atopic Status of Probands and Their Affected First Degree Relatives

Patient's Age of Onset (years)	Patient's Atopic Status: Atopic observed	Atopic expected	Non-Atopic observed	Non-Atopic expected	Total
≤ 10	44 (58%)	36 (47%)	3 (13%)	11 (48%)	47
11-29	25 (33%)	24 (32%)	6 (26%)	7 (30%)	31
≥ 30	7 (9%)	16 (21%)	14 (61%)	5 (22%)	21
Total	76	76	23	23	99

$X_2^2 = 29.04$, $p < 0.01$

Figure 3

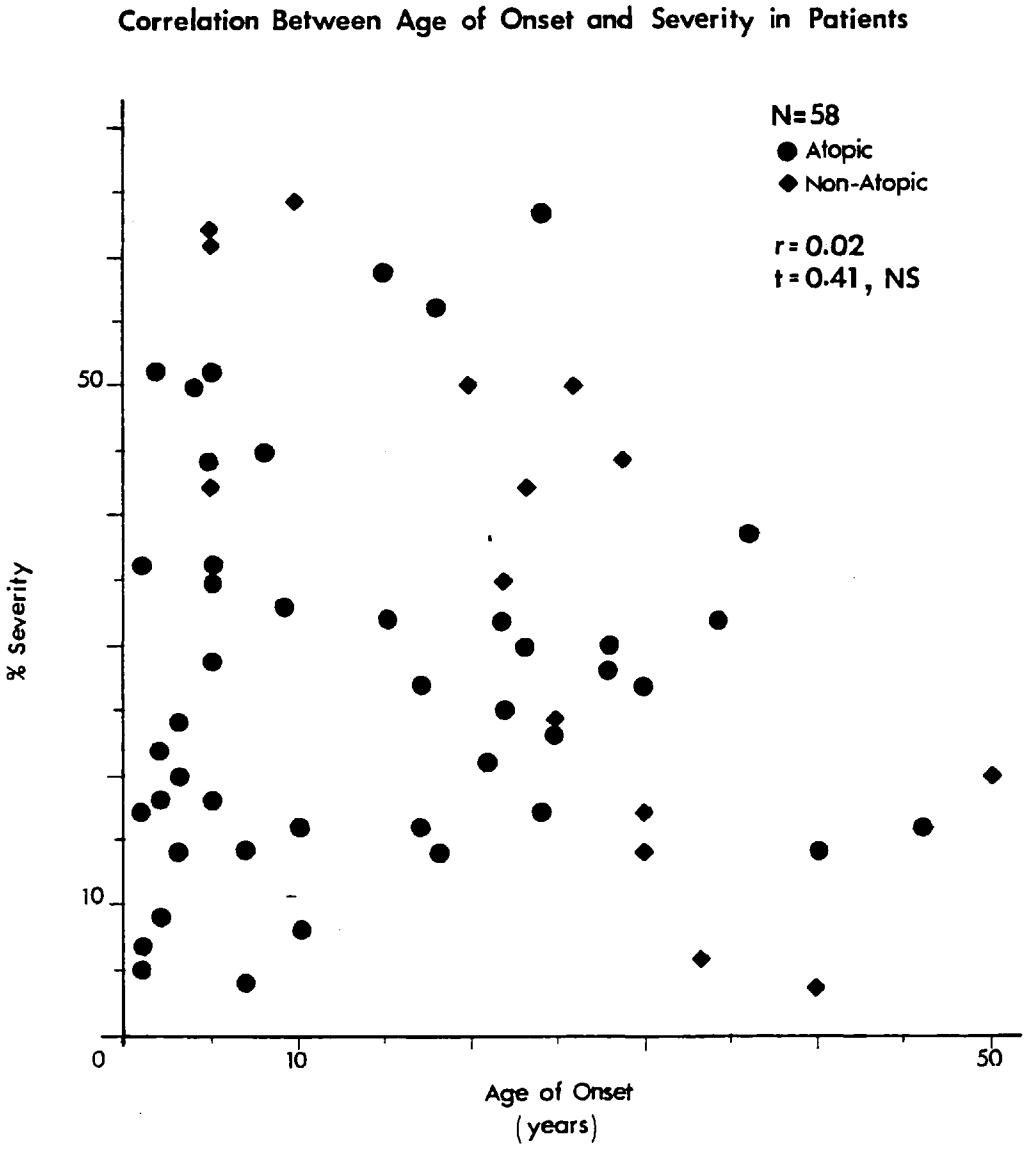

Correlation Between Age of Onset and Severity in Patients
N=58
Atopic
Non-Atopic
r = 0.02
t = 0.41, NS
% Severity
50
10
0
10
50
Age of Onset
(years)

Table 28b

Association of Age of Onset with Frequency of Attacks and Frequency of Remission for Five or More Years

Patient's Age of Onset (years)	N	Patient's Frequency of Attacks* Mean Score	Variance	Remission N	(%)
less than 10	28	4.95	3.77	5	(18)
11 - 29	21	5.86	4.12	1	(5)
30 or more	9	4.17	3.00	2	(22)

* The sum of the patient's scores on questions 2 and 5 only of section C of questionnaire (appendix C). Maximum possible score was 10.

Figure 4

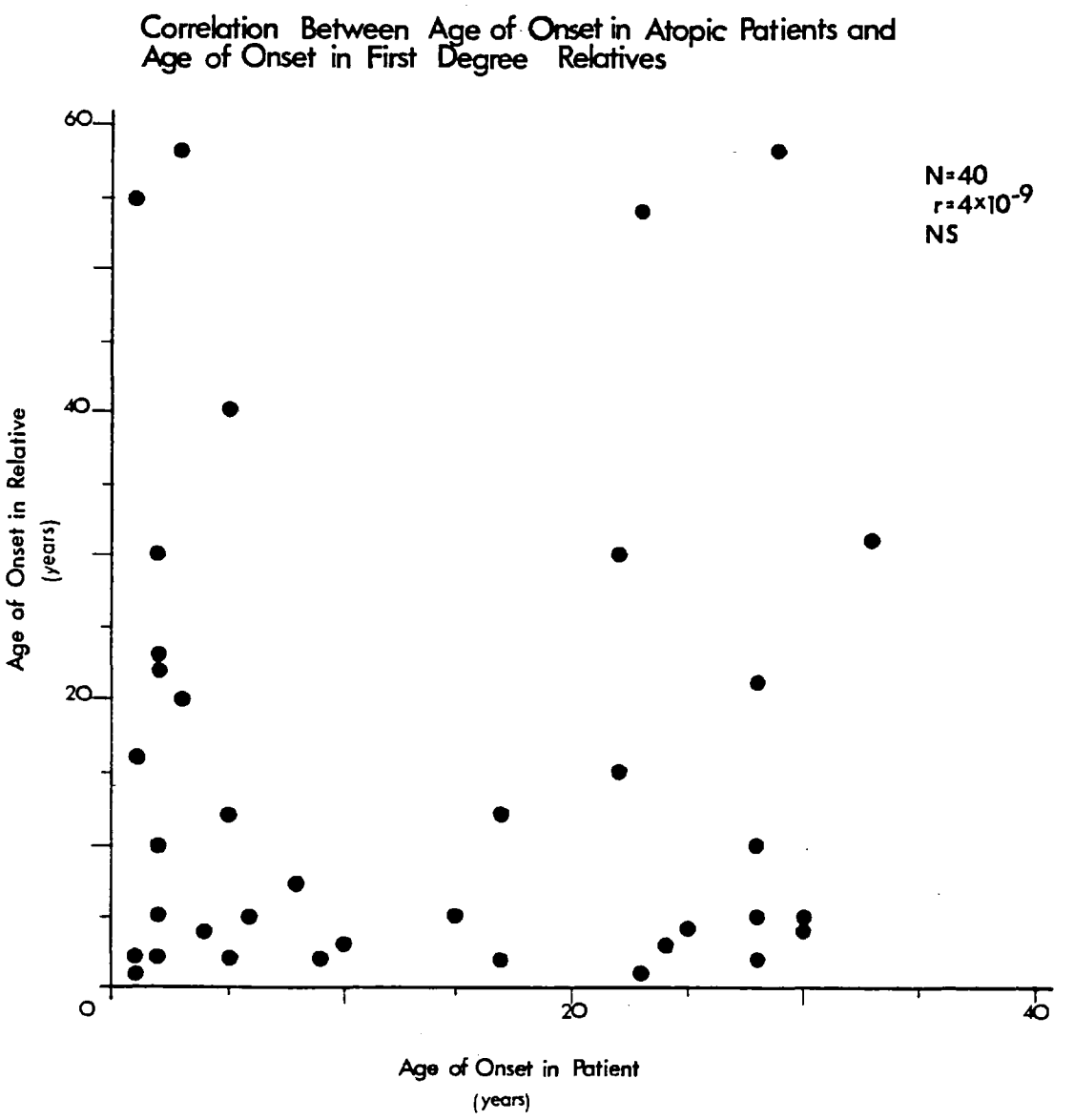

Correlation Between Age of Onset in Atopic Patients and Age of Onset in First Degree Relatives
N=40
r=4x10-9
NS
Age of Onset in Relative (years)
Age of Onset in Patient (years)
0
20
40
60

Table 29

Association Between Age of Onset of Asthma in Probands and the Prevalence of Asthma in their First Degree Relatives

Age of Onset (years)	N	Prevalence of Asthma N	(%)
$\leq$ 10	24	20/125	(16)
11-29	15	12/85	(14)
$\geq$ 30	5	2/27	(4)
Total	44	34/237	(14)

$X_2^2 = 1.22$, N.S

SEVERITY

The severity of patients' asthma was represented by a 'severity score', derived from a self-completed questionnaire, as described in Chapter four. The responses of the asthma probands to this questionnaire are shown in Table 30. The probands' mean severity score for the year immediately preceeding the study was 11 ± 2 out of a possible 50, while the mean score for previous years was 17 ± 3 out of a possible 50. Thirty-three (57%) probands had lower severity scores in the past year than in previous years, 15 (26%) showed no change, and 9 (16%) had higher scores in the past year than in previous years. The total mean score for all years was 28 ± 5 out of a possible 100.

A pilot study of 93 outpatients attending the asthma clinic of the Brompton Hospital (appendix C) showed that, in these patients, the overall mean severity score was 42 ± 6 (Table 48). Comparison of the hospital outpatients with the general practice patients, described above, shows that the severity score was singificantly lower in the general practice patients than in the hospital outpatients ($t=3.61$, $p<0.01$).

The possibility that the severity of asthma may be genetically determined was investigated in

the general practice asthma probands and their affected first degree relatives. There was no correlation between the severity of asthma in probands and the prevalence of asthma in their first degree relatives (figure 5). However, there was a significant, positive correlation between the severity of asthma in probands and the severity of asthma in their affected first degree relatives (figure 6).

Table 30: Probands' Responses to Questionnaire Section C

Q	Criteria	Score	Past Year N	Past Year (%)	Previous Years N	Previous Years (%)
1	Work Disability					
	not known	45*	9	(16)	7	(12)
	none	0	36	(62)	25	(43)
	2 weeks or less	2	7	(12)	10	(17)
	2-4 weeks	3	5	(9)	9	(16)
	over 4 weeks	5	1	(2)	7	(12)
2	Remission of 5 or more years	-10	7	(12)	-	
3	Frequency of Attacks					
	continuous	5	8	(14)	9	(16)
	daily	3	11	(19)	8	(14)
	weekly	2	10	(17)	12	(21)
	less than weekly	1	22	(38)	28	(48)
	none	0	7	(12)	1	(2)
4	Exercise Tolerance					
	normal	0	22	(38)	14	(24)
	mild	2	24	(41)	20	(34)
	moderate	3	9	(16)	11	(19)
	severe	5	3	(5)	13	(22)
5	Night Attacks					
	daily	5	3	(5)	8	(14)
	weekly	3	6	(10)	10	(17)
	monthly	2	8	(14)	8	(14)
	less than monthly	1	20	(34)	26	(45)
	none	0	21	(36)	6	(10)
6	Severity of Night Attacks					
	none	0	22	(38)	8	(14)
	mild	2	20	(34)	23	(40)
	moderate	3	9	(16)	15	(26)
	severe	5	7	(12)	12	(21)
7	Continuous Steroids	10	5	(9)	7	(12)
8	Steroid Course	5	10	(17)	12	(21)
9	Hospitilization					
	none	0	55	(95)	47	(81)
	once/year	5	2	(3)	6	(10)
	more than once/year	10	1	(2)	5	(9)

Q - question number
* Score calculated out of 45 instead of 50.

Figure 5

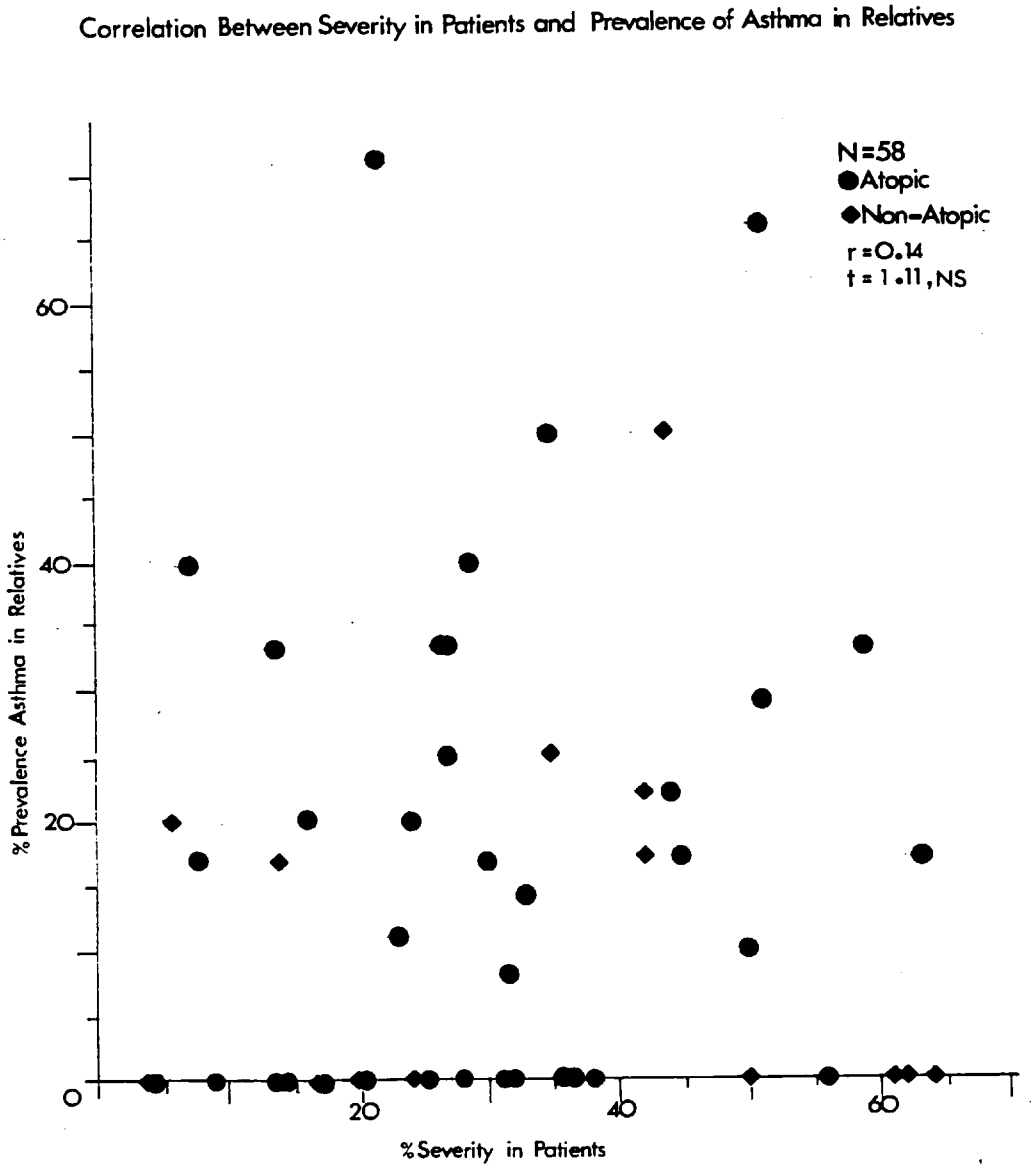
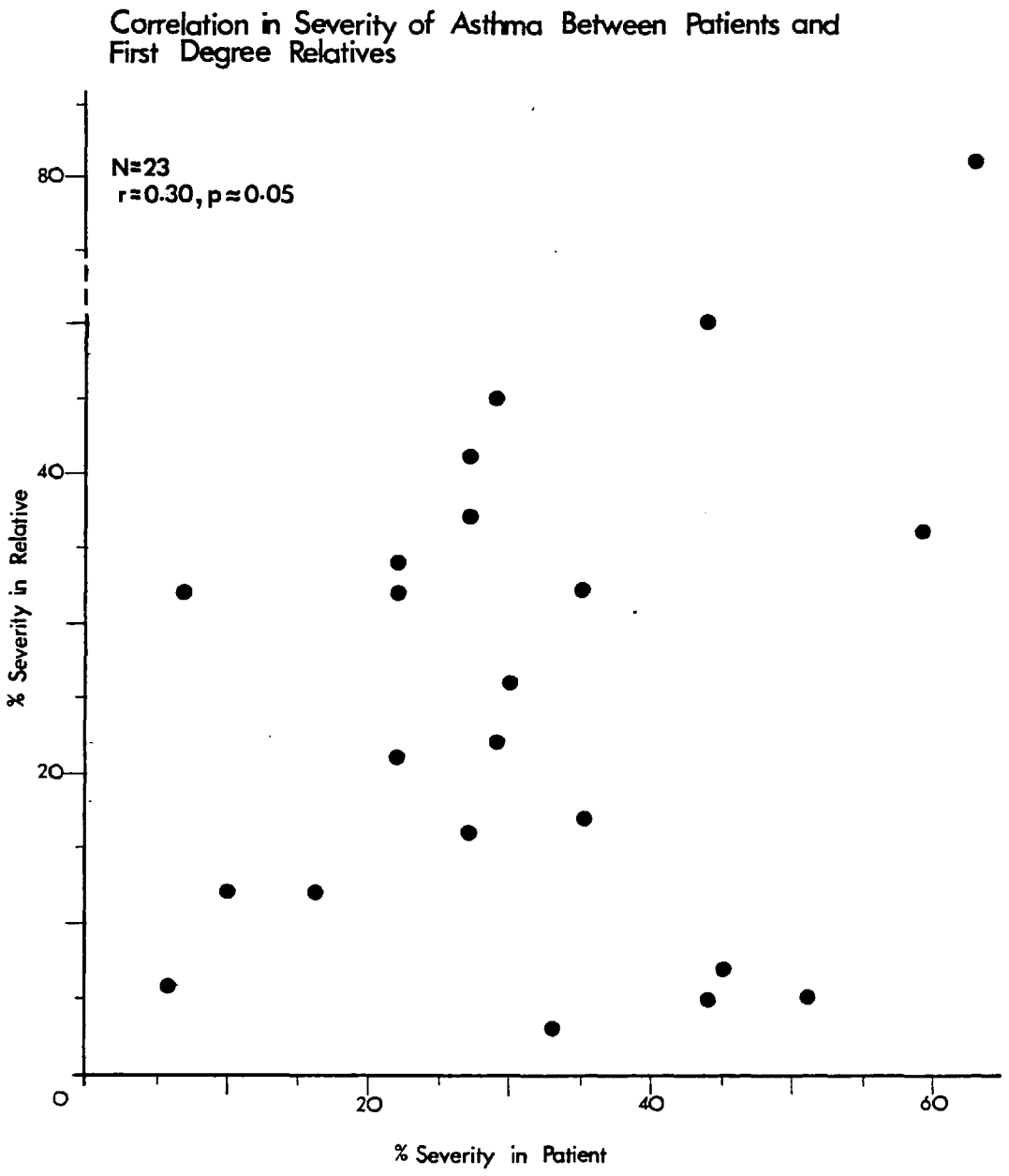

Correlation Between Severity in Patients and Prevalence of Asthma in Relatives
N=58
Atopic
Non-Atopic
r=0.14
t=1.11, NS
% Prevalence Asthma in Relatives
0
20
40
60
20
40
60
% Severity in Patients

Figure 6


Correlation in Severity of Asthma Between Patients and First Degree Relatives
N=23
r=0.30, p≈0.05
% Severity in Relative
% Severity in Patient
0
20
40
60
80
20
40

SEX DISTRIBUTION

Among 469 asthma probands attending the Brompton outpatients clinic, 298 had three or more positive skin tests, 77 had one or two positive skin tests and 31 had no positive skin tests. The sex-ratio (males/females) in these three groups of probands were 1.35, 0.83 and 0.58 respectively.

The possibility that atopic asthma is genetically sex-linked was investigated in the relatives of probands with three or more positive skin tests. Families in which only one parent had had asthma were selected and grouped according to the sex of the affected parent. The prevalences of asthma in the brothers and sisters of the probands were then recorded (Table 31). Analysis of the distribution of asthma in these relatives showed that the sons and daughters of asthmatic mothers and fathers were all equally affected.

The possibility that asthma is genetically sex-influenced was investigated in probands with no positive skin tests and in probands with three or more positive skin tests. In each group of probands, the prevalences of asthma in the male and female relatives of the male and female probands were recorded (Table 32). Analysis of the distribution of asthma in these relatives showed that, in both groups, the prevalence of asthma was evenly distributed between the male and female relatives of the male and female probands.

Table 31

Prevalence of Asthma in Siblings of Probands With One Affected Parent

Sibling	Parent					
	Mother		Father		Total	
Brother	3/26	(12%)	7/38	(18%)	10/64	(16%)
Sister	8/40	(20%)	6/47	(13%)	14/87	(16%)
Total	11/66	(17%)	13/85	(15%)	24/151	(16%)

Contingency $X^2_1=0.70$, $p > 0.10$

Table 32

Prevalence of Asthma Among Male and Female Relatives of Male and Female Asthmatics

A. Probands with Three or More Positive Prick Tests

Proband	Prevalence in Relatives (%) Male	Female	Row Significance
Male	49/464 (11)	40/466 (9)	$X_1^2=1.12$, $p > 0.10$
Female	30/388 (9)	35/394 (9)	$X_1^2=0$
Column Significance	$X_1^2=0.46$, $p > 0.05$	$X_1^2=0$	

B. Probands with No Positive Prick Tests

Proband	Prevalence in Relatives (%) Male	Female	Row Significance
Male	4/96 (4)	4/107 (4)	$X_1^2=0$
Female	9/169 (5)	13/176 (7)	$X_1^2=0.73$, $p > 0.10$
Column Significance	$X_1^2=0.32$, $p > 0.10$	$X_1^2=1.55$, $p > 0.10$	

DISCUSSION

Age of Onset

The factors governing the age of onset asthma are not yet known, but are likely to include both genetic and environmental components. In some patients, the onset of asthma may be preceeded by an environmental insult such as a lower respiratory infection, exposure to certain allergens, or even severe emotional stress. Although environmental factors cannot be identified in all cases, it is possible that an environmental stimulus of some kind is often needed to trigger the overt expression of asthma in genetically predisposed subjects. Both the nature and the strength of the stimulus may be important in determining whether or not asthma is expressed. At the same time, the genetically determined liability to asthma may vary among patients, rendering them more or less susceptible to environmental stimulation. Genetic factors could specify both the nature and the strength of the environmental stimulus which would be necessary to cause the overt expression of asthma. Thus the age of onset of asthma may be a product of the interaction between the genetically determined liability to the disease, and the nature and strength of the environmental stimulii encountered.

In the present study, as well as in previous investigations, the age of onset of asthma was found to be correlated with patients' atopic status. Atopic asthma patients tended to have earlier ages of onset than did non-atopic asthma patients. Although the reason for this association is not known, it is possible that, by enhancing the likelihood of a genetic predisposition to asthma being expressed, atopy may also lead to an earlier age of onset. One possibility is that atopy may enhance genetic liability by increasing the range of stimulii capable of triggering the overt expression of asthma.

The findings of the present study also suggest that age of onset of asthma has no genetic basis apart from its association with atopy. No correlation was found between the age of onset of asthma in atopic probands and the age of onset of asthma in their affected first degree relatives. Nor was there an association between the age of onset of asthma in atopic probands and the prevalence of asthma in their first degree relatives. Therefore, among probands with the same atopic status, there was no familial clustering of age of onset, and an early age of onset was not associated with an increased liability to asthma in relatives. However, since atopy is heritable,

and age of onset is associated with atopic status, familial clustering in age of onset may occur.

Previous studies suggested that age of onset may be associated with the frequency of attacks and the frequency of remission in patients with asthma. However, in the present study, no correlation was found between the age of onset of asthma in probands and the severity of their asthma. Nor was their an association between the age of onset of asthma and the frequency of attacks in probands. Although the relationship of age of onset to the frequency of remission could not be evaluated, the percentage of probands who had been completely free of their asthma for five or more years, did not appear to be lower in early onset than in late onset asthmatics. Thus, there was no demonstrable relationship between age of onset of asthma and severity.

The discrepancy between these findings and those of previous studies most likely arises from the differences between them in the method of assessing severity. Additional studies, employing standardised measures of severity, are needed if the relationship between age of onset and severity is to be clarified.

Severity:

The possibility that severity may have an hereditary basis has not previously been investi-

gated, at least partly because there are no well defined criteria for its measurement. Physicians may differ widely in their methods of judging the severity of a patients' asthma. However, a personal survey of five consultants, specialising in asthma at the Brompton Hospital, showed that there were several criteria which all agreed were important in assessing severity. These included: the frequency and duration of attacks, exercise liability, history of steroid use and history of hospitalisation. In addition, freedom from symptoms for a period of five or more years was considered to be representative of mild asthma. In the present study, the severity of patients' asthma was represented by a 'severity score' which was derived from a self-completed questionnaire dealing with these aspects of severity. Although the validity of this approach cannot be proven, the finding that hospital outpatients had significantly higher severity scores than did general practice patients suggests that this measure of severity was meaningful.

The use of severity scores in family studies of asthma provides the means by which the genetic basis of severity can be estimated. If severely affected probands had a greater number of asthma genes than mildly affected probands, the difference would be reflected in their family history. The

prevalence of asthma would tend to be higher in the relatives of severe asthmatics than in the relatives of mild asthmatics. Alternatively, it is possible that asthma genes have different alleles, some leading to more severe forms of asthma than others. In this case, the relatives of severe asthmatics would tend to have more severe asthma than would the relatives of mild asthmatics.

In the present study, no significant correlation was found between the severity of asthma in probands and the prevalence of asthma in their first degree relatives (figure 5). Therefore, it seems likely that severity was not determined by differences between patients in the number of asthma genes underlying the disease.

However, a significant correlation was found between the severity of asthma in probands and the severity of asthma in their affected first degree relatives (figure 6). While this finding shows that asthma genes may have alleles which differ in the severity they confer, it is also possible that the resemblance among relatives arose from shared environments. Twin studies are needed to assess the relative importance of heredity and the enviroment in this context.

Sex Distribution:

Sex-linkage and sex-influence are two ways in which heredity may give rise to sex differences in

the prevalence of a disease. Sex-linked disorders affect males more often than females; while sex-influenced disorders may result in either sex being more frequently affected than the other. Thus the preponderance of males among atopic asthmatic patients suggests this form of asthma might be either sex-linked or sex-influenced; whereas the excess of females among non-atopic asthmatic patients suggests this form of asthma might be sex-influenced.

Under the hypothesis of sex-linkage, atopic asthma would be associated with a gene linked to the X-chromosome. Since males may only inherit an X-chromosome from their mothers, this linkage is expected to result in more mother-son affected pairs than other parent-offspring combinations. However, when this prediction was tested, results showed that asthmatic mothers did not have more affected sons than daughters. Indeed, the prevalence of asthma was evenly distributed among the sons and daughters of affected mothers and fathers (Table 32). Thus atopic asthma cannot be sex-linked.

There remains the possibility that asthma is sex-influenced. Under this hypothesis, the sex which is least often affected has a greater resistance to asthma and must therefore inherit more predisposing factors in order to manifest the disease. This difference between the sexes would be reflected

in their family history of asthma. In atopic asthma where females are the sex least often affected, the prevalence of asthma in the relatives of female asthmatics is expected to exceed the prevalence of asthma in the relatives of male asthmatics. The difference in prevalence may be small, but would be seen most clearly in female relatives; female relatives of female asthmatics would be more frequently affected than female relatives of male asthmatics. Conversely, in non-atopic asthma where males are the sex least often affected, we would expect male relatives of male asthmatics to be more frequently affected than male relatives of female asthmatics.

When these predictions were tested, results showed that, in both atopic and non-atopic patients, the prevalence of asthma was evenly distributed among the male and female relatives of the male and female probands (Table 32). Thus neither form of asthma was sex-influenced.

This investigation suggests that genetics does not play a direct role in the generation of sex differences in the prevalence of asthma. Although the findings confirmed that the sexes may be unequally affected, no evidence of sex-influence or sex-linkage could be found. How then do such sex differences arise?

A possible explanation is that boys are more

frequently atopic than girls. Since atopy increases the likelihood that a genetic predisposition to asthma will be expressed, asthma would be more prevalent among boys than girls. However, this does not seem to be true, since the prevalence of atopy in boys and girls appears to be equal (Barbee et al, 1976).

A more plausible hypothesis is that sex acts indirectly, through the medium of a secondary factor, to influence the predisposition to asthma. In atopic patients, there is evidence to suggest that this secondary factor might be a lower respiratory illness, such as bronchitis. It has been shown that bronchitis preceeds asthma in many asthmatic children (Leeder et al, 1976) and many increase the frequency and persistance of wheezy attacks (Ogilvie, 1962). Moreover, boys are more often bronchitic than girls (Leeder et al, 1976). Therefore, maleness may enhance the susceptibility to bronchitis which, in turn, increases the predisposition to asthma.

In late onset asthma, sex differences in the prevalence of asthma are either absent or not pronounced, leading some to speculate that the differences may be spurious. Indeed, among the very elderly, as in children, men may more often be affected than women (Burr et al, 1979). Thus it is possible that, where sex differences in the

prevalence of asthma in adults have been observed, there has been a bias in ascertainment.

CHAPTER SIX

HEREDITY IN ASTHMA - ITS THEORETICAL AND PRACTICAL IMPORTANCE

Although previous studies did much to clarify our understanding of the genetic basis of asthma (Chapter one), a number of important issues were left unresolved. Foremost among these were the problems of whether asthma was genetically homogeneous and whether asthma had an hereditary component independent of that which underlies atopy. Also of interest was the possible role of heredity in governing the age of onset, severity and sex distribution of asthma. The importance of resolving these problems lay not only in clarifying theoretical aspects of the etiology of asthma, but also in aiding physicians to identify and counsel high risk patients.

In the present investigation, family studies were employed to help resolve these outstanding issues. The family study approach was selected in preference to other methodologies, such as twin studies or immunopharmacological studies, because of its comparative ease of application and because its flexibility permitted investigation of the many different genetic problems proposed.

In this chapter, the findings of the various family studies are drawn together to form a unified hypothesis of the role of heredity in asthma. The theoretical and practical importance of these findings is then discussed.

SYNOPSIS OF FINDINGS

The problem of genetic heterogeneity in asthma was investigated by means of family studies. 'Extrinsic', 'intrinsic', child and adult groups of asthmatic probands were studied in order that widely differing forms of the disease might be compared.

The prevalence and distribution of asthma in the first degree relatives of the probands were examined firstly for evidence that extrinsic, intrinsic, child and adult forms of asthma were all hereditary. The findings showed that, in all groups of probands, asthma tended to cluster in the relatives of asthmatics. The prevalences of asthma in the siblings of probands were higher when one or both of their parents were asthmatic than when neither parent was affected (Table 34). In addition, the prevalences of asthma in the first degree relatives of child and adult asthmatics were significantly higher than those in the relatives of a comparable group of non-asthmatic controls (Table 33). This clustering of asthma in the relatives of asthmatics suggests that extrinsic, intrinsic, child and adult forms of the disease may all have a genetic basis. However, as the relative effects of heredity and the environment cannot be distinguished in family studies, twin studies should be employed to assess the validity of this hypothesis.

Assuming that extrinsic, intrinsic, child and adult asthma are all hereditary, the family history data can be used to assess the likelihood of their sharing a common genetic basis. The findings showed that there was a strong similarity in the family history of asthma between the different groups of asthmatics. Although the proportion of probands with a positive family history of asthma varied from a minimum of 38% in children to a maximum of 48% in adults, the differences were not significant. Overall, the mean proportion of probands with at least one affected first degree relative was 39%.

Furthermore, in all groups of probands, the distribution of asthma among the first degree relatives was either even, or tended towards an increased prevalence in parents as compared with siblings or offspring (Table 35). The excess of asthma in parents might have arisen from their superior age; the younger siblings and offspring not having had the same period of time in which to express a liability to asthma. If this is true, then the distribution of asthma among the parents, siblings and offspring of probands would be even should the first degree relatives be examined at the same age.

The similarity between extrinsic, intrinsic, child and adult asthma both in the proportion of probands with at least one asthmatic first degree relative and in the distribution of asthma among

the first degree relatives of probands suggests that they may share a common genetic basis. Although the number and nature of the 'asthma' genes involved cannot be determined from these data, the findings imply that the same genetic loci underly different forms of asthma. Genetic heterogeneity could arise from multiple allelism at these loci, but this possibility cannot be evaluated until more is known of the biochemical basis of asthma. Thus, within the boundaries of this investigation, asthma appeared to be genetically homogeneous.

The relationship of asthma to atopy is intimately associated with the problem of heterogeneity. Atopy, which may be defined as the capacity to readily produce IgE in response to environmental allergens (Pepys, 1973), is known to have an hereditary basis (Marsh, Bias and Ishizaka, 1974). Thus, asthma may be said to be genetically heterogenous in so much as its association with atopy clearly differs between extrinsic and intrinsic asthmatics, and between child and adult asthmatics. The finding that extrinsic, intrinsic, child and adult asthma may share a common genetic basis and yet differ in their association with atopy is best explained if asthma and atopy are inherited independently. Indeed, family and twin studies have suggested that asthma may have an hereditary component separate from that which underlies atopy (Chapter one), although it has remained unclear whether the asthmatic component can be expressed in the absence of atopy.

In the present study, the relationship of asthma to atopy was investigated by means of family studies. Extrinsic, intrinsic, child and adult asthma probands were grouped according to their atopic status, as assessed by skin prick testing. A comparison of the family history of asthma in atopic probands with that in non-atopic probands showed that, although the proportion of probands with at least one asthmatic relative was similar, the prevalence of asthma in the first degree relatives of the atopic asthmatics tended to be higher than that in the relatives of the non-atopic asthmatics (Table 35). Indeed, the risk of asthma in the relatives of the non-atopic asthmatics often was only marginally greater than the risk to the relatives of non-asthmatic controls (Table 16 and 24). Therefore, the penetrance of asthma genes appeared to be higher in atopic than in non-atopic forms of the disease.

Examination of the distribution of atopic and non-atopic asthma in the relatives of the asthma probands showed that the prevalence of atopic asthma was higher in the relatives of atopic probands than in the relatives of non-atopic probands. In contrast, the prevalence of non-atopic asthma did not vary with the atopic status of the probands. Therefore, the difference in the family history of asthma between atopic and non-atopic probands may be attributed to

an increased prevalence of atopic asthma in the relatives of the atopic asthmatic probands.

In the control groups, the prevalences of atopic and non-atopic asthma did not differ between the relatives of the atopic and the non-atopic probands. Therefore, in non-asthmatic subjects, atopy was not associated with an increased prevalence of asthma in relatives. This finding suggests that atopy does not itself give rise to asthma.

Furthermore, there was no strict association between asthma and atopy in the asthma probands and their relatives. The asthmatic relatives of asthma probands did not always have the same atopic status as the proband (Tables 25 and 20). Thus asthma and atopy appeared able to segregate independently.

When these findings are considered together, they strongly suggest that asthma is inherited independently of atopy, but that atopy may enhance the likelihood of a genetic predisposition to asthma being expressed. The relatives of atopic asthmatics may inherit a predisposition to both asthma and atopy, and so are more likely to develop asthma than are the relatives of non-atopic asthmatics, who may only inherit a predisposition to asthma. Thus the prevalence of asthma is higher in the relatives of atopic than non-atopic asthmatics, the difference arising from an increased prevalence of atopic asthma in the relatives of atopic asthmatics.

The findings of this investigation suggest that extrinsic, intrinsic, child and adult asthma share a common genetic basis. The differences between them in their association with atopy can be explained by the finding that, although asthma and atopy may be inherited independently, atopy enhances the likelihood of a genetic predisposition to asthma being expressed. However, extrinsic, intrinsic, child and adult asthma are known to differ, not only in their association with atopy, but also in their age of onset, severity and sex-distribution. The extent to which heredity may govern these differences is of interest and has not previously been investigated.

The possibility that age of onset may have a genetic basis was investigated in adult asthmatics and their affected first degree relatives (Chapter five). The findings showed that there was no correlation between the age of onset of asthma in probands and the age of onset of asthma in their affected first degree relatives. Nor was there an association between age of onset of asthma in probands and the prevalence of asthma in their first degree relatives. Therefore, there was no demonstrable hereditary basis to age of onset.

On the other hand, age of onset was correlated with patients' atopic status. Atopic asthmatics tended to have an earlier age of onset than did non-atopic asthmatics. Thus atopy may be one of the principle factors governing the age of onset of asthma.

The possibility that the severity of patients' asthma may have a genetic basis was investigated in adult asthmatics and their affected first degree relatives (Chapter five). The findings showed that there was a significant correlation between the severity of asthma in probands and the severity of asthma in their affected relatives. However, as family studies cannot distinguish between hereditary and environmental influences, it was unclear whether this correlation was genetic or environmental in origin. Twin studies are needed to assess the relative importance of heredity in this context.

The severity of patients' asthma was also found to be associated with their atopic status. Atopic asthmatics tended to have less severe asthma than did non-atopic asthmatics. Thus atopy may influence the severity of asthma as well as its age of onset.

Sex differences in the prevalence of asthma are believed to have a genetic basis. However, the findings of the present study showed that there was no demonstrable sex-linkage or sex-influence in asthma (Table 31 and 32). Thus sex does not <u>directly</u> influence the genes governing the expression of asthma. As discussed above, it is possible that sex modifies some third variable, which in turn gives rise to the observed differences between the sexes in the prevalence of asthma.

Table 33

Prevalence of Asthma in the First Degree Relatives of Asthmatic and Control Patients

Patient	Asthma Relatives Prevalence of Asthma (%)		Control Relatives Prevalence of Asthma (%)	
Roehampton				
Atopic	43/252	(13)**	4/129	(3)
Non-Atopic	5/52	(10)	7/173	(4)
Total	39/304	(13)**	11/302	(4)
Kingston				
Atopic	34/237	(14)*	8/129	(6)
Non-Atopic	7/85	(8)	5/100	(5)
Total	41/322	(13)**	13/229	(6)

* comparison of asthma with control patients, $p < 0.05$
** comparison of asthma with control patients, $P < 0.01$

Table 34

Prevalence of Asthma in the Siblings of Asthma Patients with Neither, One or Both Parents Asthmatic

Patient	Number of Parents Affected				Significance of Difference
	N	Neither	One	Both	
Brompton and Doncaster					
Atopic	327	8%	16%	29%	$p < 0.01$
Non-Atopic	89	2%	9%	-	s.s.
Total	416	6%	15%	28%	$p < 0.01$
Roehampton					
Atopic	64	9%	6%	33%	s.s.
Non-Atopic	13	5%	0%	-	s.s.
Total	77	8%	5%	33%	N.S.
Kingston					
Atopic	44	9%	30%	-	s.s.
Non-Atopic	14	9%	11%	-	s.s.
Total	58	9%	25%	-	$p < 0.05$
Total					
Atopic	435	8%	16%	29%	$p < 0.01$
Non-Atopic	116	2%	8%	-	N.S.
Total	551	6%	14%	29%	$p < 0.01$

s.s. - sample size too small to test

N.S. - not significant

Table 35

Distribution of Asthma Among First Degree Relatives of Asthma Patients

Patient	N	Positive Family History	% Prevalence of Asthma in First Degree Relatives				Comparison of Distribution Significance
			Parents	Siblings	Offspring	Total	
Brompton and Doncaster							
Intrinsic	89	29%	8	2	4	4	$p < 0.05$
Extrinsic	327	41%	16	10	14	13	$p < 0.05$
Total	416	39%	14	8	9	11	$p < 0.01$
Brompton							
Non-Atopic	94	28%	7	4	5	5	N.S.
Atopic	375	42%	14	10	11	12	$p < 0.05$
Total	469	39%	13	8	9	10	$p < 0.01$
Roehampton							
Non-Atopic	13	31%	15	4	-	10	N.S.
Atopic	64	39%	18	9	-	13	$p < 0.05$
Total	77	38%	17	8	-	13	$p < 0.05$
Kingston							
Non-Atopic	14	43%	11	10	4	8	N.S.
Atopic	44	50%	11	15	17	14	N.S.
Total	58	48%	11	14	13	13	N.S.

MODE OF INHERITANCE OF ASTHMA

The knowledge that asthma has an hereditary basis is of limited use to physicians. Although it can be said that the children of asthmatic parents have an increased risk of themselves developing asthma, the magnitude of the risk cannot be assessed. Such advice depends on an understanding of how asthma is inherited.

Previous family and twin studies have suggested that asthma has a polygenic mode of inheritance, in which a number of genetic factors contribute to the expression of the disease (Edfors-Lubs, 1971; Leigh and Marley 1967). However, this mode of inheritance cannot be distinguished from that of dominant inheritance with incomplete penetrance, in which a single dominant gene underlies the disease, but is only expressed in a proportion of those subjects who actually possess it. Although there is no practical way of distinguishing between them, polygenic inheritance was preferred, since it is better able to account for the wide variability in the clinical presentation of asthma (Edfors-Lubs, 1971; Leigh and Marley, 1967).

The findings of the present study agree with those of previous investigations in suggesting that asthma may have a polygenic mode of inheritance. Table 35 shows that, in most groups of asthmatics, the prevalence of asthma in the parents of probands tended to be higher than that in their siblings or

offspring. Similarly, in the family study of Leigh and Marley (1967) the prevalence of asthma in the parents of asthmatics tended to be higher than that in their siblings or offspring. As discussed above, the unevenness of the distribution of asthma in first degree relatives may have resulted from their differences in age. Thus the prevalence of asthma in the parents, siblings and offspring of asthmatics would be the same, should all relatives be examined at the same age. If this is true, then the distribution of asthma in the first degree relatives of asthmatics is consistant with the hypothesis that asthma has a polygenic mode of inheritance.

Additional information on the mode of inheritance of asthma can be derived from a comparison of the prevalence of asthma in the first degree relatives of asthmatics with that in their second degree relatives. The findings of the present study (Table 24) support those of Leigh and Marley (1967) in showing that the prevalence of asthma in the second degree relatives of asthmatics is significantly less than 50% of that in their first degree relatives. Although the theory is complicated, a difference of this magnitude is expected if asthma is inherited polygenicly (Carter, 1969).

Given that asthma has a polygenic mode of inheritance, it is possible to estimate the risk

of asthma in the offspring of asthmatic parents. For simplicity in the calculations, it can be assumed that there is dominant inheritance with incomplete penetrance, since the risks with polygenic inheritance are not significantly different (Carter, 1969). The expected proportions of affected offspring from the various possible matings have been calculated in this way and are shown in Table 36. The values given are for two hypothetical gene frequencies (10% and 15%) and levels of penetrance (10% and 30%), since the actual gene frequency and penetrance are not known.

A comparison of these expected risks (Table 36) with those actually observed (Table 34) provides a measure of the extent to which the findings are consistant with polygenic inheritance. When no distinction was made between atopic and non-atopic asthma probands, there was good agreement between the observed and expected risks with a gene frequency of 10% and a penetrance of 30% (Table 37C). Thus, the findings were consistant with polygenic inheritance.

On the other hand, when atopic and non-atopic probands were examined separately, the best fits were found with a gene frequency of 15% and a penetrance of 30% in atopic asthmatics (Table 37A), as compared with a gene frequency of 15% and a penetrance of only 10% in non-atopic asthmatics (Table 37B). The

agreement between the observed and expected risks of asthma in the offspring of asthmatic parents shows that both forms of asthma may have a polygenic mode of inheritance. Furthermore, the finding that there may be a difference in penetrance between atopic and non-atopic asthmatics supports the hypothesis that atopy may enhance the likelihood of a genetic predisposition to asthma being expressed.

In summary, the findings of the present study agree with those of previous investigations in suggesting that asthma has a polygenic mode of inheritance. Although this mode of inheritance cannot be distinguished in practice from that of dominance with incomplete penetrance, the polygenic hypothesis may be preferred since it is better able to account for variability in the clinical presentation of asthma.

Table 36

Expected Proportion of Asthmatic Offspring from Various Mating Types

Mating	Mating Frequency		Expected prop. Asthmatic Offspring		Expected Prevalence of Asthma in Offspring			
	A_1=10%	A_2=15%	P_1=30%	P_2=10%	A_1P_1	A_1P_2	A_2P_1	A_2P_2
PxP								
AAxAA	.0028	.0051	.51	.190	.0014	.00053	.0026	.00097
AAxAa	.0997	.1326	.40	.145	.0400	.01446	.0530	.01923
AaxAa	.8975	.8622	.28	.097	.2513	.08706	.2414	.08363
Total	1	1			29%	10%	30%	10%
PxN								
AAxAA	.0003	.0008	.51	.190	.0001	.00006	.0004	.00015
AAxAa	.0105	.0216	.40	.145	.0042	.00152	.0086	.00313
AaxAa	.0942	.1404	.28	.097	.0264	.00914	.0393	.01362
AAxaa	.0471	.0598	.30	.100	.0141	.00471	.0179	.00598
Aaxaa	.8479	.7774	.15	.050	.1272	.04240	.1166	.03887
Total	1	1			17%	6%	18%	6%
NxN								
AAxAA	.0001	.0004	.51	.190	.0000	.00002	.0002	.00008
AAxAa	.0036	.0104	.40	.145	.0014	.00052	.0042	.00151
AaxAa	.0324	.0676	.28	.097	.0091	.00314	.0189	.00656
AAxaa	.0162	.0288	.30	.100	.0049	.00162	.0086	.00288
Aaxaa	.2916	.3744	.15	.050	.0437	.01458	.0562	.01872
aaxaa	.6561	.5184	-	-	-	-	-	-
Total	1	1			6%	2%	9%	3%

Where A_1 and A_2 are gene frequencies, and P_1 and P_2 are penetrance rates

PxP - mating with two asthmatic partners
PxN - mating with one asthmatic and one normal partner
NxN - mating with two normal partners

Sample calculations are given in appendix E.

Table 37a & b

Comparison of Observed with Expected Risks of Asthma in Offspring

A. Risk of Asthma in Offspring of Atopic Patients
Gene Frequency of 15% (A_2) and Penetrance of 30% (P_1)

Mating	N	Observed No. Affected (%)	Expected No. Affected (%)	Significance x^2
N x N	627	52 (8%)	56 (9%)	0.28
P x N	236	37 (16%)	42 (18%)	0.59
P x P	17	5 (30%)	5 (30%)	0
Total				$x^2 = 0.87$, $p > 0.10$

B. Risk of Asthma in Offspring of Non-atopic Patients
Gene Frequency of 15% (A_2) and Penetrance of 10% (P_2)

Mating	N	Observed No. Affected (%)	Expected No. Affected (%)	Significance x^2
N x N	298	7 (2%)	9 (3%)	0.44
P x N	48	4 (8%)	3 (6%)	0.33
P x P	0	-	-	-
Total				$x^2 = 0.77$, $p > 0.10$

Table 37c

C. Combined Risk of Asthma in Offspring
Gene Frequency of 10% (A_1) and Penetrance of 30% (P_1)

Mating	N	Observed No. Affected (%)	Expected No. Affected (%)	Significance X^2
N x N	925	59 (6%)	56 (6%)	0.16
P x N	284	41 (14%)	48 (17%)	1.02
P x P	17	5 (30%)	5 (29%)	0
Total				$X^2 = 1.18$, $p > 0.10$

GENETIC COUNSELLING

The dependence of asthma on multiple genetic and environmental factors makes it difficult to predict the risk of its occurring in the near relatives of asthmatic patients. For instance, it is not possible to accurately predict the likelihood that a particular relative will himself develop asthma. However, estimates of the risk can be obtained from family studies and may serve as a guide in identifying those subjects who are most likely to develop asthma.

The probability that the offspring of asthmatic parents will themselves be asthmatic is shown in Table 37. For either atopic or non-atopic subjects, the probability of having an asthmatic child is 3-4 fold greater when both parents are asthmatic, than when neither parent is affected. When only one parent is asthmatic, the risk of asthma in the offspring declines and is 2 fold greater than when neither parent is affected.

Since atopy may enhance the likelihood of a genetic predisposition to asthma being expressed, the actual probability of having an asthmatic child will be higher in the children of atopic asthmatic parents, than in the children of non-atopic asthmatic parents. For example, the findings of the present study suggest that the probability of asthma occurring in the child of an atopic asthmatic

parent is 3 fold greater than it is in the child of a non-atopic asthmatic parent. Thus a family history of asthma is most significant when it is coupled with evidence of an allergic constitution.

The expected proportions of matings involving at least one asthmatic partner are shown in Table 38. The calculations were based on the assumption that asthma was inherited as a dominant gene with a frequency of 10% and a penetrance of 30%, since previous analyses had shown that this was the most reasonable hypothesis (Table 37C). Assuming that mating is random, the expected proportion of matings involving at least one asthmatic partner is 11.4%. It follows that the majority of asthmatics will be born to families in which neither parent is asthmatic. This is because, although the likelihood of having an asthmatic child is highest when at least one parent is affected, the proportion of matings involving at least one asthmatic partner is low. (see calculations in appendix E).

These findings can be used by physicians to identify those of their patients who are most at risk for the disease. Preventative measures might then be employed to help reduce the incidence of asthma among high risk children; while close observation may lead to the earlier detection and treatment of asthma should it occur. Physicians may also counsel those parents wishing to know the likelihood of their having an asthmatic child. However, such

counselling must be done with care, since the precise risks are not known and parents' anxiety over their child's health my be needlessly increased.

Table 38: Expected Mating Frequencies

Phenotype	Genotype	Mating Frequency of Genotype	X	Probability of Phenotype	=	Expected Mating Frequency
P x P	AA x AA	.0001		.2601		.0000
	AA x Aa	.0036		.1530		.0005
	Aa x Aa	.0324		.0900		.0029
Total						0.3%
P x N	AA x AA	.0001		.4998		.0000
	AA x An	.0036		.5180		.0019
	Aa x An	.0324		.4200		.0136
	AA x aa	.0162		.5100		.0083
	Aa x an	.2916		.3000		.0875
Total						11.1%
N x N	AA x AA	.0001		.2401		.0000
	AA x An	.0036		.3290		.0012
	Aa x An	.0324		.4900		.0159
	AA x an	.0162		.4900		.0079
	Aa x an	.2916		.7000		.2041
	aa x an	.6561		1		.6561
Total						88.5%

See Sample calculations in appendix E

RELATIONSHIP OF FINDINGS TO IMMUNOPHARMACOLOGICAL STUDIES

The relationship of these genetic findings to those of immunopharmacological studies cannot yet be defined. However, a brief review of the immunopharmacology of asthma is helpful in revealing the many possible areas where genetic factors may be involved.

It is thought that asthma may be caused by a type I and/or type III inflammatory process (Chapter two). Both these processes may be mediated by IgE, a long term sensitizing antibody (Ishizaka, Ishizaka and Hornbrook, 1966), or by IgG, a short term sensitizing antibody (Parish, 1973).

The type I response is initiated by the binding of antibody to the surface of certain cells, particularly mast cells in the skin and bronchial wall. When antigen binds to the surface of such sensitized cells, intracellular levels of cAMP drop, those of cGMP rise, and the mediators of anaphylaxis are released (Kaliner et al, 1977a,b). In contrast, the type III response is antibody mediated and complement dependent. In slight antigen excess, free antibody binds to antigens forming a soluble complex which activates the C3 component of complement. These attract and are phagocytized by neutrophils which are destroyed liberating the mediators of anaphylaxis.

The principle mediators of anaphylaxis are histamine, slow reacting substance of anaphylaxis (SRS-A) and eosinophil chemotactic factor of anaphylaxis (ECF-A). Histamine may cause bronchoconstriction either directly, through stimulation of H1 receptors on smooth muscle, or indirectly, through stimulation of cholinergic nerves. SRS-A also causes smooth muscle contraction and stimulates the synthesis of prostaglandins which in turn influence muscle tone (Austen, 1973). ECF-A attracts eosinophils to the site of inflammation where they may inhibit the further release of histamine (Hubschner, 1975) and inactivate SRS-A and histamine (Gleich, 1977).

The anaphylactic response is modulated by the sympathetic and parasympathetic nervous systems and by prostaglandins. Stimulation of α adrenergic and cholinergic receptors cause bronchoconstriction either by direct stimulation of smooth muscle (Lee, Busse and Reed, 1977), or by fascillitating the alteration in mast cell levels of cAMP and cGMP (Assem, 1974; Kailiner et al, 1977a). In contrast, stimulation of β adrenergic receptors promotes smooth muscle relaxation (Lee, Busse and Reed, 1977) and causes intracellular levels of cAMP to rise, thus preventing release of the mediators of anaphylaxis (Assem, 1974; Kaliner et al, 1977a). The balance in tissue levels of prostaglandin PGE, a vasodilator, and prostaglandin $PGF_{2\alpha}$, a vasoconstrictor, also

regulates muscle tone and modulates the anaphylactic response (Cuthbert, 1975; Parker and Snider, 1973).

A genetically determined susceptibility to bronchial hyperreactivity may result either from the excess stimulation or from the excess sensitivity to stimulation of the bronchial smooth muscle. Based on our current understanding of the disease, excess stimulation may have a number of causes, the most likely of which are overproduction of the mediators of anaphylaxis or an imbalance in the tissue levels of prostaglandins. Excess sensitivity to stimulation may also be caused by a variety of factors including: (1) incompetance of β adrenergic receptors, (2) increased sensitivity of cholinergic or α adrenergic receptors, (3) increased affinity of bronchial smooth muscle for anaphylactic mediators and (4) increased sensitivity of bronchial smooth muscle to stimulation by prostaglandins.

Of these hypotheses, an imbalance in tissue levels of prostaglandins (PG) or the increased sensitivity of bronchial smooth muscle to PG stimulation seems unlikely in view of the inefficacy of aspirin based drugs, which are known to inhibit PG synthesis, and the effectiveness of atropine which does not affect the potent bronchoconstrictor, $PGF_{2\alpha}$ (Parker and Snider, 1973).

Incompetance of β receptors has seemed a more likely hypothesis based on the findings that, on bronchial challenge, cAMP levels rise more slowly in asthmatics than controls (Lee et al, 1977), and that atropine, a parasympathetic blocking agent, is effective in relieving bronchoconstriction (Kaliner, 1977b). However, it has been pointed out that the prolonged exposure of patients to β adrenergic agonists may be responsible for their diminished ability to respond to bronchial challenge by increasing cAMP levels (Conolly and Greenacre, 1976) and that atropine may improve lung function before challenge, but is unable to prevent bronchoconstriction (Fish et al, 1977). Thus the importance of incompetant β adrenergic receptors in the causation of asthma has yet to be resolved.

The possibilities that the sensitivity of cholinergic receptors or α adrenergic receptors are enhanced in asthma have seemed less likely hypotheses, but cannot be ruled out as possible causes of the disease.

Genetic factors could underly any or all of these possible abnormalities. Until more is known of the immunopharmacology of asthma, little can be done to achieve a more exact understanding of the hereditary basis of asthma. In this context, it is worth considering the finding of this study which suggests that the primary defect(s) underlying asthma may not directly involve those mechanisms giving

rise to atopy. Thus immunopharmacological studies might well benefit by concentrating on non-atopic or intrinsic patients whose asthma is not complicated by the presence of atopy.

CONCLUSION

Family studies have provided a valuable insight into the hereditary basis of asthma. The findings of these investigations have shown that:

(1) Extrinsic, intrinsic, child and adult forms of asthma are likely to share a common genetic defect which is inherited in a polygenic fashion.

(2) Asthma is inherited independently of atopy, but atopy may enhance the likelihood of a genetic predisposition to asthma being expressed.

(3) The age of onset of asthma has no demonstrable genetic basis apart from its association with atopy.

(4) A correlation exists between the severity of asthma in patients and the severity of asthma in their first degree relatives, but it is unclear whether this association is genetic or environmental in origin.

(5) Sex differences in the prevalence of asthma are not caused by genetic sex-linkage or sex-influence of the asthma genes.

The findings of this investigation are not definitive. Additional studies are needed both to verify these findings and to explore aspects of the hereditary basis of asthma not considered in this study. The family study method, used in this investigation, is limited in that hereditary and

and environmental components of the disease cannot be separated. Twin studies and immigration studies, of the kind described in Chapter one, would be of use in assessing the relative magnitude of the hereditary component in such aspects of asthma as its heritability and severity.

Other issues, not considered herein, but meriting investigation, include the possible role of heredity in governing the liability to occupational asthma and its role in determining racial/geographical differences in the prevalence of asthma.

Such studies would greatly increase our understanding of the genetic basis of asthma. However, an exact understanding must await an unambiguous definition of the disease as well as a more precise understanding of its immunopharmacology.

APPENDIX A

Separate Analyses of the Data from the Brompton Hospital and the Doncaster Royal Infirmary

Table 39

Prevalence of Asthma, Hay Fever and Eczema Among First Degree Relatives of Polar Extrinsic Asthmatics

Trait	Prevalence (%) Parents	Siblings	Offspring	All Relatives	Significance*
Brompton					
Asthma	72/416 (17.3)	49/381 (12.9)	11/61 (18.0)	132/858 (15.4)	$X_2^2=3.13$, $p > 0.05$
Hay Fever	76/416 (18.3)	53/381 (13.9)	5/61 (8.2)	134/858 (15.6)	$X_2^2=4.70$, $p > 0.05$
Eczema	27/416 (6.5)	35/381 (9.2)	7/61 (11.5)	69/858 (8.0)	$X_2^2=2.41$, $p > 0.05$
Doncaster					
Asthma	32/238 (13.5)	21/285 (7.4)	14/116 (12.1)	67/639 (10.5)	$X_2^2=4.99$, $p > 0.05$
Hay Fever	15/238 (6.3)	16/285 (5.6)	13/116 (11.2)	44/639 (6.9)	$X_2^2=3.98$, $p > 0.05$
Eczema	11/238 (4.6)	10/285 (3.5)	7/116 (6.0)	28/639 (4.4)	$X_2^2=1.32$, $p > 0.05$

* Comparison of the prevalence among parents, siblings and offspring

Table 40

Prevalence of Asthma, Hay Fever and Eczema Among First Degree Relatives of Polar Intrinsic Asthmatics

Trait	Prevalence (%) Parents		Siblings		Offspring		All Relatives		Significance *
Brompton									
Asthma	7/126	(5.6)	6/200	(3.0)	6/113	(5.3)	19/439	(4.3)	$X_2^2=1.28$, $p > 0.05$
Hay Fever	0/126	(0)	4/200	(2.0)	5/113	(4.4)	9/439	(2.0)	-
Eczema	1/126	(1.0)	2/200	(1.0)	2/133	(1.8)	5/439	(1.1)	-
Doncaster									
Asthma	7/52	(13.5)	1/90	(1.1)	1/45	(2.2)	9/187	(4.8)	-
Hay Fever	0/52	(0)	0/90	(0)	1/45	(2.2)	1/187	(0.5)	-
Eczema	0/52	(0)	1/90	(1.1)	1/45	(2.2)	2/187	(1.1)	-

*Comparison of the prevalence among parents, siblings and offspring

Table 41

Prevalence of Asthma Among Siblings of Polar Asthmatics When Neither, One or Both Parents Have Asthma

Number of Parents with Asthma	Polar Intrinsic Asthmatics N	Prevalence	(%)	Polar Extrinsic Asthmatics N	Prevalence	(%)
Brompton						
Neither	56	4/189	(2.1)	141	26/267	(9.7)
One	7	2/11	(18.1)	62	20/104	(19.2)
Both	0	-		5	3/10	(30.0)
Significance		-		$X_1^2=6.15$, $p < 0.05$		
Doncaster						
Neither	19	0/69	(0)	88	12/208	(5.8)
One	7	1/21	(4.8)	30	8/73	(10.9)
Both	0	-		1	1/4	(25.0)
Significance		-		$X_1^2=1.56$, $p > 0.05$		

Table 42

Prevalence of Hay Fever Among Siblings of Polar Asthmatics When Neither, One or Both Parents Have Hay Fever

Number of Parents with Hay Fever	Polar Intrinsic Asthmatics N	Prevalence (%)		Polar Extrinsic Asthmatics N	Prevalence (%)	
Brompton						
Neither	63	4/200	(2.0)	140	34/275	(12.4)
One	0	-		59	14/95	(14.7)
Both	0	-		9	5/11	(45.4)
Significance		-			$X^2_1=1.49$, $p > 0.05$	
Doncaster						
Neither	26	0/90	(0)	104	12/258	(4.6)
One	0	-		14	3/26	(11.5)
Both	0	-		1	1/1	(100.0)
Significance		-			-	

Table 43

Prevalence of Eczema Among Siblings of Polar Asthmatics When Neither, One or Both Parents Have Eczema

Number of Parents with Eczema	Polar Intrinsic Asthmatics N	Prevalence (%)		Polar Extrinsic Asthmatics N	Prevalence (%)	
Brompton						
Neither	62	2/196	(1.0)	183	28/345	(8.1)
One	1	0/4	(0)	25	7/36	(19.4)
Both	0	-		0	-	
Significance		-			-	
Doncaster						
Neither	26	1/90	(1.1)	108	7/258	(2.7)
One	0	-		11	3/27	(11.1)
Both	0	-		0	-	
Significance		-			-	

Table 44

Significance Table: Comparison of the Prevalence of Asthma, Hay Fever and Eczema Among First Degree Relatives of Polar Extrinsic and Polar Intrinsic Asthmatics

Trait	Brompton	Doncaster	Brompton and Doncaster
Asthma	$X_1^2=30.31$, $p < 0.001$	$X_1^2=4.84$, $p<0.05$	$X_1^2=32.20$, $p < 0.001$
Hay Fever	$X_1^2=47.70$, $P < 0.001$	$X_1^2=10.41$, $p<0.01$	$X_1^2=52.04$, $p < 0.001$
Eczema	$X_1^2=24.16$, $p < 0.001$	$X_1^2=4.66$, $p < 0.05$	$X_1^2=26.47$, $p < 0.001$

APPENDIX B

Sample Asthma Study Questionnaire

ASTHMA STUDY QUESTIONNAIRE

NAME:

AGE:

SEX:

SECTION A

1. Has a doctor ever told you that you had asthma?

☐ YES ☐ NO

2. Have you ever had any of the following symptoms?

☐ tight chest
☐ wheeziness
☐ shortness of breath
☐ recurring cough
☐ waking at night with one or more of the above symptoms

3. Has a doctor ever told you that you had chronic bronchitis?

☐ YES ☐ NO

4. Have you ever had a daily cough with phlegm or sputum production which lasted for more than 3 months each year for at least 2 years?

☐ YES ☐ NO

5. Are you now or have you ever been a smoker?

☐ NO
☐ YES

How much tobacco did you smoke each day?_____
How many years did you smoke? _____

6. Do you have heart trouble?

☐ YES ☐ NO

SECTION B

1. At what age did you have your first attack of wheeziness? _____ yrs

2. Have you ever had an allergy skin test?

☐ NO
☐ YES Were you allergic to Nothing ☐
1 or 2 things ☐
3 or more things ☐

Can you remember where these tests were done? _____
name hospital

3. Have you ever had any of the symptoms listed below when you came into contact with the following things?

	None	Sneeze, Runny nose	Watery Eyes	Nettle Rash	Wheezy attack, Asthma
Pollens	☐	☐	☐	☐	☐
Dust	☐	☐	☐	☐	☐
Animals	☐	☐	☐	☐	☐
Foods(fish, eggs, alcohol, etc.)	☐	☐	☐	☐	☐
Other _____ please specify	☐	☐	☐	☐	☐

4. Has a doctor ever told you that you had eczema?

☐ YES ☐ NO

5. Have you ever had rough, dry and itchy patches of skin in the bends (flexures) of your wrists, knees or elbows?

☐ YES ☐ NO

6. Has a doctor ever told you that you had hay fever?

☐ YES ☐ NO

7. Have you ever had a blocked or runny nose other than when you have had a cold?

☐ NO
☐ YES Do these symptoms occur at any particular time of the year?
☐ NO
☐ YES _____
name the season

SECTION C

1. How many weeks each year were you unable to go to work or school as a result of wheezy attacks?

Past Year	Previous Years	
☐	☐	Didn't work or go to school so can't say
☐	☐	No time lost
☐	☐	2 weeks or less
☐	☐	2 to 4 weeks
☐	☐	More than 4 weeks

2. Since your attacks of wheeziness began, have you ever been completely free of them for five or more years?

☐ YES ☐ NO

3. How often did you have attacks of wheeziness?

Past Year	Previous Years	
☐	☐	Continual wheeze
☐	☐	Daily
☐	☐	Weekly
☐	☐	Less than weekly
☐	☐	None

4. How severe were your attacks of wheeziness during the day?

Past Year	Previous Years	
☐	☐	None: not wheezy after heavy work or climbing 2 flights of stairs, no time lost from normal activities.
☐	☐	Mild: wheezy after heavy work or climbing 2 flights of stairs, no time lost from normal activities.
☐	☐	Moderate: wheezy after light work or climbing 1 flight of stairs, some time lost from normal activities.
☐	☐	Severe: breathless without any exercise or after walking along a flat surface, considerable time lost from normal activities

5. How often were you woken at night as a result of wheezy attacks?

Past Year	Previous Years	
☐	☐	Almost every night
☐	☐	Weekly
☐	☐	Monthly
☐	☐	Less than monthly
☐	☐	Never

6. How severe were your attacks of wheeziness during the night?

Past Year	Previous Years	
☐	☐	None: didn't wake at all
☐	☐	Mild: woken once by wheezy attack
☐	☐	Moderate: woken 2 to 3 times
☐	☐	Severe: kept awake most of the night

7. Have you ever taken steroid tablets continuously for 3 or more months for your attacks of wheeziness?

Past Year	Previous Years	
☐	☐	YES
☐	☐	NO

8. Have you ever had injections of steroids or taken steroid tablets for 3 weeks or less for an attack of wheeziness?

Past Year	Previous Years	
☐	☐	YES
☐	☐	NO

9. How often have you been in hospital for attacks of wheeziness?

Past Year	Previous Years	
☐	☐	Never
☐	☐	Once a year or less
☐	☐	More than once a year

APPENDIX C

Pilot Study of Asthma Questionnaire

PILOT STUDY OF ASTHMA QUESTIONNAIRE

The asthma questionnaire was tested in a pilot study of 93 outpatients attending the asthma clinic of the Brompton Hospital. Groups of patients with widely differing clinical presentations were deliberately selected in order to evaluate the ability of the questionnaire to discriminate between them. The groups are described in figure 7.

Patients were sent a letter outlining the purposes of the study and inviting their cooperation (appendix D). Those patients wishing to participate were sent an asthma questionnaire. Those who did not respond were sent up to two more letters of invitation. Stamped, self addressed envelopes were included in all letters.

In total, 50 patients (54%) complied, 18 (18%) could not be contacted and 25 (27%) failed to respond to the letters of invitation (Table 45).

The patients' responses to the questionnaire were coded and then transferred to punch cards. Where applicable, the coded response to each question was compared with information recorded in the patients' medical records. For each such comparison, the following statistics were obtained:

α - error of commission. The percentage of patients giving a positive response, at variance with information recorded in their medical records.

- error of omission. The percentage of patients who, according to their medical records, should have given a positive response but did not.

The results of the analysis for questionnaire sections A and B are shown in Tables 46 and 47 respectively.

Section A

The object of this section was to accurately identify all patients who had had asthma. Since, in this case, errors of omission ( ) were as undesirable as errors of commission ( ), only those questions with + less than 5% were acceptable. Table 46 shows that there were two questions meeting this criterion. Those patients who said a doctor had diagnosed them as having had asthma (Q1), or those patients who complained of at least three of the five asthma symptoms listed (Q2), could be said to have asthma. In order to exclude possible cases of cardiac asthma, it was decided a diagnosis of asthma would not be made in those patients who complained of heart trouble (Q6). Using these criteria, all cases of asthma were identified with a probability of 98%.

Questionnaire identification of patients with chronic bronchitis was poor (Table 46). A reliable diagnosis was possible (p = 100%) in those patients who said they had been diagnosed as having had chronic bronchitis by a doctor (Q3) and who also complained of the disease symptoms (Q4). However,

approximately 12% of all patients who had had chronic bronchitis could not be identified by these criteria.

Section B

The object of this section was to establish the patients' atopic status as assessed by skin prick tests and history of allergic disease. For the purposes of this study, it was important to minimise errors of commission (α). Therefore, any question with α less than 5% were acceptable.

Table 47 shows that patients who had had skin prick tests accurately identified themselves as skin test positive or skin test negative (Q2), ($p < 97\%$). However, patients were unreliable in reporting allergic provoking factors (Q3), diagnosis of eczema and its symptoms (Q4-5), and diagnosis of hay fever and its symptoms (Q6-7). Therefore, the patients' allergic history could not be used as an aid in determining his atopic status.

Section C

The object of section C was to assess the severity of patients' asthma. Although physicians may vary in their methods of judging severity, a personal survey of five consultants, specializing in asthma at the Brompton Hospital, showed that there were several criteria which all agreed were important in assessing severity. These included: loss of time from work/school, frequency and duration of attacks, exercise liability, treatment with steroids and history of hospitilization. In

addition, freedom from symptoms for a period of 5 or more years was considered to be representative of mild asthma. Questions, based on these criteria, were used as a measure of the severity of patients' asthma. The responses to the questions were weighted as shown in Table 48 and the sum of the values used to generate a severity score. The maximum possible score was 100, 50 points being allotted to morbidity in the past 12 months, and 50 points being allotted to morbidity in previous years.

The patients' responses to questionnaire section C are shown in Table 48. The severity scores for the year immediately preceeding the study were skewed towards the lower end of the scale with a mean of 29 $\pm$5/100. In contrast, the scores for previous years were skewed towards the high end of the scale with a mean of 55 $\pm$6/100. The combined mean severity score was 42 $\pm$6/100. As shown in figure 8, the combined severity scores gave the best approximation to a normal distribution and, therefore were adopted for use in the main study.

Figure 7

Description of Probands

	SKIN TEST NEGATIVE	SKIN TEST POSITIVE (3 or more positive)
NO HAY FEVER OR ECZEMA	(1) 10 males 15 females	(2) 15 males 10 females
HAY FEVER AND/ OR ECZEMA	(3) 4 males 14 females	(4) 13 males 12 females
TOTAL	43 patients	50 patients

Table 45

Response Rate Among Probands to Questionnaire Survey

Group*	Complied	No Response	Moved	Died
1	12	9	1	3
2	15	4	5	1
3	11	3	4	0
4	12	9	4	0
total	50 (54%)	25 (27%)	14(15%)	4 (4%)

* Groups are described in figure one.

Table 46

Questionnaire Section A: Patients Responses

Q	Criteria	Number*	N	(%)	N	(%)
			α		β	
1	Asthma Diagnosis	49	0		1	(2)
2	Asthma Symptoms					
	tight chest	47	-		-	
	wheezing	48	-		-	
	shortness of breath	47	-		-	
	recurring cough	36	-		-	
	waking at night with above	44	-		-	
3	Chronic Bronchitis Diagnosis	8	1	(12)	0	
4	Chronic Bronchitis Symptoms	15	3	(20)	1	(8)
5	Smoker (past or present)	22	0		1	(4)
6	Heart Trouble	2	0		0	
	Three or more Asthma symptoms	49	0		1	(2)
	Chronic Bronchitis					
	diagnosis + symptoms	7	0		1	(12)
	diagnosis + symptoms + smoking	3	0		4	(57)

* Number giving a positive response to question

Table 47: Questionnaire Section B: Patients Responses

Q	Criteria	Number*	N α	(%)	N β	(%)
1	Age of Onset (years)					
	10	25	0		1	(4)
	11- 30	9	1	(11)	0	
	30	16	0		0	
2	Skin Test					
	negative (no reactions)	19	0		1	(5)
	positive (1 or more reactions)	29	1	(3)	0	
3	Allergic Provoking Factors					
	chest	36				
	skin	8				
	eyes	20				
	nose	29				
	any of the above	37	23	(70)	2	(12)
	none of the above	13	2	(15)	23	(68)
4	Eczema Diagnosis	14	3	(21)	1	(8)
5	Eczema Symptoms	18	9	(50)	2	(18)
6	Hay Fever Diagnosis	14	7	(50)	6	(46)
7	Hay Fever Symptoms	5	3	(60)	11	(85)

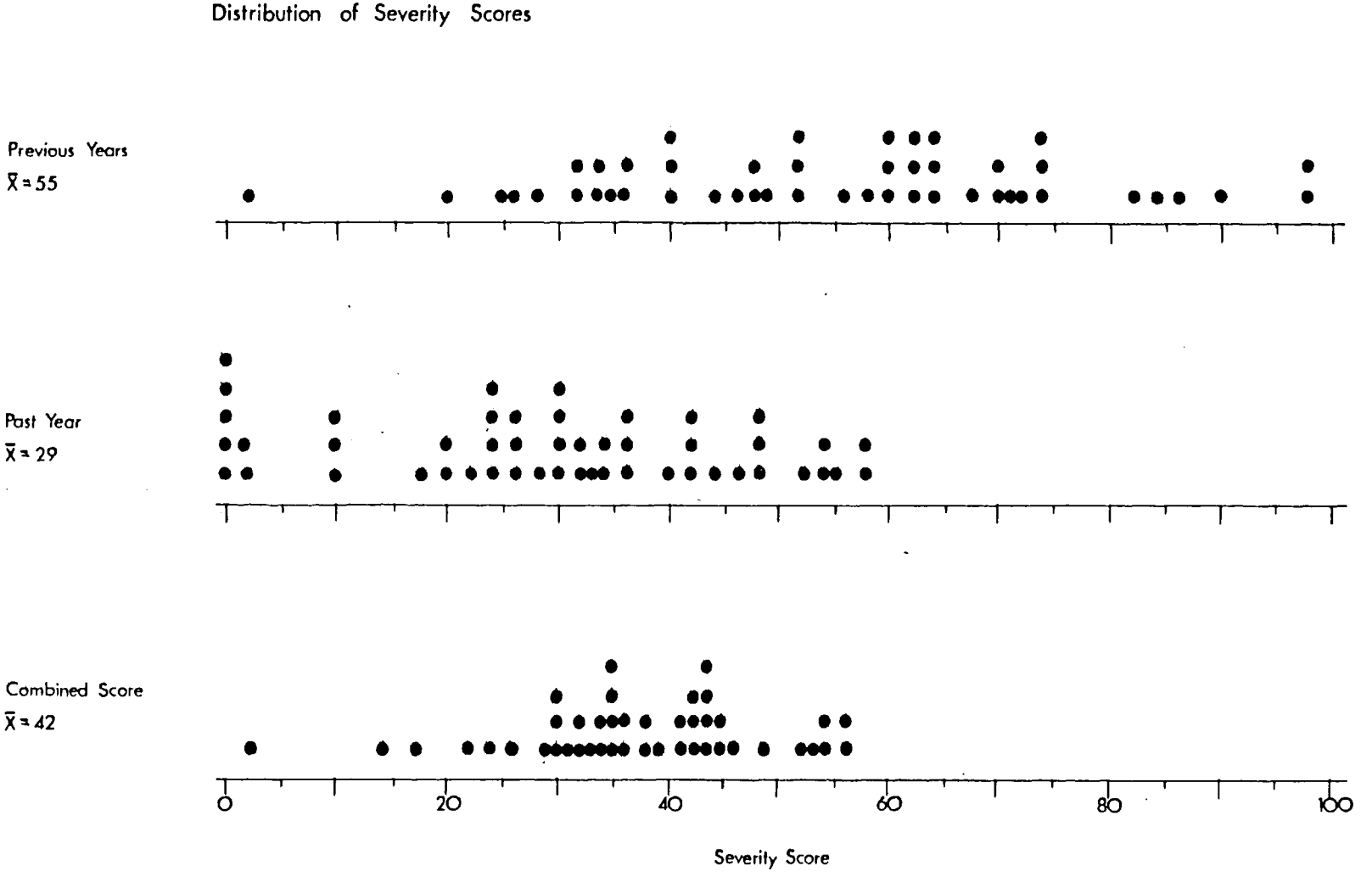
* The α and β for these responses were calculated by comparing the patients response with his atopic status, as discussed in the text. Patients in group three were not included in these calculations because of their unusual clinical presentation (figure 7) and their rareity.

Table 48: Questionnaire Section C: Patients Responses

Q	Criteria	Score	Past Year N	Past Year (%)	Previous Years N	Previous Years (%)
1	Work Disability					
	not known	*45	8	(16)	11	(22)
	none	0	20	(41)	3	(6)
	2 weeks or less	2	13	(26)	13	(26)
	2-4 weeks	3	5	(10)	10	(20)
	over 4 weeks	5	3	(6)	12	(24)
2	Remission of 5 or more years	-10	3	(6)	-	
3	Frequency of Attacks					
	continuous	5	6	(12)	9	(18)
	daily	3	3	(6)	11	(22)
	weekly	2	11	(22)	16	(33)
	less than weekly	1	24	(49)	13	(26)
	none	0	5	(10)	0	(0)
4	Exercise Tolerance					
	normal	0	16	(33)	6	(12)
	mild	2	20	(41)	10	(20)
	moderate	3	8	(16)	15	(31)
	severe	5	5	(10)	18	(37)
5	Night Attacks					
	daily	5	3	(6)	13	(26)
	weekly	3	10	(20)	13	(26)
	monthly	2	5	(10)	7	(14)
	less than monthly	1	17	(34)	14	(28)
	none	0	15	(30)	3	(6)
6	Severity of Night Attacks					
	none	0	16	(32)	6	(12)
	mild	2	19	(38)	18	(36)
	moderate	3	11	(22)	12	(24)
	severe	5	4	(8)	14	(28)
7	Continuous Steroids	10	12	(24)	25	(50)
8	Steroid Course	5	11	(22)	20	(40)
9	Hospitilization					
	none	0	45	(90)	21	(42)
	once/year	5	5	(10)	21	(42)
	more than once/year	10	0	(0)	8	(16)

Q - question number
* score calculated out of 45 instead of 50.

Figure 8


Distribution of Severity Scores
Previous Years
X̄ = 55
Past Year
X̄ = 29
Combined Score
X̄ = 42
0
20
40
60
80
100
Severity Score

APPENDIX D

Sample Letters

LETTER TO ASTHMATICS

BROMPTON HOSPITAL
FULHAM ROAD
LONDON SW3 6HP

TELEPHONE 01-352 8121
Ext. 4192.

Dear

At the Brompton Hospital in London, we are studying asthma in families and need your help to make this research a success. Doctors are often asked, "What are the chances that a person with asthma will have an asthmatic child?" The only way we can find the answer to questions such as this, is to study the families of people with asthma and to see how they are different from the families of people without asthma. We would be grateful if you and your family would help us with this important work.

Your doctors have given us the names of patients whom they think would be willing to participate in this research. If you would like to help, please fill in the form at the bottom of this page and return it to us in the stamped addressed envelope provided. A research assistant will then arrange to interview you. All you will be asked to do is complete a short questionnaire and to give us the names and addresses of other family members to whom we will also send questionnaires. All information will be kept strictly confidential.

Please help us to find out more about asthma by giving us a little of your time.

With best wishes.

I would like to participate in the asthma study.

NAME .....

ADDRESS .....

TELEPHONE NUMBER .....(home)

.....(work)

LETTER TO CONTROLS

BROMPTON HOSPITAL
FULHAM ROAD
LONDON SW3 6HP

TELEPHONE 01-352 8121
Ext. 4192

Dear

At the Brompton Hospital in London, we are studying asthma in families and need your help to make this research a success. Doctors are often asked, "What are the chances that a person with asthma will have an asthmatic child?" The only way we can find the answer to questions such as this, is to study the families of people with asthma and to see how they are different from the families of people without asthma. Therefore, although you may not have asthma, your help would be greatly appreciated.

Your doctors have given us the names of patients whom they think would be willing to participate in this research. If you would like to help, please fill in the form at the bottom of this page and return it to us in the stamped addressed envelope provided. A research assistant will then arrange to interview you. All you will be asked to do is complete a short questionnaire and to give us the names and addresses of other family members to whom we will also send questionnaires. All information will be kept strictly confidential.

Please help us to find out more about asthma by giving us a little of your time.

With best wishes.

- -

I would like to participate in the asthma study.

NAME. . . . . .

ADDRESS. . . . . .

TELEPHONE NUMBER . . . . . .(home)

. . . . . .(work)

APPENDIX E

Sample Calculations for Tables 36 and 38

Genotype Mating Frequencies

If A = 10%, the AA = 0.01, Aa = 0.18 and aa = 0.81

It follows that: AA x AA = $(0.01)^2$ = 0.0001

AA x Aa = 2(0.01 x 0.18) = 0.0036

Aa x Aa = $(0.18)^2$ = 0.0324

etc.

Expected Proportion of Asthmatic Offspring Given Mating Genotypes

If penetrance of A is 30%, then

genotype	probability asthmatic	probability non-asthmatic
AA	$(.3)^2+2(.3x.7)$ = 0.51	$(.7)^2$ = 0.49
Aa	.3	.7
aa	0	1

It follows that:

for mating type,	proportion of progency with A	X	probability 'A' expressed	=	expected proportion asthmatic offspring
AA x AA	100% AA		0.51		0.51
AA x Aa	50% AA		0.51		.5(.51)+.5 (.3)
	50% Aa		0.30		=0.40
Aa x Aa	25% AA		0.51		.25(.51)+.5 (.3)
	50% Aa		0.30		=0.28

ETC.

Expected Frequencies of Mating Phenotypes Given Mating Genotypes

Mating Genotypes	Mating Phenotypes	Probability mating genotype will express the given phenotype
AA x AA	P x P	$(.51)^2 = 0.2601$
	P x N	$2(.51 \times .49) = 0.4998$
	N x N	$(.49)^2 = 0.2401$

where P - asthmatic phenotype, N - non-asthmatic phenotype

Expected Proportion of Asthmatics With At Least One Asthmatic Parent

Mating Phenotypes	Mating Frequency*	X	Probability of Asthmatic Offspring**	=	Expected Proportion (% total)
P x P	0.003		0.29		0.00087 (1%)
P x N	0.111		0.17		0.01887 (26%)
N x N	0.885		0.06		0.05310 (73%)
Total					0.0784 (100%)

* see Table 38 for derivation of values

** see Table 37C for derivation of values

REFERENCES

REFERENCES

ANDERSON H. 1974. The epidemiological and allergic features of asthma in the New Guinea highlands. Clinical Allergy 4: 171.

ANDREWS R.H., BAYLIS J.H. and BALDRY P.E. 1975. Skin tests and clinical features of asthma. A report to the research committee of the British Thoracic and Tuberculosis Association. British Journal of Diseases of the Chest 69: 125.

ARNAUD P., CHAPUIS C.C., SOUILLET C., CARRON R., WILSON G., CREYSELL R. and FUDENBERG H. 1976. High frequency of deficient Pi phenotypes of alpha-1-antitrypsin in nonatopic infantile asthma. Trans-Atlantic Association of American Physicians 89: 205.

ASSEM E.S.K. 1974. Adrenergic mechanisms and immediate-type allergy. Clinical Allergy 4: 185.

AUSTEN K.F. 1973. A review of immunological, biochemical, and pharmacological factors in the release of chemical mediators from human lung. Chapter eight, Asthma. Austen K.F. and Lichtenstein L.M. (eds). Academic Press. London.

BARBEE R.A., LEBOWITZ M.D., THOMPSON H.C. and BURROWS B. 1976. Immediate skin test reactivity in a general population sample. Annals of Internal Medicine 84: 129.

BLACK P.L., MARSH D.G., JARRETT E., DELESPESSE G.J. and BIAS W.B. 1976. Family studies of the association between HLA and specific immune responses to highly purified pollen allergens. Immunogenetics 3: 349.

BLAIR H. 1977. Natural history of childhood asthma - 20 year follow-up. Archives of Disease in Childhood 52: 613.

BLAIR H. 1978. A long-term study of the morbidity of childhood asthma in general practice. Proceedings of the Third Charles Blackley Symposium. April, 1978.

BLUMENTHAL M.N., AMOS D.B., NOREEN H., MENDELL N.R., and YUNIS E.J. 1974. Genetic mapping of Ir locus in man: linkage to second locus of HLA. Science 183: 1301.

BROSTOFF J., MOWBRAY J.F., KAPOOR A., HOLLOWELL S.J., RUDOLF M. and SAUNDERS K.B. 1976. Is intrinsic asthma a recessive disease ? Lancet 2: 872.

BRUCE C.A., BIAS W.B., NORMAN P.S., LICHENSTEIN L.M. and MARSH D.G. 1976. Studies of HLA antigen frequencies, IgE levels and specific allergic sensitivities in patients having ragweed hayfever, with and without asthma. Clinical and Experimental Immunology 25:67.

BURR M.L., ST.LEGER A.S., BEVAN C. and MERRETT T.G. 1975. A community survey of asthmatic characteristics. Thorax 30: 663.

BURROWS B., LEBOWITZ M.D. and BARBEE R.A. 1976. Respiratory disorders and allergy skin test reactions. Annals of Internal Medicine 84/2: 134.

CADE J.F. and PAIN M.C.F. 1971. Role of bronchial reactivity in etiology of asthma. Lancet 2: 186.

CARTER C.O. 1969. Genetics of common disorders. British Medical Bulletin 25: 52.

CHARPIN J. and ARNAUD A. 1971. Facteurs genetiques dans l'asthme et les allergies respiratoires. Le Poumon et le Coeur 27: 111.

CIBA SYMPOSIUM. 1971. Identification of asthma. Ciba Foundation Study Group No. 38. Porter R. and Birch J. (eds). Churchill Livingstone Press. Edinburgh.

CONOLLY M.E. and GREENACRE J.K. 1976. The lymphocyte B-adrenoceptor in normal subjects and patients with bronchial asthma. Journal of Clinical Investigations 58: 1307.

COOKE R.A. and VANDER VEER A. 1916. Human sensitization. Journal of Immunology 1: 201.

CUTHBERT M.F. 1975. Prostaglandins and asthma. British Journal of Clinical Pharmacology 2: 293.

EDFORS-LUBS M.L. 1971. Allergy in 7000 twin pairs. Acta Allergolica (Kbh) 26: 249.

FAGERHOL M. and HAUGE H. 1969. Serum Pi types in patients with pulmonary disease. Acta Allergolica 24: 107.

FISH J.E., ROSENTHAL R.S., SUMMER W.R., MENKES H., NORMAN P.S and PERMUTT S. 1977. The effect of atropine on acute antigen-mediated airway constriction in subjects with allergic asthma. American Review of Respiratory Disease 115: 371.

FLAHERTY D.K., GELLER M., BACH F. and REED C. 1977. Frequency of W4 and W6 antigens in perennial, non-allergic asthmatics. Journal of Allergy and Clinical Immunology 60: 236.

GERRARD J.W., VICKERS P. and GERRARD C.D. 1976. The familial incidence of allergic disease. Annals of Allergy 36: 10.

GLEICH G.J. 1977. The eosinophil: new aspects of structure and function. Journal of Allergy and Clinical Immunology 60: 73.

GREGG I. 1977. Epidemiology. Chapter eleven, Asthma. Clark T.J.H. and Godfrey S. (eds). Chapman and Hall. London

HORN M.E.C., BRAIN E., GREGG I., YEALLAND S.J. and INGLIS J.M. 1975. Respiratory viral infection in childhood. A survey in general practice, Roehampton 1967-72. Journal of Hygiene (Camb) 74: 157.

HORN M.E.C., BRAIN E., GREGG I., INGLIS J., YEALLAND S. and TAYLOR F. 1979. Respiratory viral infection and wheezy bronchitis in childhood. Thorax 34: 23.

HORN ME.C. and GREGG I. 1973. Role of viral infection and host factors in acute episodes of asthma and chronic bronchitis. Chest 63 (supplement): 44.

HUBSCHER T. 1975. Role of the eosinophil in allergic reactions. Journal of Immunology 114: 1379.

ISHIZAKA K., ISHIZAKA T. and HORNBROOK M. 1967. Allergen-binding activity of YE, YG and YA antibodies in sera from atopic patients. Journal of Immunology 98: 490.

KALINER M. 1977a. Human lung tissue and anaphylaxis. Journal of Clinical Investigations 60: 951.

KALINER M. 1977b. Human lung tissue and anaphylaxis 1. The role of cyclic GMP as a modulator of the immunologically induced secretory response. Journal of Allergy and Clinical Immunology 60: 204.

KATZ R.M., LIEBERMAN J. and SIEGEL S.C. 1976. Alpha-1-antitrypsin levels and prevalence of Pi variant phenotypes in asthmatic children. Journal of Allergy and Clinical Immunology 57: 41.

KSENOFONTOV Y.P. 1974. Study of genetic markers in bronchial asthma and diabetes mellitus. Soviet Genetics 8: 648.

KSENOFONTOV Y.P. and RUMYANTZEV S. 1976. Genetic markers and several indicies of immune reactivity. Genetika 12: 150.

LEBOWITZ M.L., KNUDSON R., MORSE J. and ARMET D. 1978. Closing volume and flow volume abnormalities in alpha-1-antitrypsin phenotype groups in a community population. American Review of Respiratory Disease 117: 179.

LEE T.P., BUSSE W.W. and REED C.E. 1977. Effect of beta adrenergic agonist, prostaglandins and cortisol on lymphocyte levels of cyclic adenosine monophosphate and glycogen: abnormal lymphocyte metabolism in asthma. Journal of Allergy and Clinical Immunology 59: 408.

LEEDER S.R., CORKILL R.T., IRWIG L.M., HOLLAND W.W. and COLLEY J.R.T. 1976. Influence of family factors on asthma and wheezing during the first five years of life. British Journal of Preventative and Social Medicine 30: 213.

LEIGH D. and MARLEY E. 1967. Bronchial Asthma. Pergammon Press Ltd. London.

LEVINE B.B., STEMBER R.H. and FOTINO M. 1972. Ragweed hay fever: genetic control and linkage to HLA haplotypes. Science 178: 1201.

LEIBERMAN J. 1969. Heterozygous and homozygous alpha-1-antitrypsin deficiency in patients with pulmonary emphysema. New England Journal of Medicine 291: 279.

MANO K., HARADA S. and MUJAHARA H. 1975. The distribution of polymorphic traits in atopic asthmatic patients. Acta Allergolica (Kbh) 30: 80.

MANTLE J. and PEPYS J. 1974. Asthma amongst Tristan da Cunha islanders. Clinical Allergy 4: 161.

MARSH D.G., BIAS W.B., HSU S.H. and GOODFRIEND L. 1973. Association of HLA-A7 cross-reacting group with a specific reaginic antibody response in allergic man. Science 179: 691.

MARSH D.G., BIAS W.B. and ISHIZAKA K. 1974. Genetic control of basal serum immunoglobin E level and its effect on specific reaginic sensitivity. Proceedings of the National Academy of Science 71: 3588.

MATHEW D.J., TAYLOR B., NORMAN A.P., TURNER M.W., and SOOTHILL J.F. 1977. Prevention of eczema. Lancet 1: 321.

McKUSICK V.A. 1969. Human Genetics. Suskind S. and Hartman P. (eds). Prentice-Hall Inc. New Jersey.

McNICOL K.N. and WILLIAMS H.E. 1973. Asthma in children 1. Clinical and physiological components 2. Allergic components. British Medical Journal 4: 7.

MOLINA C., BRUN J., COULET M., BETAIL G. and DELAGE J. 1977. Immunopathology of the bronchial mucosa in 'late onset' asthma. Clinical Allergy 7: 137.

MORRISON SMITH J. 1973. Skin tests and atopic allergy in children. Clinical Allergy 3: 269.

MORRISON SMITH J. 1976. The prevalence of asthma and wheezing in children. British Journal of Diseases of the Chest 70: 73.

MORSE J., LEBOWITZ M., KNUDSON R. and BURROWS B. 1975. A community study of the relation of alpha-1-antitrypsin levels to obstructive lung diseases. New England Journal of Medicine 292: 278.

MORSE J., LEBOWITZ M., KNUDSON R. and BURROWS B. 1977. Relation of protease inhibitor phenotypes to obstructive lung diseases in a community. New England Journal of Medicine 296: 1190.

MRC Definition and Classification of Chronic Bronchitis. 1965. Lancet 1: 775.

OGILVIE A.G. 1962. Asthma. A study in prognosis of 1000 patients. Thorax 17: 183.

PARISH W.E. 1973. A human heat-stable anaphylactic or anaphylactoid antibody which may participate in pulmonary disorders. Chapter six, Asthma. Austen K.F. and Lichtenstein L.M. (eds). Academic Press. London.

PARKER C. and SNIDER D. 1973. Prostaglandins and asthma. Annals of Internal Medicine 78: 963.

PEPYS J. 1973. Types of allergic reaction. Clinical Allergy 3 (supplement): 491.

RACHELEFSKY G., PARK M.S., SIEGEL S., TERASAKI P.J., KATZ R. and SAITU S. 1976. Strong association between B-lymphocyte group-2 specificity and asthma. Lancet 2: 1042.

RACHELEFSKY G.S., TERASAKI P.J., KATZ R.M and SIEGEL S.C. 1977. B-lymphocyte and histocompatibility antigens in extrinsic asthma. Monographs Allergy 11: 35.

RACKEMANN F.M. and EDWARDS M.C. 1952. Asthma in children. New England Journal of Medicine 246: 815.

SCHWARTZ M. 1952. Heredity in Bronchial Asthma. Munksgaard Press. Copenhagen.

SPAICH D. and OSTERTAG M. 1936. Untersuchungen uber allergische erkrankungen bei zwillingen. Ztschr. Vererb. u. Konstitutionslehre 19: 731. as reported in Leigh and Marley, 1967.

TAUSSIG L.M. and LEBOWITZ M.D. 1976. Cough and wheeze syndromes in children. American Review of Respiratory Disease 113/114: 45.

THORSBY E., ENGESET A. and LIE O.K. 1971. HLA antigens and susceptibility to disease. Tissue Antigens 1: 147.

TIPS R.L. 1954. A study of the inheritance of atopic hypersensitivity in man. American Journal of Human Genetics 6: 328.

TOWNLEY R., GUIRGES H., BEWTRA A., WATT G., BURKE K., CARNEY K. and SOUTHARD J. 1976. IgE levels and methacholine inhalation responses in homozygous and dizygous twins. American Review of Respiratory Disease 113/114: 119.

TOWNLEY R., RYNING F., LYNCH H. and BRODY W. 1970. Obstructive lung disease in hereditary alpha-1-antitrypsin deficiency. Journal of the American Medical Association 214: 325.

TURNER M.W., BROSTOFF J., WELLS R.S., STOKES C.R. and SOOTHILL J.F. 1977. HLA in eczema and hay fever. Clinical and Experimental Immunology 27: 43.

TURNER-WARWICK M. 1971. Provoking factors in asthma. British Journal of Diseases of the Chest 65: 1.

TURTON C.W.G., MORRIS L., BUCKINGHAM J.A., LAWLER S.D. and TURNER-WARWICK M. 1979. Histo-compatibility antigens in asthma - population and family studies. Thorax 34: 670.

de la VEGA R. and CORTES G. 1976. Genetic polymorphism of ABO and Rh system in relation to bronchial asthma. Allergolica Immunopathologica 4/5: 305.

WAITE D.A., EYLES E.F., TONKIN S.L and O'DONNELL T.V. 1980. Asthma prevalence in Tokelauan children in two environments. Clinical Allergy 10: 71.

WAGATSUMA Y., YAKURA H., NAKAYAMA E., WAKISAKA A., AIZAWA M., MIYATA M., MATSUYAMA R., SATO M. and ITAKURA K. 1976. Inheritance of asthma in families and its linkage to HLA haplotypes. Acta Allergolica (Kbh) 31: 455.

WEINER A.S., ZIEVE I and FRIES J.H. 1936. The inheritance of allergic disease. Annals of Eugenics 7: 141.

WILKEN-JENSEN K. 1978. Fate of asthmatic children seen in decade 1949-1959. Proceedings of the Third Charles Blackley Symposium. April, 1978.

WILLIAMS H. and McNICOL K. 1969. Prevalence, natural history and relationship of wheezy bronchitis and asthma in children. British Medical Journal 4: 321.

VITA

Name:	Mrs. Bonnie Suzanne Sibbald (nee Woodhouse)
Place and year of birth:	Montreal, Canada, 1953
Education:	Lindsay Place High School, 1966-70 Pte. Claire, Canada
	McGill CEGEP, 1970-72 Montreal, Canada D.C.S., First Class Honours
	McGill University, 1972-75 Montreal, Canada B.Sc. (Hons.Biol.),First Class
	Queens University, 1975-77 Kingston, Canada M.Sc. (Biol.)
	University of London, 1977-80 London, England
Experience:	Demonstrator 1974-75, Dept. of Biology McGill University
	Demonstrator 1975-76, Dept. of Biology Queens University
	Research Assistant, Dept. of Clinical Epidemiology in General Practice Cardiothoracic Institute, Brompton Hospital, London 1980-
Awards:	McGill Scholar 1972,1974,1975
	McLaughlin Scholar 1975-76 Queens University
	National Research Council Scholar PGS (2) 1976-77 PGS (3) 1977-78 (declined)
	Medical Research Council Scholar 1977-78 (declined)
	Commonwealth Scholar 1977-80 University of London,England.

Publications:

Bonnie Sibbald, Extrinsic and intrinsic asthma: influence of classification on family history of asthma and allergic disease. Clinical Allergy 10: 313-318. 1980.

Bonnie Sibbald, Genetic basis of sex-differences in the prevalence of asthma. British Journal of Diseases of Chest 74: 93-94. 1980.

Bonnie Sibbald, Mary E.C.Horn, Elizabeth Brain and Ian Gregg. Genetic factors in childhood asthma. Thorax 35: 671-674. 1980.

Bonnie Sibbald, Mary E.C.Horn and Ian Gregg. A family study of the genetic basis of asthma and wheezy bronchitis in children. Archives of Disease in Childhood 55: 354-357. 1980.

Bonnie Sibbald and Margaret Turner-Warwick. Factors influencing the prevalence of asthma among first degree relatives of extrinsic and intrinsic asthmatics. Thorax 34: 332-337. 1979.

R. Harmsen, Mr. Rose and B. Woodhouse. A general mathematical model for insect outbreak. Proceedings of the Entomological Society of Ontario 107: 11-18. 1976.

K. Sittmann and B. Woodhouse. Sex-modified and sex-limited genetic defects in swine: cryptorchidism. Canadian Journal of Genetics and Cytology 19: 487-502. 1977.

Bonnie Sibbald, Extrinsic and intrinsic asthma: influence of classification on family history of asthma and allergic disease. Clinical Allergy 10: 313-318. 1980.

Bonnie Sibbald, Genetic basis of sex-differences in the prevalence of asthma. British Journal of Diseases of Chest 74: 93-94. 1980.

Bonnie Sibbald, Mary E.C.Horn, Elizabeth Brain and Ian Gregg.
Genetic factors in childhood asthma. Thorax 35: 671-674. 1980.

Bonnie Sibbald, Mary E.C.Horn and Ian Gregg. A family study of the genetic basis of asthma and wheezy bronchitis in children. Archives of Disease in Childhood 55: 354-357. 1980.

Bonnie Sibbald and Margaret Turner-Warwick. Factors influencing the prevalence of asthma among first degree relatives of extrinsic and intrinsic asthmatics. Thorax 34: 332-337. 1979.

GENETIC FACTORS IN CHILDHOOD ASTHMA

BY

BONNIE SIBBALD, MARY E C HORN,
ELIZABETH A BRAIN, and IAN GREGG

Reprinted from THORAX
September 1980 *Vol* 35 *No* 9 *p* 671

BRITISH MEDICAL ASSOCIATION
TAVISTOCK SQUARE, LONDON
WC1H 9JR

Thorax, 1980, **35**, 671–674

Genetic factors in childhood asthma

BONNIE SIBBALD, MARY E C HORN, ELIZABETH A BRAIN AND IAN GREGG

From the Departments of Medicine and Clinical Epidemiology in General Practice, Cardiothoracic Institute, Brompton Hospital, London

ABSTRACT The prevalences of asthma and atopy were examined in the families of 77 asthmatic and 87 control children attending a London general practice. The prevalence of asthma in first degree relatives of asthmatic children was found to be significantly higher than in relatives of control children, and this difference was more pronouced for relatives of atopic probands than for relatives of non-atopic probands. Among the relatives of asthmatics, atopic asthma was more common than non-atopic asthma, irrespective of the atopic status of the proband. However, among the relatives of control children, neither the prevalence of asthma nor the atopic status of the asthmatic relatives was influenced by the atopic status of the proband. These findings support the hypothesis that asthma and atopy are inherited independently. Although atopy itself does not predispose to asthma, it may enhance a genetic susceptibility to the condition, thus increasing the likelihood that the latter will be expressed.

Two forms of asthma can be distinguished: *atopic asthma* in which patients give a positive immediate reaction on skin prick testing, and *non-atopic asthma* in which patients give no positive reactions.

Although family and twin studies have established that asthma has an hereditary basis[1 2] no evidence has been presented to show whether or not both the atopic and the non-atopic forms of the disease can be inherited. However, it has been shown that the prevalence of asthma is higher in relatives of atopic asthmatics than in relatives of non-atopic asthmatics.[3] Therefore, if there is a genetic basis in both forms, the heritability of atopic asthma is likely to be greater than that of non-atopic asthma.

Current studies suggest that this difference in heritability might arise from an increase in the susceptibility to asthma of patients who inherit a predisposition to both asthma and atopy. Pepys[4] has shown that the prevalence of asthma in first degree relatives of asthmatics increases with the number of positive skin tests in the probands, indicating that atopy may enhance the manifestation of asthma. However, the prevalence of hay fever and eczema in these relatives was more strongly associated with the atopic status of the probands than was the prevalence of asthma, suggesting that asthma may be inherited independently of atopy.

In the present study, family study methods have been used to investigate the hypotheses that atopic and non-atopic asthma are both heritable, and that asthma may be inherited independently of atopy. Patients have been selected from a general practice population, since the findings of previous investigations may have been biased by studying hospital outpatients who were likely to have had a more severe form of asthma than occurs in the general population.

Methods

The study group consisted of 164 children, aged 1–12 years, and their families attending a general practice in Roehampton, South-West London. The data were collected in the course of a survey of asthma and wheezy bronchitis, carried out between 1967–76.[5–7]

The first child from each family recruited in the original survey was designated the proband for the purposes of the present study. Probands were grouped according to their history of lower respiratory illness as follows.

Children in whom wheeze had occurred *only* in association with symptoms suggestive of respiratory infection were diagnosed as suffering from wheezy bronchitis and have been excluded from

Address for reprint requests: Mrs Bonnie Sibbald, Cardiothoracic Institute, Brompton Hospital, Fulham Road, London SW3 6HP.

the present study. The clinical relationships between these children and those with asthma has been discussed by Horn *et al*,[7] while the genetic relationship has been reported by Sibbald *et al*.[15]

Children in whom wheezy episodes occurred in response to allergens, exercise, or emotion, as well as with symptoms suggestive of respiratory infection, were diagnosed as having asthma. On auscultation there was high-pitched wheezing over most parts of the lungs.

The control group consisted of children with no history of wheezy illness. Although the majority had experienced one or more episodes of bronchitis, wheeze had never been detected on auscultation.

The asthma and control groups were each subdivided into atopic and non-atopic groups dependent on the proband's skin prick test response to pollens, house dust mite, animal danders, and moulds. The criterion for a positive response was a weal of 2 cm or more in diameter in the absence of any equivalent reaction in the control solution. Children with one or more positive reactions were designated atopic, while those with no positive reactions were designated non-atopic.

The age, sex, and personal history of hay fever and eczema were recorded for every proband. The history of asthma in the parents and siblings of probands was obtained through interview with one or more members of the family and from scrutiny of medical records. Estimation of the prevalence of atopy, as shown by the presence of positive skin tests, was carried out in all accessible relatives. Complete information was available for the 30 (34%) of the control children (applicable to table 3).

Results

The probands are described in table 1. There were significantly more children with atopy, hay fever, and eczema among asthmatic probands than control subjects. Similarly the proportion of probands with a positive family history of asthma was higher in the asthmatics than the controls. The sex ratio and mean age of the probands did not differ between groups.

The family history of asthma differed between asthmatic and control children (table 2). The overall prevalence of asthma was higher in relatives of asthmatic probands than controls, and this difference was more pronounced for relatives of atopic than for relatives of non-atopic probands. Furthermore, the prevalence of asthma was higher in parents than siblings in the families of asthmatics, while the parents and siblings of controls were equally affected.

The distribution of atopic and non-atopic asthma among relatives is shown in table 3. In relatives of asthmatics, the prevalence of atopic asthma exceeded the prevalence of non-atopic asthma irrespective of the atopic status of the proband. In contrast, the prevalences of atopic and non-atopic asthma were equal in relatives of atopic and non-atopic controls.

Table 1 *Clinical characteristics of the probands*

Proband	*Number* (% *total*)	*Males* *No* (%)	*Hay fever* *No* (%)	*Eczema* *No* (%)	*Family history of asthma* *No* (%)	*Mean age* (*yr*)
Asthma						
Atopic	64 (83)†	42 (66)	25 (39)*	33 (52)*	25 (39)†	7·5
Non-atopic	13 (17)	9 (69)	0 (0)	0 (0)	4 (31)	5·4
Total	77	51 (66)	25 (32)†	33 (43)†	29 (38)†	7·1
Control						
Atopic	38 (44)	25 (66)	5 (13)	8 (21)	4 (10)	6·0
Non-atopic	49 (56)	24 (49)	0 (0)	8 (16)	5 (10)	5·4
Total	87	49 (56)	5 (6)	16 (18)	9 (10)	5·6

Excess as compared with control: *$p < 0.05$ and †$p < 0.01$.

Table 2 *Prevalance of asthma in first degree relatives of probands*

Proband	*Prevalence* (%) *of asthma in*			*Significance*
	Parents	*Siblings*	*All relatives*	*Parents versus siblings*
Asthma				
Atopic	23/128 (18)	11/124 (9)	34/252 (13)	$p < 0.05$
Non-atopic	4/26 (15)	1/26 (4)	5/52 (10)	SS
Total	27/154 (17)	12/150 (8)	39/304 (13)	$p < 0.05$
Control				
Atopic	2/76 (3)	2/53 (4)	4/129 (3)	SS
Non-atopic	5/98 (5)	2/75 (3)	7/173 (4)	SS
Total	7/174 (4)	4/128 (3)	11/302 (4)	NS
Significance				
Asthma versus control		Atopic	$p < 0.01$	
		Non-atopic	SS	
		Total	$p < 0.001$	

SS = sample too small for analysis, NS = not significant.

Table 3 *Prevalence of atopic and non-atopic asthma in relatives of probands*

Proband	*Number of relatives at risk*	*Affected relatives*		*Row significance*
		Atopic asthma *No* (%)	*Non-atopic asthma* *No* (%)	
Asthma				
Atopic	101	10 (10)	3 (3)	$\chi^2 = 3.78$, $p < 0.10$
Non-atopic	14	2 (14)	0 (0)	$\chi^2 = 2.00$, $p > 0.10$
Total	115	12 (10)	3 (3)	$\chi_2^2 = 5.78$, $p < 0.10$
Control				
Atopic	35	1 (3)	1 (3)	$\chi^2 = 0$
Non-atopic	69	2 (3)	2 (3)	$\chi^2 = 0$
Total	104	3 (3)	3 (3)	$\chi_2^2 = 0$

Table 4 *Prevalence of atopy in first degree relatives of probands*

Proband	*Prevalence (%) of atopy in*			*Significance*
	Parents	*Siblings*	*All relatives*	*Parents versus siblings*
Asthma				
Atopic	34/56 (61)	27/45 (60)	61/101 (60)	NS
Non-atopic	3/8 (37)	2/6 (33)	5/14 (36)	SS
Total	37/64 (58)	29/51 (57)	66/115 (57)	NS
Control				
Atopic	11/20 (55)	9/15 (60)	20/35 (57)	NS
Non-atopic	18/40 (45)	11/29 (38)	29/38 (42)	NS
Total	29/60 (48)	20/44 (43)	49/104 (47)	NS
Significance				
Asthma versus control		Atopic	NS	
		Non-atopic	NS	
		Total	NS	

Abbreviations as in table 2.

The family history of atopy was similar in asthmatic and control children (table 4). The prevalence of atopy in relatives did not differ significantly between groups of probands. However, there was a tendency for atopy to occur more frequently in the families of atopic probands than in the families of non-atopic probands. The parents and siblings of probands were equally affected in all groups.

Discussion

The findings of this study support those of previous investigations in showing that asthma clusters in families.[1 8] The overall prevalence of asthma in the first degree relatives of asthmatics was found to be 13%, while that in the relatives of controls was only 4%. These figures agree well with those of Leigh and Marley[1] whose family data were collected by similar methods. They found a prevalence of 13·2% in the first degree relatives of asthmatics and a prevalence of only 1·5% in the relatives of controls. Although this familial aggregation of asthma may arise partly from shared family environments, twin studies have shown that shared genetic factors must also play an important role.[2 9]

The increased prevalence of asthma in the relatives of both atopic and non-atopic asthmatics, as compared with the relatives of controls, suggests that both forms of asthma may be hereditary. Furthermore, the similarity between atopic and non-atopic patients in the distributions of asthma among their parents and siblings shows that, if they are hereditary, they may share a common genetic defect. Although the mode of inheritance cannot be decided accurately from the available data, the evenness of the distribution of asthma among the relatives is compatible with either polygenic inheritance or dominance with incomplete penetrance.

Despite this similarity in their modes of inheritance, the increase in the prevalence of asthma in the relatives of asthmatic as compared with control patients was greater for atopic than non-atopic probands. Thus the hereditary component underlying atopic asthma may be greater than that underlying non-atopic asthma.

Within the families of asthmatics, there appeared to be no correlation between the type of asthma in first degree relatives and the atopic status of the proband. This is best illustrated by our findings that the prevalence of atopic asthma exceeded the prevalence of non-atopic asthma in relatives of both atopic and non-atopic probands. The absence of any strict association between atopy and asthma strongly suggests that asthma may be inherited independently of atopy. Additional support for this hypothesis comes from our observation that asthma was more prevalent in the relatives of asthmatics than in the relatives of controls, whereas the prevalence of atopy did not differ significantly between groups.

Although it has been established that atopy is at least partly hereditary,[9 10] neither the prevalence nor the type of asthma in the relatives of controls were influenced by the atopic status of the proband. Thus atopy itself did not predispose to asthma.

If, as the results suggest, atopy and asthma are inherited independently and atopy itself does not predispose to asthma, it seems likely that the increased risk of asthma in relatives of atopic asthmatics must arise from an increased susceptibility to asthma of patients who inherit a predisposition to both asthma and atopy. Thus, the findings of this study support the hypothesis of Sibbald and Turner-Warwick[3] that clinically different forms of asthma may have a common genetic defect, whose manifestation may be enhanced in the presence of atopy.

The control children used in this study were not strictly normal in that 62 (71%) had had one or more episodes of bronchitis. The prevalence of atopy (44%) and the sex ratio (1 : 29) in these probands were higher than are generally found in children of this age,[11 12] suggesting that the control children may have possessed some genetic factors in common with the asthmatic children.

Development of positive skin prick tests may be age-dependent, reaching a maximum in early adulthood.[11] Since the majority of children in the

present study were young (see table 1), the prevalence of atopy among the probands and their siblings might have been underestimated. Therefore, the relationship between atopy and asthma should now be investigated in the families of adults to avoid any bias which may have been introduced by the youth of our probands.

We would like to acknowledge the financial support of the National Heart and Chest Hospitals. BS was supported by a research scholarship from the British Council.

References

1 Leigh D, Marley E. *Bronchial asthma. A genetic, population and psychiatric study.* Oxford: Pergamon Press, 1967.
2 Edfors-Lubs ML. Allergy in 7000 twin pairs. *Acta Allergol* 1971; **26**:249–85.
3 Sibbald B, Turner-Warwick M. Factors influencing the prevalence of asthma among first degree relatives of extrinsic and intrinsic asthmatics. *Thorax* 1979; **34**:332–7.
4 Pepys J. Types of allergic reaction. *Clin Allergy* 1973; **3**:491–509.
5 Horn MEC, Gregg I. Role of viral infection and host factors in acute episodes of asthma and chronic bronchitis. *Chest* 1973; **63**:44–8.
6 Horn MEC, Brain EA, Gregg I, Yealland SJ, Inglis JM. Respiratory viral infection in childhood. A survey in general practice, Roehampton 1967–72. *J Hyg* 1975; **74**:157–68.
7 Horn MEC, Brain EA, Gregg I, Inglis JM, Yealland SJ, Taylor P. Respiratory viral infection and wheezy bronchitis in childhood. *Thorax* 1979; **34**:23–8.
8 Schwartz M. *Heredity in bronchial asthma.* Copenhagen: Munksgaard, 1952.
9 Townley R, Guirgis H, Bewtra A *et al.* IgE levels and methacholine inhalation responses in monozygous and dizygous twins. *Am Rev Respir Dis* 1976: **113**:119.
10 Marsh DG, Bias WB, Ishizaka K. Genetic control of basal serum immunoglobulin E level and its effect on specific reaginic sensitivity. *Proc Natl Acad Sci USA* 1974; **71**:3588–92.
11 Barbee RA, Lebowitz MD, Thompson HC, Burrows R. Immediate skin-test reactivity in a general population sample. *Ann Intern Med* 1976; **84**:129–33.
12 Smith JM. Skin tests and atopic allergy in children. *Clin Allergy* 1973; **3**:269–75.
13 Burrows B, Lebowitz MD, Barbee RA. Respiratory disorders and allergy skin-test reactions. *Ann Intern Med* 1976; **84**:134–9.
14 Williams HE, McNicol KN. Prevalence, natural history and relationship of wheezy bronchitis and asthma in children. An epidemiological study. *Br Med J* 1969; **4**:321–5.
15 Sibbald B, Horn MEC, Gregg I. A family study of the genetics of asthma and wheezy bronchitis. *Arch Dis Child* 1980; **55**:354–7.

A FAMILY STUDY OF THE GENETIC BASIS OF ASTHMA AND WHEEZY BRONCHITIS

BY
B SIBBALD, M E C HORN, AND I GREGG

Reprinted from Archives of Disease in Childhood, May 1980, Vol. 55, No. 5, 354–357

LONDON
BRITISH MEDICAL ASSOCIATION
TAVISTOCK SQUARE, LONDON WC1H 9JR

Archives of Disease in Childhood, 1980, **55**, 354–357

A family study of the genetic basis of asthma and wheezy bronchitis

BONNIE SIBBALD, MARY E C HORN, AND IAN GREGG

Department of Medicine and Department of Clinical Epidemiology in General Practice, Cardiothoracic Institute, Brompton Hospital, London

SUMMARY The family histories relating to asthma and wheezy bronchitis were examined in 77 asthmatic, 78 wheezy bronchitic, and 87 control children, aged between 1 and 12 years. The percentage of children with at least one asthmatic relative was significantly greater in the asthmatic and wheezy bronchitic probands than in the controls; and asthma was more prevalent in the relatives of both groups of wheezy probands than in the relatives of controls. Similarly, the percentage of children with at least one wheezy bronchitic relative tended to be greater in asthmatic and wheezy bronchitic probands than in the controls; and wheezy bronchitis tended to be more prevalent in the relatives of both groups of wheezy probands than in the relatives of controls. However these differences did not reach significance. The strong similarities between asthmatic and wheezy bronchitic children in their family histories of asthma and wheezy bronchitis suggest that these two forms of wheezy illness share a common genetic defect.

Childhood wheezy bronchitis is characterised by recurrent episodes of wheeze which occur only in association with a respiratory infection. It can be distinguished from asthma in which episodes of wheeze may be provoked by allergens, exercise, or emotion, and by infection.

The clinical differences between these two forms of wheezy illness are not well defined, resulting in confusion about the relationship of wheezy bronchitis to asthma. Although many children with wheezy bronchitis grow out of this tendency, some develop frank asthma later. Moreover wheezy bronchitis is known to precede asthma in many childhood asthmatics. Therefore it is possible that asthma and wheezy bronchitis have a common defect, as suggested by Williams and McNicol.[1]

Other findings suggest that the aetiologies of the disorders may differ. Despite the viewpoint expressed by Williams and McNicol,[1] their data showed that the incidence of hay fever, skin test sensitivity, and nasal eosinophilia was lower in children with wheezy bronchitis than in those with asthma. Taussig and Lebowitz[9] confirmed these observations and they showed also that wheezy bronchitic children have fewer abnormalities in pulmonary function than asthmatic children. Therefore, it is possible that aetiologies of asthma and wheezy bronchitis differ, the former depending on factors which are not essential for the development of wheezy bronchitis.

Since it is well established that asthma has a hereditary basis,[2–3] the relationship between asthma and wheezy bronchitis may be clarified by family studies designed to assess the degree of genetic similarity between them. If the disorders have a common genetic basis, we would expect family histories to be similar in asthmatic and wheezy bronchitic children. On the other hand, if they do not have a common hereditary defect, family histories would differ. In this paper, we report the findings of a family study in which comparison was made of the hereditary similarities and differences between asthma and wheezy bronchitis.

Methods

The study group comprised 242 children, aged between 1 and 12, and their families attending a general practice in Roehampton, south-west London. The data had been collected for a survey on asthma and wheezy bronchitis carried out between 1967 and 1976.[4–6]

MARY E C HORN, 6 Genoa Avenue, London SW15 6DY
Cardiothoracic Institute
Department of Medicine
BONNIE SIBBALD, postgraduate student
Department of Clinical Epidemiology in General Practice
IAN GREGG, head of department

The first child from each family to be recruited in the survey was designated the proband for the purposes of the present study. Probands were classified into the following groups according to history of respiratory illness.

Wheezy bronchitis: one or more episodes of wheezing which occurred only in association with symptoms suggesting respiratory infection. On auscultation there would be a high pitched wheeze over most parts of the lungs in addition to medium crepitations or rhonchi.

Asthma: recurrent episodes of wheezing which occurred in response to allergens, exercise, or emotion, as well as with symptoms suggesting respiratory infection. On auscultation there would be a high pitched wheeze over most parts of the lungs.

Control: no history of wheeze. Although most children had experienced at least one episode of respiratory infection, wheeze had never been detected on auscultation.

The groups were each subdivided into atopic and nonatopic groups according to the proband's reactions to skin prick tests of house dust, pollens, house dust mite, animal danders, and moulds. The criterion for a positive reaction was a weal of at least 2 mm in diameter in the absence of any equivalent reaction to the control solution. A patient with at least one positive reaction was designated atopic, while a patient with no positive reactions was designated nonatopic.

The age, sex, and history of hay fever and eczema were recorded for each proband. The history of asthma and wheezy bronchitis in each of the proband's first-degree relatives (that is, parents and siblings) was obtained by interviewing at least one member of his family and by scrutinising medical records.

A relative was said to have a history of wheezy bronchitis if, at any time during his life, he had had at least one episode of wheezing which occurred only in association with symptoms suggesting respiratory infection. On the other hand, if the relative had had wheezy episodes which occurred in response to allergens, exercise, or emotion as well as with symptoms suggesting respiratory infection, then he was said to have a history of asthma.

Results

Table 1 summarises the clinical characteristics of the probands in each of the asthma, wheezy bronchitis, and control groups. There were no significant differences between groups in the proportion of males or the mean age of the probands. The prevalences of atopy, hay fever, and eczema were all significantly higher in asthmatic than in wheezy bronchitic or control children. The proportion of children with a positive family history of asthma was greater in both the asthma and wheezy bronchitis groups than in the control group, but the proportion with a positive family history of wheezy bronchitis did not differ significantly among groups.

The prevalences of asthma and wheezy bronchitis in the first-degree relatives of probands are summarized in Table 2. The overall prevalence of asthma was higher in the relatives of both asthmatic and wheezy bronchitic probands than in the relatives of controls ($\chi^2=16{\cdot}02$; $P<0{\cdot}01$). A similar trend was observed in the prevalence of wheezy bronchitis, but the differences did not reach significance ($\chi^2=1{\cdot}94$, $P>0{\cdot}10$).

Table 1 *Characterisation of probands*

Proband	*No.*	(%)	*Males*		*Hay fever*		*Eczema*		*Family history*				*Mean age (years)*
									Asthma		*Wheezy bronchitis*		
			No.	(%)	*No.*	(%)	*No.*	(%)	*No.*	(%)	*No.*	(%)	
Asthma													
Atopic	64	(83)**	42	(66)	25	(39)*	33	(52)*	25	(39)**	17	(26)	7·5
Nonatopic	13	(17)	9	(69)	0	(0)	0	(0)	4	(31)	5	(38)	5·4
Total	77		51	(66)	25	(32)**	33	(43)**	29	(38)**	22	(28)	7·1
Wheezy bronchitis													
Atopic	36	(46)	26	(72)	4	(11)	5	(14)	13	(36)*	8	(22)	6·2
Nonatopic	42	(54)	25	(59)	0	(0)	5	(12)	12	(29)	13	(31)	4·6
Total	78		51	(65)	4	(5)	10	(13)	25	(32)**	21	(27)	5·3
Control													
Atopic	38	(44)	25	(66)	5	(13)	8	(21)	4	(10)	4	(10)	6·0
Nonatopic	49	(56)	24	(49)	0	(0)	8	(16)	5	(10)	13	(26)	5·4
Total	87		49	(56)	5	(6)	16	(18)	9	(10)	17	(19)	5·6

Excess as compared with control value: *$P<0{\cdot}05$, **$P<0{\cdot}01$.

Table 2 *Prevalences of asthma and wheezy bronchitis in the first-degree relatives of the probands*

Proband	*Prevalence in first-degree relatives*			
	Asthma		*Wheezy bronchitis*	
	No.	(%)	*No.*	(%)
Asthma				
Atopic (n = 252)	34	(13)**	17	(7)
Nonatopic (n = 52)	5	(10)	6	(11)
Total (n = 304)	39	(13)**	23	(8)
Wheezy bronchitis				
Atopic (n = 127)	18	(14)**	8	(6)
Nonatopic (n = 163)	14	(9)*	17	(10)
Total (n = 290)	32	(11)**	25	(9)
Control				
Atopic (n = 129)	4	(3)	4	(3)
Nonatopic (n = 173)	7	(4)	13	(7)
Total (n = 302)	11	(4)	17	(6)

Excess as compared with control value: *P<0·10, **P<0·10.
It was not possible to compare nonatopic asthmatic probands with nonatopic control probands because of the small size of the sample.

In all groups, there was no significant difference between the relatives of atopic and nonatopic probands in the prevalences either of asthma or wheezy bronchitis. However, in the asthma and wheezy bronchitis groups, the prevalence of asthma tended to be higher in relatives of atopic probands; whereas the prevalence of wheezy bronchitis tended to be higher in relatives of nonatopic probands (Table 2).

Discussion

There was a strong similarity in the family history of asthma between asthmatic and wheezy bronchitic probands. The percentage of children with at least one asthmatic relative was significantly greater in the asthmatic and wheezy bronchitic probands than in the controls; and the prevalence of asthma was significantly higher in the relatives of both groups of wheezy probands than in the relatives of controls. This clustering of asthma in the families of wheezy children supports the hypothesis that at least some of the genetic factors underlying asthma may also be present in wheezy bronchitis.

The family history of wheezy bronchitis was similar to that of asthma. The percentage of children with at least one wheezy bronchitic relative tended to be greater in asthmatic and wheezy bronchitic probands than in controls; and the prevalence of wheezy bronchitis tended to be higher in the relatives of both groups of wheezy probands than in the relatives of controls. Although these differences did not reach significance, the tendency of wheezy bronchitis to cluster in the families of wheezy children lends support to the idea that wheezy bronchitis and asthma share a common genetic defect.

The composition of our control group may have contributed to the absence of a significant difference between wheezy and control probands in their family histories of wheezy bronchitis. Control children were not normal in that 62 (71%) had had at least one episode of bronchitis. The prevalence of atopy (44%) and the sex-ratio (1·29) were higher in these probands than is generally found in children of this age,[7–8] suggesting the control children may have had some genetic factors in common with the asthmatic and wheezy bronchitic children.

As wheezy bronchitis often precedes asthma in children, some of the probands with wheezy bronchitis may have had incipient asthma. Their presence would be expected to enhance the similarity in the family histories of asthma and wheezy bronchitis between asthmatic and wheezy bronchitic probands. However, the pronounced differences between the two groups of probands in their histories of atopy and allergic disease (Table 1) suggest there were not many children with incipient asthma among those with wheezy bronchitis. Therefore, it is unlikely that the family histories of asthma and wheezy bronchitis were altered appreciably by this bias.

The prevalences of atopy, hay fever, and eczema were lower in wheezy bronchitic than asthmatic probands. Although these differences may have arisen, in part, from the slightly lower age of the wheezy bronchitic compared with the asthmatic children,[7] other investigations dealing with children of uniform age have also found that atopy and allergy were less prevalent in wheezy bronchitics.[1 9] These findings suggest that the reduced predisposition to asthma of many wheezy bronchitic children may result from their failure to inherit a predisposition to atopy or allergy. Our finding that the prevalence of wheezy bronchitis was higher in the relatives of nonatopic than atopic probands, whereas the reverse was true of asthma, lends support to this hypothesis.

In summary, the similarity between asthmatic and wheezy bronchitic children in their family histories of asthma and wheezy bronchitis suggests that these diseases share a common genetic defect. However the manifestation of asthma may be influenced by other factors, for instance atopy, which are not essential to the development of wheezy bronchitis.

We acknowledge financial support from the National Heart and Chest Hospitals. B S was supported by a research scholarship from the British Council.

References

[1] Williams H, McNicol K. Prevalence and natural history of wheezy bronchitis and asthma in children. An epidemiological study. *Br Med J* 1969; iv: 321–5.

[2] Leigh D, Marley E. *Bronchial asthma. A genetic, population, and psychiatric study.* Oxford: Pergamon, 1967.
[3] Edfors-Lubs M-L. Allergy in 7000 twin pairs. *Acta Allergol (Kbh)* 1971; **26**: 249–85.
[4] Horn M E C, Gregg I. Role of viral infection and host factors in acute episodes of asthma and chronic bronchitis. *Chest* 1973; 63: Supplement, 44–8S.
[5] Horn M E C, Brain E A, Gregg I, Yealland S J, Inglis J M. Respiratory viral infection in childhood. A survey in general practice, Rochampton 1967–72. *J Hyg (Camb)* 1975; **74**: 157–68.
[6] Horn M E C, Brain E A, Gregg I, Inglis J M, Yealland S J, Taylor P. Respiratory viral infection and wheezy bronchitis in childhood. *Thorax* 1979; **34**: 23–8.
[7] Barbee R A, Lebowitz M D, Thompson H C, Burrows R. Immediate skin-test reactivity in a general population sample. Ann Intern Med 1976; **84**: 129–33.
[8] Morrison-Smith J. Skin tests and atopic allergy in children. *Clin Allergy* 1973; **3**: 269–75.
[9] Taussig L, Lebowitz M. Cough and wheeze syndromes in children (abstract). *Am Rev Respir Dis* 1976; **113** and **114**: 45.

Correspondence to Mrs B Sibbald, Cardiothoracic Institute, Brompton, Hospital, Fulham Road, London SW3 6HP.

Received 10 July 1979

FACTORS INFLUENCING THE PREVALENCE OF ASTHMA AMONG FIRST DEGREE RELATIVES OF EXTRINSIC AND INTRINSIC ASTHMATICS

BY

BONNIE SIBBALD and MARGARET TURNER-WARWICK

Reprinted from THORAX
June 1979 *Vol* 34 *No* 3 *p* 332

BRITISH MEDICAL ASSOCIATION
TAVISTOCK SQUARE, LONDON
WC1H 9JR

Thorax, 1979, 34, 332–337

Factors influencing the prevalence of asthma among first degree relatives of extrinsic and intrinsic asthmatics

BONNIE SIBBALD AND MARGARET TURNER-WARWICK

From the Department of Medicine, Cardiothoracic Institute, Brompton Hospital, London, UK

ABSTRACT The prevalence of asthma, hay fever, and eczema was examined in first degree relatives of extrinsic (atopic) and intrinsic (non-atopic) asthmatics attending the asthma clinics of the Brompton Hospital and the Doncaster Royal Infirmary.

In both the Doncaster and Brompton populations the prevalence of asthma, hay fever, and eczema was significantly higher among relatives of extrinsic than among relatives of intrinsic asthmatics. Furthermore, the prevalence of these traits tended to be higher among siblings of extrinsic probands with one or both parents affected than among siblings of probands with neither parent affected. Most importantly, the prevalence of asthma among first degree relatives was positively correlated with the prevalence of hay fever or eczema or both among relatives and with the degree of atopy in the probands.

These findings are consistent with the results of previous investigations in which the expression of asthma was shown to depend on a genetic predisposition to the trait as well as exposure to environmental provoking agents. We further suggest that the presence of atopy in genetically predisposed individuals increases the risk of developing asthma.

Asthma may be defined as partial obstruction of airways that is reversible either in time or with treatment. Two broad forms of the disease are recognised. Extrinsic asthma, in which individuals are atopic, generally has an early age of onset (under 20 years) and boys are more often affected than girls (Williams and McNicol, 1969; Gregg, 1977). Intrinsic asthma, in which individuals are non-atopic, generally has a late age of onset (over 30 years) and the sex-ratio is even, or biased in favour of women (Gregg, 1977; Molina *et al*, 1977).

There is much evidence that asthma is partially hereditary in nature. Family studies have shown that the prevalence of asthma among relatives of asthmatic patients is significantly higher than it is among relatives of non-asthmatic patients (Leigh and Marley, 1967; Charpin and Arnaud, 1971; Gregg, 1977) and the risk of having an asthmatic child is significantly greater when one or both parents are asthmatic than when neither parent is affected (Charpin and Arnaud, 1971; Higgins and Keller, 1975). In addition, familial clustering in measures of forced expiratory volume in one second (Higgins and Keller, 1975) and in peak expiratory flow rate (Leeder *et al*, 1976) have been reported, while twin studies have shown that the concordance rate is significantly higher in monozygotic than in dizygotic twins (Edfors-Lubs, 1971).

Although genetic studies on asthma have provided strong evidence for a hereditary component, the mode of inheritance has yet to be determined. The reason previous investigations have not resolved this problem may be partly the result of failing to differentiate between extrinsic and intrinsic forms of the trait. A comprehensive study of asthma in families of extrinsic and intrinsic asthmatics was therefore begun, the preliminary results of which form the basis of this paper.

Methods

Probands were selected from patients attending the asthma clinics of the Brompton Hospital and the Doncaster Royal Infirmary during 1973–7. All had a history of episodic wheeziness or breathlessness and most showed reversible airways obstruction either between successive visits or on treat-

ment with a bronchodilator. Clearly atopic patients were selected as extrinsic probands and clearly non-atopic probands as intrinsic probands to increase the probability of detecting differences between these two forms of asthma. These probands were designated "polar."

Polar extrinsic probands had three or more positive skin prick tests of the 21 common allergens tested for. (Any weal of 2 mm or more in diameter in the absence of any equivalent reaction in the control tests was recorded as positive.) In addition, extrinsic probands had either a history of eczema or hay fever or both, or asthma provoked by pollens, dust, or animals. Only individuals whose age of onset was under 20 years were accepted. In contrast, polar intrinsic probands had no positive skin prick tests, no history of eczema or hay fever, and no asthma provoked by pollens, dust, or animals. Only individuals whose age of onset was over 30 years were accepted. Most asthmatics do not meet these criteria for polar intrinsic or polar extrinsic asthma. Individuals in this intermediate category have been described in detail and will be discussed in a later paper (Sibbald, in preparation). To give a more complete view of the asthma spectrum we now describe our findings in a sample of these asthmatic patients. Probands were selected from outpatients attending the Brompton clinic, and were classified into two groups that we have termed non-polar intrinsic asthma and intermediate type asthma.

Non-polar intrinsic asthmatics were skin test negative and had no allergic provoking factors. Unlike the polar group, however, they possessed one or both of the following factors: age of onset under 30 years; a positive history of hay fever or eczema or both. Intermediate asthmatics had either one or two positive skin prick test reactions; no other criteria were imposed when selecting these probands.

Information on the first degree relatives of probands was taken from an asthma questionnaire completed by a doctor on the proband's first visit to the clinic. For each proband the following information was recorded: total number of siblings and offspring, the number with asthma, hay fever or eczema or both; number of parents with asthma, hay fever or eczema or both; and sex of affected relatives.

The chi-square test was used to assess differences between groups (Mulholland and Jones, 1968). The P-values for one degree of freedom have been given except where otherwise indicated.

Results

In most respects the Brompton and Doncaster populations were similar (table 1). There were no measurable differences between Brompton and Doncaster extrinsic probands or between Brompton and Doncaster intrinsic probands. In addition, the prevalences of asthma, hay fever, and eczema among the first degree relatives of intrinsic asthmatics did not differ between the two populations. The prevalences of these traits, however were higher among relatives of Brompton extrinsic asthmatics than among relatives of Doncaster extrinsic asthmatics.

The data were analysed separately in the

Table 1 *Comparison of Doncaster and Brompton populations*

Character	*Doncaster*		*Brompton*		*Significance*
	Value	*Percent*	*Value*	*Percent*	
Extrinsic asthma					
Probands					
Proportion in sample	119/379	31·4	208/787	26·4	NS
Sex-ratio M:F	0·83	—	1·12	—	NS
Proportion with hayfever/eczema	86/119	72·3	163/208	78·4	NS
No relatives/proband	5·4	—	4·1	—	NS
First degree relatives					
Prevalence of asthma	67/639	10·5	132/858	15·4	$P < 0.05$
Prevalence of hay fever	44/639	6·9	134/858	15·6	$P < 0.01$
Prevalence of eczema	28/639	4·4	69/858	8·0	$P < 0.05$
Instrinsic asthma					
Probands					
Proportion in sample	26/379	6·9	63/787	8·0	NS
Sex-ratio M:F	0·73	—	0·66	—	NS
No relatives/proband	7·2	—	7·0	—	NS
First degree relatives					
Prevalence of asthma	9/187	4·8	19/439	4·3	NS
Prevalence of hay fever	1/187	0·5	9/439	2·0	NS
Prevalence of eczema	2/187	1·1	5/439	1·1	NS

Brompton and Doncaster populations. The relative differences between extrinsic and intrinsic asthmatics in prevalences of asthma, hay fever, and eczema were similar in the two populations. In addition, the populations did not differ in the distribution of asthma either among parents, siblings, and offspring or among siblings of asthmatic patients with neither, one, or both parents affected.

This high degree of similarity between the two populations suggested that the factors precipitating asthma were probably common to both. Therefore we have combined the populations and have presented the results for the pooled data.

POLAR EXTRINSIC PROBANDS

Among the 1166 patients examined, 327 (28·0%) fulfilled the criteria for polar extrinsic asthma. Of these, 164 were men. The prevalence of hay fever did not differ between the sexes, while eczema was slightly more common among male than female probands (table 2).

The prevalence of asthma, hay fever, and eczema among the first degree relatives of the polar extrinsic probands is summarised in table 3. The prevalence of asthma among parents, siblings, and offspring was not evenly distributed; there were more affected parents and fewer affected siblings than expected.

The prevalence of asthma among siblings of probands with neither, one, or both parents affected tended to increase as the number of asthmatic parents increased (table 4). The lowest prevalence of asthma occurred in families where neither parent was affected and the highest prevalence where both parents were affected. Similarly, the prevalence of hay fever/eczema among siblings increased as the number of parents with these traits increased.

POLAR INTRINSIC PROBANDS

Among the 1166 patients examined, 89 (7·6%) fulfilled the criteria for polar intrinsic asthma. Of these, 53 were women. The sex ratio of 0·68 was not significantly different from 1·00 ($P>0·05$). The prevalence of asthma, hay fever, and eczema

Table 2 *Prevalence of hay fever and eczema among polar extrinsic probands*

Probands	*N*	*Hay fever only*		*Eczema only*		*Hay fever and eczema*	
		No affected	*Percent affected*	*No affected*	*Percent affected*	*No affected*	*Percent affected*
Men	164	48	29·3	41	25·0	35	21·3
Women	163	51	31·3	25	15·3	49	30·1
Total	327	99	30·3	66	20·2	84	25·7
Significance		$x^2=0·16$, $P>0·05$		$x^2=3·88$, $P>0·05$		$x^2=2·33$, $P>0·05$	

Table 3 *Prevalence of asthma, hay fever, and eczema among first degree relatives of polar extrinsic probands*

Trait	*Prevalence (%)* *Parents*	*Siblings*	*Offspring*	*All relatives*	*Comparison of parents, siblings and offspring Significance (df=2)*
Asthma	104/654 (15·9)	70/666 (10·5)	25/177 (14·1)	199/1497 (13·3)	$x^2=7·19$, $P<0·05$
Hay fever	91/654 (13·9)	69/666 (10·4)	18/177 (10·2)	178/1497 (11·9)	$x^2=3·86$, $P>0·05$
Eczema	38/654 (5·8)	45/666 (6·8)	14/177 (7·9)	97/1497 (6·5)	$x^2=1·65$. $P>0·05$

Table 4 *Prevalence of asthma and hay fever/eczema among siblings of extrinsic probands with neither, one, or both parents affected*

Affected parents	*N*	*Asthma*			*N*	*Hay fever/eczema*		
		Siblings at risk	*Siblings affected*	*Percent affected*		*Siblings at risk*	*Siblings affected*	*Percent affected*
Neither	229	475	38	8·0	223	960	167	17·4
One	92	177	28	15·8	91	154	29	18·8
Both	6	14	4	28·6	13	18	8	44·4
Significance (df=2)		$x^2=16·14$, $P<0·001$				$x^2=8·58$, $P<0·05$		

among the first degree relatives of the polar intrinsic probands is summarised in table 5. The prevalence of asthma was again unevenly distributed among the parents, siblings, and offspring; there were more affected parents and fewer affected siblings than expected.

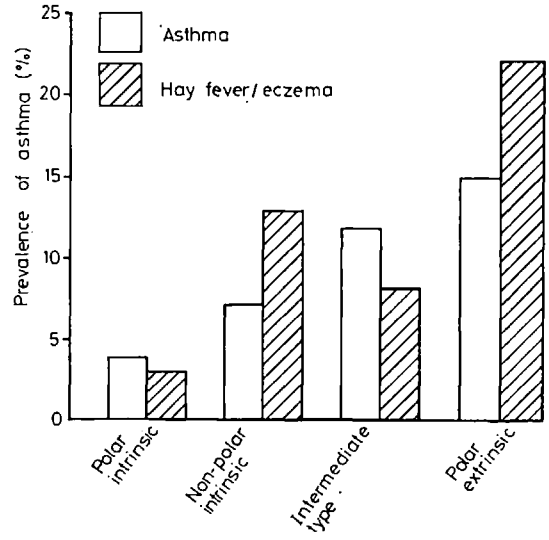
Sample sizes were too small to permit analysis of the number of affected siblings when neither, one, or both parents had asthma or hay fever/eczema (table 6). The prevalence of asthma, however, tended to be higher when one parent was asthmatic than when neither parent was affected.

The overall prevalence of asthma among first degree relations of intrinsic probands was significantly lower than that among relatives of extrinsic probands ($P<0.001$). Similarly, the prevalence of hay fever/eczema was lower among relatives of extrinsic asthmatics ($P<0.001$).

INTERMEDIATE FORMS OF ASTHMA

A small number of asthmatic patients who did not fulfil the criteria for polar extrinsic or intrinsic asthma were selected for comparison with the polar groups from the same population. Of the 787 patients attending the Brompton clinic, 22 (2·8%) were non-polar intrinsic and 271 (34·4%) were intermediate type. From the latter group 14 randomly selected patients were included in the present study. The prevalence of asthma among relatives of non-polar intrinsic asthmatics was 7/96 (7·3%) and that of the intermediate type asthmatics was 10/81 (12·3%). The prevalence of hay fever or eczema or both was 13/95 (13·5%) in the former group and 6/81 (7·4%) in the latter.

The prevalence of asthma and hay fever/eczema among the first degree relatives of the four groups (for instance, polar intrinsic and extrinsic, non-polar intrinsics, and intermediate type) is shown (see figure). When the groups of probands are ranked in order of increasing atopy, as assessed by skin test sensitivity, the prevalence of asthma among relatives increases linearly. Between any two adjacent groups of probands, the prevalence of asthma is not significantly different. Between



Prevalence of asthma and hay fever/eczema among first degree relatives of probands.

Table 5 *Prevalence of asthma, hay fever, and eczema among first degree relatives of polar intrinsic probands*

Trait	*Prevalence (%) Parents*	*Siblings*	*Offspring*	*All relatives*	*Comparison of parents, siblings and offspring Significance (df=2)*
Asthma	14/178 (7·9)	7/290 (2·4)	7/158 (4·4)	28/626 (4·5)	$x^2=7·27$, $P<0·05$
Hay fever	0/178 (0)	4/290 (1·4)	6/158 (3·8)	10/626 (1·6)	$x^2=1·67$, $P>0·05$*
Eczema	1/178 (0)	3/290 (1·0)	3/158 (1·9)	7/626 (1·1)	$x^2=1·33$, $P>0·05$

*Comparison between siblings and offspring (df = 1)

Table 6 *Prevalence of asthma and hay fever/eczema among siblings of intrinsic probands with neither, one, or both parents affected*

Affected parents	*N*	*Asthma*			*N*	*Hay fever/eczema*		
		Siblings at risk	*Siblings affected*	*Percent affected*		*Siblings at risk*	*Siblings affected*	*Percent affected*
Neither	74	258	4	1·6	88	248	13	5·2
One	14	32	3	9·4	1	4	0	0
Both	0	—	—	—	0	—	—	—

alternate groups and between the two extremes, however, the differences are significant (polar intrinsic and intermediate type, $P<0.05$; non-polar intrinsic and polar extrinsic, $P<0.05$; polar extrinsic and intrinsic $P<0.001$).

The prevalence of hay fever/eczema among first degree relatives was also positively correlated with the degree of atopy in the probands (Spearman rank correlation coefficient of 0·8).

Discussion

The Doncaster and Brompton populations were remarkably similar, the sole difference being the relatively higher prevalence of asthma, eczema, and hay fever among relatives of Brompton extrinsic asthmatics than among relatives of Doncaster extrinsic asthmatics. Although the cause of this difference cannot be elucidated in this study, this may reflect a difference in the degree of atopy or the severity or both of the asthma in probands. If Brompton probands were more atopic or more severely affected, their increased predisposition to asthma, eczema, and hay fever might be associated with a higher prevalence of these traits among first degree relatives.

Among extrinsic and intrinsic probands there was no distortion in the sex-ratio and little difference between the sexes in the prevalence of hay fever/eczema. The excess of male extrinsic asthmatics often found in other studies was not observed here. This discrepancy may reflect a bias in ascertainment or may have arisen by chance. In the present study the absence of sexual differences suggests that these traits are neither sex-linked nor sex-influenced.

The increased prevalence of asthma among siblings of probands with one or both parents affected supports the hypothesis that this trait is hereditary. At least part of this familial association, however, may have resulted from a common family environment, which would also tend to increase this prevalence. Similarly the increased prevalence of hay fever/eczema among siblings of probands with one or both parents affected, supports, but does not prove, the concept that atopic manifestations are partly hereditary.

The prevalence of asthma is significantly higher among relatives of extrinsic asthmatics than among relatives of intrinsic asthmatics. Although this difference may result from dissimilarities in the family environments, such that relatives of extrinsic asthmatics are exposed to more environmental provoking factors, it seems more reasonable to suggest that this difference is genetic. If this is true then extrinsic asthmatics have a stronger genetic predisposition to asthma than do intrinsic asthmatics.

It is important to note that this clear separation of the extrinsic and intrinsic populations results from the deliberate selection of highly atopic and clearly non-atopic probands. In practice, most asthmatic patients fall between these two extreme forms of asthma, thus forming a continuous spectrum.

A comparison of the intermediate type of asthma to the two polar forms shows a positive correlation between the prevalence of asthma among first degree relatives and the degree of atopy in the probands (see figure). If we assume that the prevalence of hay fever and eczema provides an estimate of the frequency of atopy, then the prevalence of asthma among relatives is also correlated with the degree of atopy in these same relatives. In addition, the prevalence of asthma and hay fever/eczema is low among relatives of intrinsic asthmatics and high among relatives of extrinsic asthmatics. This strong association between atopy and asthma indicates that atopy may enhance a genetic predisposition to asthma.

The above findings together with the results of previous investigations suggest that the expression of asthma is dependent on (*a*) genetic factor(s) that predispose individuals to asthma and (*b*) environmental factor(s) that precipitate asthma in genetically predisposed individuals. Pure environmental or genetic hypotheses may be ruled out since twin and family studies have shown that there is both an environmental and a genetic component to asthma (see introduction for summary).

The particular mode of inheritance of the genetic factor(s) cannot be determined in the present study. The gradual increase in the number of affected siblings with increases in the number of asthmatic parents, however, suggests that asthma may be polygenic. In addition, the excess of affected parents and the slight deficit of affected siblings indicates that one or more of the contributing genes may be recessively inherited.

The results of the present study further suggest that atopy and its manifestations (for instance, hay fever/eczema) may enhance the predisposition to asthma in genetically predisposed individuals. Since atopy is, itself, partly hereditary (Pepys, 1973) relatives of extrinsic asthmatics would then inherit a predisposition to asthma as well as an increased likelihood of its being expressed. Hence the prevalence of both asthma and atopic manifestations, such as hay fever and eczema, would be higher among relatives of extrinsic than among relatives of intrinsic asthmatics.

In addition, atopy may lower the age of onset of

asthma thus giving rise to the characteristically early age of onset in extrinsic asthma. This latter hypothesis is supported by Pepys (1973), who observed a significant negative correlation between age of onset and the degree of atopy in the patient.

We have proceeded to evaluate the hypotheses described above in a population of asthmatic and normal children attending a large general practice. The findings support the conclusions of the present study and will be discussed in detail in a later publication.

We are particularly grateful to Dr Hugh Smyllie and his secretary, Mrs Jean Brodie, for providing the Doncaster data. We also thank Professor J Pepys and Dr J Slack for their valuable advice. During the course of this study, BS was supported by the British Council.

References

Charpin, J, and Arnaud, A (1971). Facteurs génétiques dans l'asthme et les allergies respiratoires. *Le Poumon et le Coeur*, **27**, 111–119.

Edfors-Lubs, M L (1971). Allergy in 7000 twin pairs. *Acta Allergologica*, **26**, 249–285.

Gregg, I (1977). *Asthma*, edited by T J H Clark and S Godfrey, ch 11. Chapman and Hall, London.

Higgins, M, and Keller, J (1975). Family occurence of childhood respiratory disease and familial resemblance in ventilatory capacity. *Journal of Chronic Disease*, **28**, 239–251.

Leeder, S R, Corkhill, R T, Wysocki, M J, Holland, W, and Colley, J R T (1976). Influence of personal and family factors on ventilatory function of children. *British Journal of Preventative and Social Medicine*, **30**, 219–224.

Leigh, D, and Marley, E (1967). *Bronchial Asthma, A Genetic, Population and Psychiatric Study*. Pergamon Press, Oxford.

Molina, C, Brun, J, Coulet, M, Betail, G, and Delage, J (1977). Immunopathology of the bronchial mucosa in "late onset" asthma. *Clinical Allergy*, **7**, 137–145.

Mulholland, H, and Jones, C R (1968). *Fundamentals of Statistics*, pp 178–194. Butterworths, London.

Pepys, J (1973). Types of allergic reaction. *Clinical Allergy*, **3** (suppl), 491–509.

Williams, H E, and McNicol, K N (1969). Prevalence, natural history and relationship of wheezy bronchitis and asthma in children. An epidemiological study. *British Medical Journal*, **4**, 321–325.

Requests for reprints to: Mrs B Sibbald, Department of Medicine, Cardiothoracic Institute, Brompton Hospital, Fulham Road, London SW3.

Clinical Allergy, 1980, Volume 10, pages 313–318

Extrinsic and intrinsic asthma: influence of classification on family history of asthma and allergic disease

BONNIE SIBBALD

Department of Medicine, Cardiothoracic Institute, Brompton Hospital, London

(Received 24 August 1979; accepted for publication 6 November 1979)

Summary

The distributions of asthma, hay fever and eczema were examined in the first degree relatives of 516 asthmatics grouped according to atopic status, history of hay fever/eczema and history of asthma provoked by pollens, dust or animals. The prevalences of both asthma and eczema in relatives were strongly correlated with the presence of hay fever/eczema in probands and to a lesser extent with their atopic status. The prevalence of hay fever in relatives was strongly correlated with both the presence of hay fever/eczema and the degree of atopy in probands. In contrast, allergic provocation of asthma in probands did not influence the prevalences of asthma, hay fever or eczema.

These findings are consistent with the hypothesis that there is an increased risk of asthma in relatives of atopic asthmatics which may arise from the enhanced susceptibility to asthma of individuals who inherit both a predisposition to asthma and a predisposition to atopy.

Introduction

Asthma is often classified into an extrinsic and an intrinsic form according to the nature of the provoking factors involved. Extrinsic asthma is provoked by known external agents associated with reaginic or precipitating antibody. Atopy is usually present and a positive immediate reaction may be elicited on skin prick testing. In contrast, intrinsic asthma appears unrelated to any demonstrable immunological stimulus. Atopy is never present and no reaction is elicited on skin prick testing, even when a wide range of allergens is used. (Turner-Warwick, 1971).

Although it has long been established that asthma has an hereditary component (Edfors-Lubs, 1971; Leigh & Marley, 1967), the genetic relationship of extrinsic to intrinsic asthma was not investigated until recently. In a family study of 416 highly selected hospital outpatients, Sibbald & Turner-Warwick (1979) found that the prevalence of asthma was higher in relatives of extrinsic rather than intrinsic patients,

Correspondence: Dr Bonnie Sibbald, Department of Medicine, Cardiothoracic Institute, Brompton Hospital, Fulham Road, London SW3 6HP.

0009-9090/80/0500-0313$02.00

although the proportion of patients with a family history of asthma did not differ significantly between groups. Analysis of the distributions of asthma and allergic disease in these families suggested that the enhanced risk of asthma in the relatives of extrinsic patients may have resulted from an increase in the susceptibility to asthma of patients who inherited a predisposition to both asthma and atopy.

At present it is not known whether this genetic relationship between atopy and asthma exists in asthmatic patients who fail to meet the stringent criteria adopted for extrinsic and intrinsic asthma. Additional confusion arises since different physicians employ different criteria for the use of the words 'extrinsic' and 'intrinsic' in relation to asthma. Therefore, the influence of the system of classification on the family history of asthma and allergic disease is of considerable importance in clarifying the genetic basis of asthma.

In the present study, three criteria commonly used to differentiate extrinsic and intrinsic asthma were selected, and their influence on the prevalences of asthma, hay fever and eczema in the first degree relatives of asthmatic patients was assessed. These criteria are: (1) atopy as assessed by skin prick testing, (2) history of hay fever and/or eczema and (3) history of asthma provoked by animals, dust or pollens.

Materials and methods

Probands were selected from outpatients attending the asthma clinic of the Brompton Hospital in London during 1973–77. All patients had a history of episodic wheeziness and the majority demonstrated reversible airways obstruction either between successive visits or on treatment with a bronchodilator.

Skin prick tests to twenty-one common allergens were routinely performed on all patients. The allergens used included moulds, animal danders, house dust, pollens and foods. A positive reaction was defined as a weal with a diameter greater than that in the control tests. Individuals with one or more positive tests were said to be atopic, while those with no positive reactions were said to be non-atopic.

Patients were asked if they had ever suffered from hay fever or eczema, and if they believed that their asthma was provoked by pollens, dust or animals.

Information on the first degree relatives of asthmatics was taken from an asthma questionnaire completed by a physician on the patient's first visit to the clinic. For each patient, the following data were available: number of parents, siblings and offspring, and the number of these relatives with asthma, hay fever or eczema.

Probands were classified in groups according to (1) their number of positive skin tests, (2) their history of hay fever and/or eczema (HES) and (3) their history of asthma provoked by pollens, dust or animals (PA). The groups are described in Table 1.

The influence of each of the three clinical characteristics on the family history of asthma was assessed by examining the differences in the prevalence of asthma between groups of patients who resembled each other in two of the characters, but differed with respect to the third or independent variable. A chi-square value was calculated for each such comparison and the sum of these values used to assess the effect of the independent variable. The influence of each of the three clinical characters on the prevalences of hay fever and eczema was assessed in like manner.

Results

The prevalence of asthma in the first degree relatives of the probands is shown in Table 2. When the probands' history of HES and PA were held constant, there was no

Table 1. Classification of Probands

Probands' allergic history	Probands' skin test response: Negative *(N)*	1 or 2 positive *(N)*	3 or more positive *(N)*
PA-negative HES-negative	82	51	62
PA-negative HES-positive	10	10	60
PA-positive HES-negative	8	8	56
PA-positive HES-positive	7	8	154
Total	107	77	332
Family history of asthma*	32(38%)	31(40%)	142(43%)

PA, History of asthma provoked by pollens, dust or animals.
HES, History of hay fever and/or eczema.
* Proportion with a family history of asthma does not differ among groups ($P > 0{\cdot}05$).

significant association between the prevalence of asthma in relatives and the number of positive skin tests in the probands (Table 3). However, when probands were grouped according to number of positive skin tests, irrespective of their histories of HES or PA, the prevalence of asthma did increase with the number of positive skin tests in the probands ($\chi^2_2 = 34{\cdot}50$, $P < 0{\cdot}001$). The prevalence of asthma also rose when the proband had a positive history of hay fever/eczema, but was not influenced by the probands' history of allergic provocation (Table 3).

The prevalence of hay fever in the first degree relatives of the probands is shown in Table 2. Atopy and a positive history of hay fever/eczema in the probands were both associated with an increased prevalence of hay fever in the first degree relatives. However, allergic provoking factors in probands again had no influence on the prevalence (Table 3).

The prevalence of eczema in first degree relatives of probands is shown in Table 2. When the probands' history of HES and PA were held constant, the prevalence of eczema was not influenced by the number of positive skin tests in the probands. However, when probands were grouped according to their skin test sensitivity, irrespective of their histories of HES or PA, the prevalence of eczema in relatives rose with the number of positive skin tests in the probands ($\chi^2_2 = 13{\cdot}75$, $P < 0{\cdot}01$). The prevalence of eczema also rose when the proband had a positive history of hay fever/eczema, but was not influenced by the probands' history of asthma provoked by pollens, dust or animals. (Table 3).

The distributions of asthma, hay fever and eczema among the parents, siblings and offspring of the probands were examined. In many groups, the sample sizes were too small for statistical analysis. However, in those groups which were sufficiently large to test, the prevalence of asthma tended to be higher in the parents and offspring than the

Table 2. Prevalences of asthma, hay fever and eczema in first degree relatives of probands

	Probands' skin test response		
	Negative prevalence (%)	1 or 2 positive prevalence (%)	3 or more positive prevalence (%)
Asthma			
group A	20/529 (3·8)	24/313 (7·7)	26/305 (8·5)
B	8/53 (15·1)	4/49 (8·2)	39/246 (15·8)
C	3/50 (6·0)	4/43 (9·3)	20/258 (7·7)
D	5/37 (13·5)	5/61 (8·2)	108/667 (16·2)
Total	36/669 (5·4)	37/466 (7·9)	193/1476 (13·1)
Hay fever			
group A	11/529 (2·1)	5/313 (1·6)	23/305 (7·5)
B	2/53 (3·8)	3/49 (6·1)	36/246 (14·6)
C	0/50 (0)	2/43 (4·6)	17/259 (6·6)
D	1/37 (2·7)	1/61 (1·6)	109/667 (16·3)
Total	14/669 (2·1)	11/466 (2·4)	185/1476 (12·5)
Eczema			
group A	10/529 (1·9)	8/313 (2·5)	8/305 (2·6)
B	2/53 (3·8)	4/49 (8·2)	14/246 (5·7)
C	0/50 (0)	2/43 (4·6)	13/258 (5·0)
D	0/37 (0)	2/61 (3·3)	52/667 (7·8)
Total	12/669 (1·8)	16/466 (3·4)	87/1476 (5·9)

A, proband: no allergic provocation or hay fever/eczema
B, proband: no allergic provocation, but hay fever/eczema present
C, proband: allergic provocation present, but no hay fever/eczema
D, proband: allergic provocation and hay fever/eczema present

Table 3. Influence of atopy, hay fever/eczema (HES) and allergic provoking factors (PA) in probands on the prevalences of asthma, hay fever and eczema in their first degree relatives

Factor in proband	Influence on Prevalence of		
	Asthma	Hay fever	Eczema
Atopy	$\chi^2_1=12{\cdot}11$, $P>0{\cdot}05$	$\chi^2_1=42{\cdot}98$, $P<0{\cdot}001$	$\chi^2_4=4{\cdot}71$, $P>0{\cdot}10$
HES	$\chi^2_2=16{\cdot}11$, $P<0{\cdot}01$	$\chi^2_3=19{\cdot}70$, $P<0{\cdot}001$	$\chi^2_2=4{\cdot}85$, $P<0{\cdot}10$
PA	$\chi^2_3=0{\cdot}12$, $P>0{\cdot}10$	$\chi^2_2=0{\cdot}41$, $P>0{\cdot}10$	$\chi^2_2=3{\cdot}55$, $P>0{\cdot}10$

siblings of probands, and this difference was highly significant when all groups were pooled ($\chi^2_2=53{\cdot}1$, $P<0{\cdot}001$). Hay fever was most prevalent in parents, intermediate in siblings and least prevalent in offspring; these differences reaching significance when all groups were pooled ($\chi^2_2=13{\cdot}0$, $P<0{\cdot}01$). Eczema was evenly distributed over the parents, siblings and offspring of probands ($\chi^2_2=0{\cdot}3$, $P>0{\cdot}05$). (Table 4)

Table 4. Distribution of asthma, hay fever and eczema among the parents, siblings and offspring of asthmatics*

Prevalence of	Parents *n* (%)	Siblings *n* (%)	Offspring *n* (%)	Significance (d.f. = 2)
Asthma	134/1030 (13)	98/1201 (8)	35/380 (9)	$\chi^2 = 53{\cdot}1$, $P < 0{\cdot}001$
Hay fever	108/1030 (10)	80/1201 (7)	22/380 (6)	$\chi^2 = 13{\cdot}0$, $P < 0{\cdot}01$
Eczema	43/1030 (4)	56/1201 (5)	16/380 (4)	$\chi^2 = 0{\cdot}3$, $P > 0{\cdot}05$

* The prevalences have been calculated from the pooled data.

Discussion

The similarity in the distributions of asthma among the relatives of clinically different groups of asthmatic patients shows that, if these various forms of asthma are hereditary, they are likely to have similar modes of inheritance. The evenness of the distribution of asthma among the parents, siblings and offsprings of asthmatics further suggests that the mode of inheritance may be polygenic. Thus, the findings support the hypothesis that atopic and non-atopic forms of asthma share a common genetic defect.

Nonetheless, the risk of asthma was found to be higher for relatives of atopic than non-atopic asthmatic patients. Although the proportion of patients with a positive family history of asthma did not vary with the atopic status of the probands, the prevalence of asthma in their first degree relatives increased with the probands' number of positive skin prick tests. Therefore the number of asthmatic relatives per family increased with the degree of atopy in the proband; a finding which is consistent with the hypothesis that atopy may enhance the manifestation of asthma.

Since only a portion of all atopic individuals actually suffer from allergic disease, other factors must exist which act in conjunction with atopy to produce allergic disease. That these factors could be hereditary and may also enhance the manifestation of asthma, was indicated by the strong association between the presence of hay fever/eczema in the probands and the prevalence of asthma in their relatives.

The prevalence of hay fever in relatives was more closely associated with the atopic status of probands than was the prevalence of asthma. In a study of 1000 asthmatic patients and their families, Pepys (1973) also found that the correlation between the atopic status of patients and the prevalence of hay fever in their first degree relatives was greater than that between the atopic status of patients and the prevalence of asthma. This suggests that the manifestation of hay fever is more strongly dependent on the presence of atopy than is the manifestation of asthma. Thus the development of asthma is likely to involve genetic factors which are separate from those leading to clearly atopic disease.

Allergic provocation of asthma in probands was not associated with differences in the prevalences of asthma, eczema or hay fever, and therefore appears to have had little or no influence on the genetics of asthma.

In summary, the findings of this study support the hypothesis that clinically different forms of asthma share a common hereditary defect. The genetic factors giving rise to asthma appear to be inherited independently of those underlying atopy.

However, the presence of atopy and allergic disease may increase the likelihood that a genetic predisposition to asthma will be expressed.

In these studies, the family history data were limited to the patients' knowledge of their relatives. While it is undeniable that this dependence on interview with the proband might have biased the estimated prevalence of asthma and allergic disease, this bias could not have given rise to the observed differences between groups of patients (Table 2), since all groups would be equally subject to its influence. Furthermore, the large numbers of patients interviewed minimizes any chance variations arising from patients differing in their knowledge of their families. Thus the data were not unsuited to the type of analysis employed.

Future investigations should concentrate on the pattern of transmission of asthma and atopy in individual families. In this way, the nature of the shared genetic factors and their relationship to atopy may be clarified.

References

EDFORS-LUBS, M.L. (1971) Allergy in 7000 twin pairs. *Acta Allergolica (Kbh)*, **26**, 249.

LEIGH, D. & MARLEY, E. (1967) *Bronchial Asthma. A Genetic, Population and Psychiatric Study*. Pergamon Press, London.

PEPYS, J. (1973) Types of allergic reaction. *Clinical Allergy*, **3** (suppl.), 491.

SIBBALD, B. & TURNER-WARWICK, M. (1979) Factors influencing the prevalence of asthma among first degree relatives of extrinsic and intrinsic asthmatics. *Thorax*, **34**, 332.

TURNER-WARWICK, M. (1971) Provoking factors in asthma. *British Journal of Diseases of the Chest*, **65**, 1.

Br. J. Dis. Chest (1980) 74, 93

Short Communication

GENETIC BASIS OF SEX DIFFERENCES IN THE PREVALENCE OF ASTHMA

BONNIE SIBBALD

Department of Medicine, Cardiothoracic Institute, Brompton Hospital, London

Summary

The possibility that sex differences in the prevalence of asthma are caused by a genetic sex influence was investigated in 298 asthmatic patients with three or more positive skin tests (sex ratio = 1.35) and in 94 asthmatic patients with no positive skin tests (sex ratio = 0.58). The distribution of asthma among the male and female relatives of the male and female patients was uniform in both groups, indicating there was no genetic sex influence.

INTRODUCTION

It has long been known that the prevalence of atopic asthma is higher among males than females (Smith 1961), while the prevalence of non-atopic asthma is often higher among females than males (Molina et al. 1977). Although this dichotomy is not strict, the trend is of sufficient importance to warrant further investigation. In this paper, the possibility that these sex differences are caused by a genetic sex influence has been investigated.

Materials and Methods

Probands were selected from out-patients attending an asthma clinic at the Brompton Hospital during 1973–7. All patients had a history of episodic wheeziness and the majority demonstrated reversibility in airways obstruction either between successive visits or on treatment with a bronchodilator.

Skin prick tests to 21 common allergens were routinely performed on all patients. A positive reaction was defined as a weal with a diameter greater than that in the control test.

Information on first-degree relatives was obtained from a questionnaire completed by a physician on the patient's first visit to the clinic. The total number of first-degree relatives, the number with asthma and the sex of the relatives was recorded for each proband.

RESULTS

Among 469 patients attending the clinic, 298 had three or more positive skin prick tests and 94 had no positive tests. The sex ratio (males: females) was 1.35 in patients with three or more positive skin tests and 0.58 in patients with no positive reactions. In both groups, the prevalences of asthma did not differ between the male and female relatives of the male and female patients (Table I).

Table I. Prevalence of asthma among male and female relatives of male and female asthmatics

Probands	*Prevalence in relatives*		*Row significance*
	Male	Female	
With three or more positive prick tests			
Male ($n=171$)	49/464 (10.6%)	40/466 (8.6%)	$\chi^2=1.12$, $P>0.10$
Female ($n=127$)	30/388 (8.9%)	35/394 (8.9%)	$\chi^2=0$, $P=1.00$
Column significance	$\chi^2=0.46$, $P>0.10$	$\chi^2=0$, $P=1.00$	
With no positive prick tests			
Male ($n=35$)	4/96 (4.2%)	4/107 (3.7%)	$\chi^2=0$, $P=1.00$
Female ($n=59$)	9/169 (5.3%)	13/176 (7.4%)	$\chi^2=0.73$, $P>0.10$
Column significance	$\chi^2=0.32$, $P>0.10$	$\chi^2=1.55$, $P>0.10$	

Discussion

Under the hypothesis that asthma is genetically sex-influenced, the sex which is least often affected must inherit more predisposing genetic factors in order to manifest the disorder. The family history of asthma in affected members of this sex is increased correspondingly. Therefore, in atopic asthma where females are the sex least often affected, we would expect the prevalence of asthma to be higher in relatives of female asthmatics than in relatives of male asthmatics. This difference in prevalence should be most noticeable in female relatives; female relatives of female asthmatics should be more frequently affected than female relatives of male asthmatics. Conversely, in non-atopic asthma where males are the sex least often affected, we would expect male relatives of male asthmatics to be more frequently affected than male relatives of female asthmatics.

In the present study, there were no differences in the prevalence of asthma between the male and female relatives of males and females with either atopic or non-atopic asthma. This uniformity in the distribution of asthma shows that neither form of asthma is sex-influenced. Therefore the sex differences observed in many clinical populations must arise from factors other than those associated with the genetics of sex determination.

Acknowledgements

I would like to thank Professor M. Turner-Warwick and Dr J. Slack for their help in preparing this manuscript. The work was supported by the British Council.

References

Molina, C., Brun, J., Coulet, M., Betail, G. & Delage, J. (1977) Immunopathology of the bronchial mucosa in 'late onset' asthma. *Clin. Allergy 7*, 137.

Smith, J. M. (1961) The prevalence and natural history of asthma in schoolchildren. *Br. med. J. 1*, 711.